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Clinical Development

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12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study

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12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study

Trial Identification Number:
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Trial Status:
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Reporting Date:
December 30, 2024

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Clinical Trial Site:

J. B. Roy State Ayurvedic Medical College and Hospital (formerly known as *Ashtanga Ayurvedic Vidyalaya*) in Kolkata, West Bengal, India, was founded on February 10, 1916, with Kaviraj Jamini Bhusan Roy's dream, dedication, and devotion, and is recognized by the Central Council of Indian Medicine as the country's oldest Ayurvedic academic institute. The institute's foundation stone was placed by Mahatma Gandhi, the father of the nation.

The institute is directly overseen by the Department of Health and Family Welfare, Government of West Bengal, and the Ministry of AYUSH, Government of India, has bestowed upon it the title of 'State Model College of Ayurveda.

Since its foundation, the institute has preserved the history of classical Indian system medicine via instruction, treatments, and research while incorporating modern scientific advancements. The institute's scholarly students have established themselves in many parts of the country and abroad due to their expertise. Aside from National Health Mission programs, several national and international-funded research projects have been completed and are still ongoing. This institute participates in the National Human Genomic Research Projects (supported by IGIB, CSIR, and the Government of India) on Indian-origin South Asian populations using conventional and modern methodologies.
For further details visit: http://www.wbuhs.ac.in

Important Date:

May 10, 2023	Project Enquiry
June 7, 2023	Project Proposal Submitted
July 4, 2023	Institutional Ethical Clearance Received
July 7, 2023	Test Medicine Received
July 13, 2023	First Installment Received
September 1, 2023	Clinical Staff Recruited
September 1, 2023	Project Started
September 15, 2023	Research Protocol Training
November 2, 2023	CTRI Registration Received
November 6, 2023	First Patient Recruited
January 28, 2024	Second Installment Received
June 28, 2024	Interim Report Submitted
August 2, 2024	Final Installment Received
August 12, 2024	Final Patient Recruited
November 11, 2024	Final Follow-up Completed
November 30, 2024	Trial Completed
December 12, 2024	Study Out-put Presented
December 30, 2024	Final Draft Report Submitted
January 15, 2025	Final Report Submitted

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Ref. No.: JBR/RU/BR-HR-25/2024 Date: December 30, 2024

Statement of Investigator

NCT Identification No.:	CTRI/2023/11/059465
Status:	Completed
Study Tenure:	October 1, 2023 to November 30, 2024
Study Title:	12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Test Substance:	Body Revival
Study Type:	Interventional (Clinical)
Study Sponsor:	M/s Health Reactive, Excellency Bldg, 1st Floor, 4 Bungalow, MHADA Layout, Andheri (W), Mumbai-400053, INDIA
Report Date:	December 30, 2024

[1] The study was designed and executed in compliance with "Good Clinical Practice for Clinical Trials", ICMR, Govt. of India and relevant SOPs of Institutional Ethics Committee of J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata for research involving human participants under our supervision in the time period of November 2023 to November, 2024. Institutional Ethics Committee has been reviewed the study related documents. CTRI registration obtained on November 2, 2023.

[2] We were not implemented any deviation from or changes of the protocol without agreement by the Sponsor. To the best of our knowledge, there was no deviation from the study protocol affecting the quality or integrity of the study.

[3] We maintained confidentiality of the identification of all participating subjects and assured security and confidentiality of study data.

[4] This study was designed and carried out in South-Asian post-surgical breast cancer patients to evaluate the effect of a specific dose of Body Revival® on breast cancer

patients in combination with or without a regular therapeutic regimen to improve quality of life (QoL) and progression-free survival (PFS) while mitigating the previous treatment related side effects.

[5] These data are the property of M/s Health Reactive, Excellency Bldg, 1st Floor, 4 Bungalow, MHADA Layout, Andheri (W), Mumbai-400053, www.bodyrevival.in and are considered confidential for all purposes except compliance with Good Clinical Practice for Clinical Trials, ICMR, Govt. of India (2017).

[6] The study report and data have been edited in accordance with the study protocol and the Standard Operating Procedure (SOP). This report accurately reflects the raw data and accurately describes the methods and standard operation procedures used in this study.

[7] The present report was prepared following the CONSORT 2010 Statement Updated Guidelines for reporting parallel group randomized trials.

[8] Considering all, we advised breast cancer patients to use Body Revival® to enhance their quality of life and everyday functioning. Furthermore, it improved physical endurance in daily activities while reducing the adverse effects of radiation and chemotherapy.

[9] Body Revival® is a safe and well-tolerated herbal supplement for individuals undergoing cancer treatment.

[10] Body Revival® is recommended for cancer patients as a safe therapy when administered by a physician or in a medical setting.

Signature of the Investigators:

Srikanta Pandit 15-01-2025

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Glossary of Terms

I. Clinical Trial Associated Terms & Definitions:

I. **Adverse Drug Reaction:** An adverse drug reaction (ADR) can be defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product. Adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspect reactions to medicines that are unlicensed or being used off-label in addition to the authorized use of a medicinal product in normal doses.

II. **Adverse Events:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

III. **Case Record Form (CRF):** A printed, optical or electronic document designed to record all of the protocol required information to be reported for each subject/patient in a clinical trial. The CRF is the tool used by the sponsor/investigator of the clinical trial to collect data from each participating patient. All data on each patient participating in a clinical trial are held and/or documented in the CRF, including adverse events.

IV. **Informed Consent (IC):** Informed consent is a process for getting permission before conducting a healthcare intervention on a person, or for disclosing personal information. A health care provider may ask a patient to consent to receive therapy before providing it, or a clinical researcher may ask a research participant before enrolling that person into a clinical trial. Informed consent is collected according to guidelines from the fields of medical ethics and research ethics.

V. **Serious Adverse Event (SAE):** A serious adverse event in human drug trials is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

II. Disease & Treatment Associated Terms:

I. **Stages of breast cancer:** After diagnosed breast cancer, the stage of the cancer has to be established. The stage helps determine the prognosis and the best treatment options. Stage 0, which is non-invasive ductal carcinoma *in situ* (DCIS), and stages I through IV, which are used for invasive breast cancer. Stage IV breast cancer (metastatic breast cancer) indicates that it has spread to other parts of the body. The stage of the cancer may be determined after surgery. Breast cancer stages also takes into account the cancer's grade; the presence of tumor markers, such as receptors, for estrogen, progesterone and HER2; and proliferation factors.

II. **Tests and procedures used to stage breast cancer:** (i) Blood tests, such as a complete blood count; (ii) Mammogram of the other breast to look for signs of cancer; (iii) Breast CT scan/MRI

III. **Treatment Procedures:**

(i) Surgery-

(a) Lumpectomy: During a lumpectomy, which is also referred to as breast-conserving surgery or wide local excision, the surgeon removes the tumor and a small margin of surrounding healthy tissue. A lumpectomy may be recommended for removing smaller tumors. For larger tumors, patients may have to undergo chemotherapy to shrink the tumor to make it possible to remove it by a lumpectomy procedure.

(b) Mastectomy: A mastectomy is an operation to remove breast tissue completely. Most mastectomy procedures remove the lobules, ducts, fatty tissue and some skin, nipple and areola (total or simple mastectomy). Newer surgical techniques such as skin-sparing mastectomy and nipple-sparing mastectomy are increasingly becoming common.

(c) Sentinel node biopsy: The surgeon will remove the lymph nodes that are the first to receive the lymph drainage from the tumor, to determine whether cancer has spread to the lymph nodes. If the tests are negative, no other nodes will need to be removed as there is very little chance of finding cancer in any of the remaining nodes.

(d) Axillary lymph node dissection: In case, cancer is found in the sentinel lymph nodes, the surgeon will remove additional lymph nodes in the armpit.

(e) Contralateral prophylactic mastectomy: Some women with cancer in one breast may choose to have their other healthy breast removed, because of a genetic predisposition or strong family history of cancer.

(ii) Therapy-

(a) Radiation therapy: Radiation therapy uses high-energy, such as X-rays and protons, to destroy undetectable cancer cells and reduce the risk of cancer recurring. Breast cancer radiation can last from three days to six weeks, depending on the treatment. The kinds of radiation therapy that may be considered are –

- External beam breast cancer radiation is most commonly used. A machine outside the body aims a beam of radiation on the area affected.
- Internal breast cancer radiation is newer treatments that inject radioactive cancer-killing treatments only in the affected area.
- Brachytherapy (internal radiation) delivered through an implantable device, which is placed inside the breast during surgery or shortly thereafter which carries targeted radiation to the tumor bed.

Side effects of radiation therapy include fatigue and a red, sunburn-like rash where the radiation is aimed. Breast tissue may also appear swollen or more firm. Rarely, more-serious problems may occur, such as damage to the heart or lungs or, very rarely, second cancers in the treated area.

(b) Chemotherapy:

- **Adjuvant therapy -** Chemotherapy uses drugs to destroy the fast-growing cancer cells. If the cancer has a high risk of returning or spreading to another part of the body, doctors may recommend chemotherapy after surgery to decrease the chance of the cancer recurring.
- **Neo-adjuvant therapy -** Chemotherapy is sometimes given before surgery for women with larger breast tumors to shrink the tumor to a size to make it easier to remove with surgery.

Chemotherapy has some side effects depending on the drugs given. Hair loss, nausea, vomiting, fatigue and an increased risk of developing an infection are the common side effects. Rare side effects can include premature menopause, infertility (if premenopausal), damage to the heart and kidneys and nerve damage.

(c) Hormone therapy:

Hormone therapy is used to treat breast cancers that are sensitive to hormones. These cancers are referred to as estrogen receptor positive (ER positive) and progesterone receptor positive (PR positive) cancers. It can be used before or after surgery or other treatments to decrease the chance of the cancer recurring. If

the cancer has already spread, hormone therapy may shrink and control it. Treatments that can be used in hormone therapy include:

- Medications that block hormones from attaching to cancer cells: selective estrogen receptor modulators
- Medications that stop the body from making estrogen after menopause: aromatase inhibitors
- Surgery or medications to stop hormone production in the ovaries

Hormone therapy side effects depend on specific treatment, but may include hot flashes, night sweats and vaginal dryness. More serious side effects include a risk of bone thinning and blood clots.

(d) Targeted therapy:

Targeted drug treatments attack specific abnormalities within cancer cells without harming normal cells. This therapy may block the action of an abnormal protein (such as HER2) that stimulates the growth of breast cancer cells.

(e) Immunotherapy:

Immunotherapy employs the patient's immune system to combat the disease when the body's immune system which normally battles illness may not attack the cancer cells because they generate proteins that render the immune system cells blind. Immunotherapy might be an option for triple-negative breast cancer, which means that the cancer cells do not have receptors for estrogen, progesterone or HER2. Immunotherapy is combined with chemotherapy to treat advanced cancer that has spread to other parts of the body.

(f) Palliative care:

Palliative care is specialized medical care that provides relief from pain and other symptoms of serious illness through surgery, chemotherapy, or radiation. When it is used along with other treatments, people with cancer may feel better and live longer. The aim is to improve the quality of life for people with cancer. This form of care is offered along with curative or other treatments the patient may be receiving.

(g) Alternative medicine:

Complementary and alternative medicine therapies may help to cope with the side effects of treatment when combined with the doctor's care. Many breast cancer survivors experience fatigue that can continue for many years. Complementary and alternative medicine therapies may help relieve fatigue, pain, anxiety and other serious side effects of conventional therapy of breast cancers.

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AYUSH	Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy
BR	Body Revival®
CA-15.3	Cancer antigen 15.3
CBC	Complete blood count
CDSCO	Central Drug Standard Control Organization
CI	95% Confidence Intervals
CRF	Case record form
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTRI	Clinical Trials Registry of India
DALYs	Disability adjusted life years
DCIS	Ductal carcinoma *in situ*
EC	Ethics Committee
ER	Estrogen receptor
GBD	Global Burden of Disease
GCP	Good Clinical Practice
HDI	Human Development Index
HER2	Human epidermal growth factor receptor 2
IARC	International Agency for Research on Cancer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IDC	Infiltrating ductal carcinoma
IEC	Institutional Ethics Committee
ITT	Intent-to-Treat Population
KPS	Karnofsky Performance Status
MRI	Magnetic Resonance Imaging
PFS	Progression free survival
PIS	Patient Information Sheet
PR	Progesterone Receptor
QoL	Quality of life
RAD	Radiation therapy
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SD	Standard Deviation
SOP	Standard Operating Procedure
WHO	World Health Organization

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1. Title and Synopsis

1a. Title

12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study

1b. Synopsis

Condition or Disease	Intervention/Treatment	Phase
Breast cancer • Post-operative • Chemotherapy • Radiation therapy	Drug: Body Revival® Control: without Body Revival®	Phase II

Clinical Trial No. (NCT):	CTRI/2023/11/059465
Research ID:	HR-BR-BC0523
Study Type:	Interventional (Clinical)
Present Status:	Completed
Official Title:	12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Brief Title:	12 Weeks Intervention of Body Revival® in Breast Cancer Patients
Trial Phase:	Phase – II
Trial Product:	Body Revival® (Batch No. HRB0043; Mfg. dt. 06/2023)
Product License No.:	HP-177-AY
Trial Comparator:	NIL
Trial Sponsor:	M/s Health Reactive Excellency Bldg., 1st Floor, 4 Bungalow, MHADA Layout, Andheri (W), Mumbai-400053, Maharashtra, INDIA www.bodyrevival.in
Study Site:	Research Unit, Department of Kayachikitsa J.B. Roy State Ayurvedic Medical College & Hospital 170-172 Raja Dinendra Street, Kolkata-700004, INDIA

Trial Investigators:	[1] Prof. (Dr) Srikanta Pandit, BAMS, MD (Ay.), Ph.D [2] Prof. (Dr) Tuhin Kanti Biswas, BAMS, MD (Ay.), Ph.D [3] Prof. (Dr) Utpalendu Jana, MD (Ay.), Ph.D
Trial Design:	Longitudinal, cross-sectional, open-label, randomized, case-control cohort study at a single center
Primary Objective:	To assess the effect of selected dose of Body Revival (BR) on breast cancer patients in combination with / or without regular therapeutic regimen to improve quality of life (QoL) and progression free survival (PFS) and counteract the affirmed side effects
Secondary Objective:	I. To assess the effect of BR on KPS II. To assess the safety and tolerability of BR III. To assess the effect of BR on conventional breast cancer treatment associated AEs
Methods: **Eligibility Criteria:**	○ Ages Eligible for Study: ≥ 18 years ○ Sexes Eligible for Study: Female ○ Accepts Healthy Volunteers: No ✓ Diagnosed of breast cancer (stage II–IV) ✓ Treated with surgery/chemotherapy / radiotherapy ✓ Treatment-free interval ≤6 months after surgery / CT/ RAD
Sample Size	○ 44 participants completed the study
Study Arms:	The groups or arms was as follows: • Arm I: CT - Control (N=12) • Arm II: CT - Body Revival (N=12) • Arm III: RAD - Control (N=10) • Arm IV: RAD - Body Revival (N=10)
Randomization:	Stratified by 1:1 case control vs. treatment of four arms
Screening Assessment:	○ Medical History ○ Physical examinations & vital signs ○ Karnofsky Performance Status (KPS) ○ Quality of Life (QoL) ○ Progression Free Survival (PFS): serum CA 15.3 ○ Blood analyses: CBC, Glucose, LFT, BUN, Cr ○ Adverse Events: CTCAE v.5 criteria
Treatment Schedule:	Body Revival® suspension, per oral, 6 ml in every 6th day interval before going to bed (preferably in night) for 12 weeks
Follow up Visits:	○ 1st Follow-up: 4 wks. after randomization (± 5days) ○ 2nd Follow-up: 4 wks. after 1st Follow-up (± 5days) ○ 3rd Follow-up: 4 wks. after 2nd Follow-up (± 5days)

Data Analysis:	○ ANOVA with post-hoc Friedman's Chi-Square test, paired t-test and 95% CI was applied wherever applicable. ○ Co-relation was done using Pearson's Correlation ○ Reliability was checked by Cronbach's Alpha. ○ P-value adjusted at less than 0.05 significant levels.
Results:	I. Body Revival® (BR) treatment enhanced Quality of Life for patients with breast cancer in terms of physical well-being and psychological well-being. II. BR improved physical activity and performance in daily life. III. BR lowered the breast cancer tumor biomarker CA-15.3 and lowered the progression of disease. IV. It lowered the side effects of chemotherapy and radiation in cancer patients. V. BR treatment enhanced appetite, physical stamina and endurance while reduced nausea, constipation, muscle weakness, dizziness and fatigue in cancer patients. VI. BR decreased liver enzymes and enhanced protein and hemoglobin levels in blood. VII. BR improved WBC and neutrophil count and immunological function in chemotherapy-induced cancer patients. VIII. BR exhibited safe, effective and well-tolerated oral herbal medication for cancer patients. IX. BR can alleviate chemotherapy and radiation-related adverse effects in cancer patients.
Conclusion:	Breast cancer survivors' life expectancy can be enhanced with BR. Its adjuvant therapy may be advantageous to breast cancer patients who are experiencing side effects from their current chemotherapy and radiation therapies.
Publication:	**Sur TK, Pandit S.** A Randomized Case Control Study of Body Revival® to Improve Quality of Life and Progression Free Survival in Breast Cancer Patients. Presented at 10th International World Ayurveda Congress, Dehradun, Uttarakhand, December 12-15, 2024, #AB5204.
Date of Reporting:	December 30, 2024
Contact s & Locations:	**Contact: Dr. Srikanta Pandit** +91 (983)172-3650 **Location:** Research Unit, J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata, INDIA

2. Background and objectives

2a.1 Scientific background

Cancer is a term implicated for an uncontrolled cell division that may invade nearby tissues and spread to other body parts via blood and lymph systems. The major risk factors for this disease include age, family history, hormones, tobacco use, irradiations, chronic inflammation, diet, and sedentary lifestyle. The leading risk factors contributing to global cancer burden in 2019 were behavioral, whereas metabolic risk factors found the largest increases between 2010 and 2019 (GBD 2019 Cancer Risk Factors Collaborators, 2022). The Cancer registry specifies 18.1 million new cases and 10 million global deaths due to cancer in 2020. The most common cancers are breast, lung, colorectal and prostate, contributing 12.5%, 12.2%, 10.7% and 7.8% respectively to the total number of new cases diagnosed in 2020 (Sung et al., 2021).

Breast cancer is the most common cancer diagnosed worldwide, with an estimated 2.3 million new cases in 2020 alone (American Cancer Society; 2021). Incidence rates have historically been elevated in higher human development index (HDI) countries in North America and Western Europe, reflecting a longstanding prevalence of reproductive, hormonal, and lifestyle risk factors in these regions. However, breast cancer incidence has been rising in Asian countries like Japan, China and India where rates have historically been low (Cardoso et al., 2018). Recent data suggest, 1 in 9 Indians has a lifelong risk of developing cancer. The most common malignancies among men and women, respectively, were lung and breast cancers (Kumar et al., 2022).

It is well established that cancer cells display significant difference in their metabolic pathways than the normal cells. Furthermore, the tumor microenvironment and the amount of oxygen and nutrients available for uptake have a major impact on tumor cell metabolism. The major hallmarks of cancer cells are 'self-sufficiency in growth signals', 'insensitivity to anti-growth signals', 'evasion of apoptosis', 'limitless replicative potential', 'sustained angiogenesis', 'tissue invasion and metastasis', 'deregulating cellular energetics and metabolism' and 'avoiding immune destruction' (Hanahan & Weinberg 2011). The microenvironment at the invasive front of tumors is significantly different than that of the tumor core (Quail & Joyce, 2013). Excessive fatty acid metabolism

is one of the key hallmarks for several breast cancer types exhibiting fat metabolism-based therapeutic opportunities (Ruidas et al., 2022).

Breast cancer is a genetically and clinically heterogeneous disease. Unlike colon cancers, defining the progression of breast cancer has not been possible due to lack of markers that define hyperplasia (typical and atypical), carcinoma *in situ* and invasive cancer (Malhotra et al., 2010). There has been much progress in our understanding of the pathology and molecular biology of breast cancer in the last few years. In 2012, WHO updating and classified breast cancers based on traditional tumor classification, precursor lesions, lesions of low malignant potential, benign epithelial proliferations, fibroepithelial, myoepithelial and mesenchymal neoplasms, among others (IARC, 2012). In contrast to Ductal carcinoma *in situ* (DCIS), where the use of molecular markers is still debated, the utility of ER, PR and HER2/neu is well accepted for infiltrating ductal carcinoma (IDC) and it is recommended that their status be determined on all invasive carcinomas (Harris et al., 2007). Now-a-days five main molecular classes of breast cancer are recognized: Luminal A, Luminal B, HER2, Basal and Unclassified (Shawarby et al., 2016).

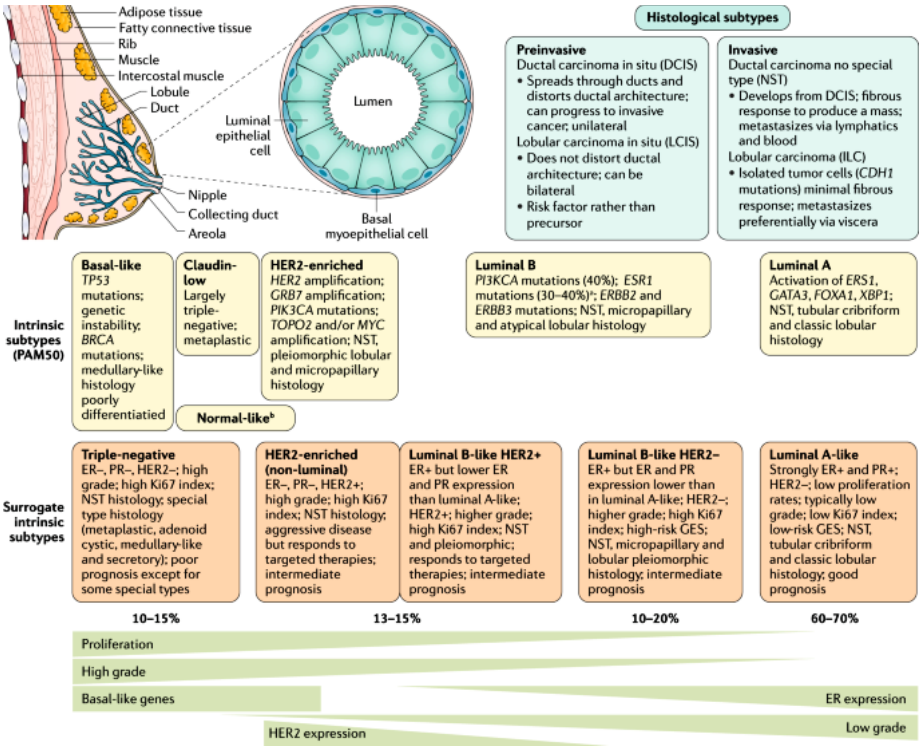


Fig 1. Sub-Types of Breast Cancer

Breast cancer is treated in 5 ways, depends on the kind of breast cancer and how far it has spread. These are surgery (removal of cancer tissue), chemotherapy (special medicines to kill the cancer cells), hormonal therapy (blocks cancer cells), radiation therapy (high-energy rays to kill the cancer cells) and biological therapy (improve immune system to fight cancer cells or to control side effects from other cancer treatments)(WHO, 2006). But the disadvantages associated with these treatments exceed their desired therapeutic outcomes. For instance, an increased wound complication with damage to surrounding tissues during radiation therapy, site-specific complications with more risks of infections after surgery, and systemic toxicities following systemic therapy are few of the uncontrolled circumstances reported after treatment. Single or more than one type of treatments is frequently given to patients with breast cancer. All the chemotherapeutic medicines and radiation therapy have serious side effects including anorexia, vomiting, abdominal pain, diarrhea, hot flashes, headache, dyspnea, skin rash, fever, back pain, muscle cramps, fatigue, dizziness, edema (periorbital & peripheral) etc. (NIH, 2023; CDC, 2023; ACS, 2023). To overcome these barriers, numerous herbal medicines are being used in combination with chemotherapy or radiotherapy to improve the efficacy of cancer therapy and reduce side effects and complications (Yin et al., 2013; Abdullah et al., 2003; Dash 2021). Clinical trials for herbs and herbal products are also increasing where studies are performed to evaluate the effectiveness and therapeutic safety (Ahmad et al., 2020).

The word "cancer" was coined by a Greek physician, Hippocrates (460–370 BC). He used the terms "*carcino*" and "*carcinoma*" to describe non-ulcer forming and ulcer-forming tumours (ACS, 2018). Prior to that, two well-known Ayurvedic classics from India, *Charaka Samhita* and *Sushruta Samhita*, refer to cancer as either an inflammatory or non-inflammatory swelling and refer to it as either *Granthi* (a little neoplasm) or *Arbuda* (a big neoplasm). The tissues are affected by aggravated *Vata* and *Kapha doshas*, which leads to the development of a round, hard, big, deeply rooted, slowly expanding fleshy growth accompanied by slight pain. Based on the aggravating *dosha* and the tissue implicated, Ayurveda has identified six different types of tumors: *Vataj, Pittaj, Kaphaj, Medoj, Mamsaj*, and *Raktarbuda* (CCRAS, 2023). Various Ayurvedic scriptures provide detailed descriptions of numerous remedies for both internal and exterior neoplasms (Balachandran & Govindarajan, 2005). Ayurvedic remedies work to strengthen the body's natural defenses and immunity, revitalize important body systems,

and encourage long-term recovery from illness (Arnold, 2022). Additionally, Ayurvedic oncology is a comprehensive method of treating cancer that blends contemporary cancer therapies with age-old Ayurvedic concepts. The significance of Ayurvedic oncology lies in its potentials to (i) integrate complementary therapies (herbal remedies), (ii) address cancer prevention (lifestyle modifications and diet), (iii) improve quality of life (alleviating cancer symptoms and enhancing patients overall well-being), (iv) offer personalize treatment, (v) enhance cancer treatment outcome (reduce recurrence rate and increase survival rate) and (vi) reduce cancer treatment side effects (mitigate chemotherapy and radiation side effects).

Numerous research investigations have been carried out based on data from folk and traditional medicines across the globe, using modern approaches for finding anticancer medications from natural resources. Several anticancer drugs extracted from plant sources after purification are tested in both in vitro and in vivo models and then sent to clinical trials (Sinha et al., 2021). Newman and Cragg reported that of 98 new small-molecules anticancer drugs that had been approved by the US Food and Drug Administration (FDA) between 1981 and 2010, only 20 were synthetic. The remaining 78 drugs either were natural products (11) or were derived from natural products (67) based on a series of classifications (Newman & Cragg, 2010). The substances of natural origin that exhibit antitumor or anticancer properties belong to various groups of compounds, such as alkaloids, diterpenes, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, etc. (Subramaniam et al., 2019). The amount of data regarding the use of herbal products in cancer clinical trials at times creates a great challenge for oncologists to prescribe or counsel patients. It urges critical evaluation of the quality of clinical trials. On the basis of three commonly used scales, namely the Jadad, Delphi, and Cochrane scales, Ahmad and his colleagues (2020) have critically analyzed clinical trials for herbs used in cancer, and they found that only 16.4% of the studies had excellent quality, mostly because suitable research design was lacking.

The cancer patients experience a variety of symptoms. Inadequate management of symptoms might hamper the performance of the daily activities of an individual. The quality of life (QoL) is one of the most concerning health issues for oncology patients. WHO defines QoL as *"an individual's perception of their position in life in relation to their goals, expectations, standards, and concerns in the*

context of the culture and value systems in which they live". QoL is a specific and multidimensional type of patient-reported outcomes (PROs) which is perceived by patients as something that encompasses the patients' social, financial, psychosocial, and physical activities (Nayak et al., 2017). To evaluate the QoL of cancer patients in an Indian context, the majority of researchers employed the QoL questionnaire version II, which was created and validated by Latha et al. (2011) and has a reliability of 0.90 Cronbach's alpha and 0.80 split-half reliability. Despite chemotherapy having a therapeutic effect, it is associated with the development of severe unfavorable drug reactions which can have adverse effects on the QoL of an individual. Moreover, anticancer therapy requires an extended duration of administration to obtain the required effect. Frequent hospitalizations put an undue burden on cancer patients. Thus, anticancer therapy engenders a colossal personal, mental, and emotional anguish among cancer individuals, affecting their overall QoL (Ramasubbu et al., 2021). Herbal medicines in general are applied to hopefully increase the therapeutic benefit and QoL. The treatment of symptoms will help relieve the suffering and improve the QoL (Alam et al., 2020).

Progression-free survival (PFS) is defined as the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical benefit for drug approvals. Living longer is the priority for patients with breast cancer and the time when disease is not progressing is meaningful when coupled with improvements in QoL and no added treatment toxicity (Mertz et al., 2022).

Serum tumor marker CA15.3 antigen (a protein derived from transcription of the MUC1 gene) is commonly used in conjunction with imaging provides a cost-effective way of supporting the diagnosis of breast cancer and also monitoring the response of the disease to therapy. CA15.3 has been reported to be raised in up to 80% of patients of breast cancer (Duffy et al., 2000; Gaughran et al., 2020).

The Karnofsky Performance Status (KPS) is a widely used method to assess the functional status of a patient. It was introduced by David A. Karnofsky and Joseph H. Burchenal in 1949 (Karnofsky & Burchenal, 1949). The KPS describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death). In the last three decades years various studies have demonstrated the

prognostic value of the KPS, primarily for various cancers (Schag et al., 1984). Furthermore, independent of the role it plays in treatment modality decisions, the KPS has also established itself as a salient prognostic factor in a variety of tumor entities, including breast cancers (Marechal et al., 2007). The importance of the KPS as a tool for assessing QoL is a regularly discussed topic in the relevant literatures (Peus et al., 2013).

2a.2 Interventional medicine: Body Revival®

Body Revival®—an adjuvant micro herbal rejuvenator—has been developed to enhance immunity to regenerate vital cells to combat cancers. The nine natural ingredients of Body Revival® are selected from the Indian traditional medicine as mentioned in the Ayurvedic Pharmacopoeia of India (API, 2008). It contained *Aegle marmelos* (Indian Bael) fruit pulp powder, *Acorus calamus* (Vacha) rhizome, *Withania somnifera* (Ashwagandha) root, *Blumea lacera* (Kukrondha) fruit, *Rumex vesicarius* (Chukrika) whole plant, *Rubia cordifolia* (Manjishtha) root, *Cucumis melo* (Muskmelon) seed, *Symplocos racemosa* (Lodhra) stem bark and honey (**Table 1**). It is used to improve the body's immune mechanism, detoxify harmful body toxins and gut microbes, repair damaged tissues, and rejuvenates healthy cells and is helpful to improve QoL and enhance disease-free longevity in cancer patients in the last 25 years.

Table 1. Composition of Body Revival®

Herbs	Indian Names	Parts Used	Amount (5ml)
Aegle marmelos	Indian Bael	fruit pulp	150 mg
Acorus calamus	Vacha	rhizome	175 mg
Withania somnifera	Ashwagandha	root	325 mg
Blumea lacera	Kukrondha	fruit	115 mg
Rumex vesicarius	Chukrika	whole plant	240 mg
Rubia cordifolia	Manjishtha	root	200 mg
Cucumis melo	Muskmelon	seed	200 mg
Symplocos racemosa	Lodhra	stem bark	95 mg
Honey	Madhu		Qs.

2a.2.1 Pharmaceutical properties: The laboratory-based therapeutic pharmaceutical and nutraceuticals analyses reported for Body Revival® have found polyphenolic therapeutic compounds, water soluble vitamins, essential minerals, and fibers. A remarkable amount of three major biologically active polyphenols like gallic acid, p-coumaric acid, and apigenin are found in Body Revival®. The four most important anticancer phytoconstituents present in Body Revival are cucurbitacin, symconosides, withaferin, and quercetin. The proximate composition and nutraceutical role of ingredients present in Body Revival® and its formulation by chemical analysis provide unequivocal testimony to this fact. Chemical analysis reveals it has maximum carbohydrate and fiber, a lesser amount of protein, and practically zero fat. It contains all important water-soluble vitamins like vitamin C, thiamine, riboflavin, niacin, pantothanic acid, pyridoxin, and folic acid. It has rich sources of essential elements and microelements like sodium, potassium, calcium, magnesium, iron, chromium, copper, and selenium. Considering all this, it may therefore be inferred that Body Revival® possesses important micronutrients and may be helpful as therapeutic supplements (Khan et al., 2020).

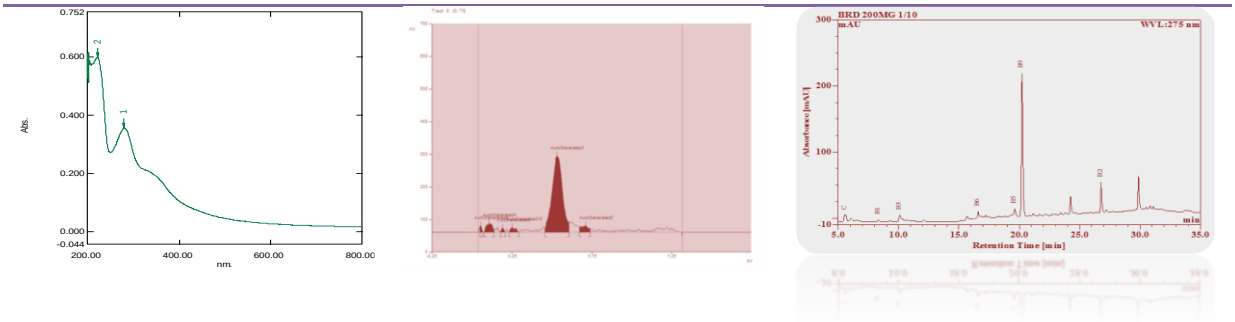


Fig 2. Chemical Analysis of Body Revival®

2a.2.2 Animal studies: Preclinical animal studies revealed that Body Revival® significantly and dose-dependently lowered the ADP and collagen-induced platelet aggregating actions. Furthermore, it reduced the levels of serum creatinine kinase, aspartate transaminase, alanine transaminase, and myocardial tissue lipid peroxides and nitric oxides and thereby protected myocardial infarction in rats induced by isoproterenol. It also lowers the blood lipids in high-fed diet-induced rats (Sur et al., 2011).

In another study, Body Revival® significantly and dose-dependently (200–400 mg/kg) improved the leukocyte, granulocyte, and lymphocyte counts in

peripheral blood and cellularity in bone marrow in cyclophosphamide-induced immune suppressive mice, indicating its potential action on chemoprevention in cancers (Khan et al., 2020). The 50% effective dose (ED_{50}) of Body Revival® for chemoprevention has been determined to be 200 mg/kg.

2a.2.3 Safety studies: According to OECD guidelines 423, Body Revival® did not show any signs of toxicity or mortality up to 2 g/kg per oral dose in mice. The 50% lethal dose (LD_{50}) of Body Revival® could be more than 2000 mg in mice (Sur et al., 2011).

The results of 28-day toxicological studies (OECD guidelines 423) in rats exhibited that Body Revival® is devoid of any toxic materials. Body Revival® showed no morbidity or adverse signs or symptoms. The no observed adverse effect level (NOAEL) of Body Revival® in rats is 1 g/kg.

2a.2.4 Therapeutic index: The therapeutic index is the range of doses at which a medication is effective without unacceptable adverse events.

$$\textit{Therapeutic Index} = LD_{50}/ED_{50} = >10$$

The therapeutic index **of** Body Revival® is not less than 10.

2a.2.5 Anticancer activities: The research on modern literature and traditional texts revealed that the ingredients and their active components have anticancer properties. They include β-asarone, cucurbitacin, 1-hydroxytectoquinone, marmelin, methylglyoxal, mollugin, quercetin, symconosides, withanone, withanolid, withaferin, and more. Cucurbitacin, symconosides, withaferin, and quercetin are the four major anticancer phytoconstituents in Body Revival®.

Most of these active components present in Body Revival® target the plasma membrane, trans-membrane receptors, tyrosine kinases, and G-protein coupled receptors. Therefore, possible modes of anticancer actions of Body Revival® are: stimulating the immune system; protecting DNA from injury; lowering oxidative impairment; antiproliferation; cancer/tumor cell cycle arrest; initiation of apoptosis and suppression of angiogenesis and metastasis; restoring normal cells from toxic chemicals (chemoprevention); and chemopreventive or restoring/protecting normal cells from harmful effects of radiation (Khan et al, 2022).

Fig 3. Multifaceted Anticancer Action of Body Revival®

Body Revival's anticancer activities are multifaceted. It primarily boosts the immune system to protect DNA from damage, reduces oxidative stress, disrupts the cancer cell cycle, and induces apoptosis. Furthermore, it inhibits angiogenesis and metastasis via autophagy (Sur & Pandit, 2024).

2a.2.6 Anticancer activities of ingredients of Body Revival®

Aegle marmelos. *Aegle marmelos* known as "bael" is associated with in the family of Rutaceae. It contains marmelin, lupeol, marmelosin, furocoumarins and scopoletin. It has antioxidant, antiproliferative, cytoprotective, anticancer, radio-protective, immunomodulatory and hepatoprotective properties. Marmelin stimulates tumor necrosis factor-α (TNF-α) and caspases to triggers apoptosis in the malignant cells. Fruit pulp extract of *Aegle marmelos* exhibited anti-

proliferative activity through suppressing the breast tumor growth rate. It did not increase ERα mRNA levels in MCF7 and MDA-MB-231and thereby reduced the viability of cancer cells. It can protect blood lymphocytes from γ-radiation.

Acorus calamus. *Acorus calamus* well-known as "bach" is associated in Acoraceae family. The rhizome contains two main bioactive principles, α-asarone and β-asarone. It has antioxidant, anti-inflammatory, anti-cancer, radioprotective, gastoprotective, neuroprotective and cardioprotective effects. β-Asarone showed chemo preventive and anticancer effect on all kinds of cancer cell lines, such as Hep3 (hepatic carcinoma), MDA-MB-435S (breast cancer), AGS (gastric cancer), HSKMC (fibroblast), LoVo (Colon cancer), HT29 (colorectal cancer) and HeLa (cervical cancer) cells. It has been reported that β-asarone by activating the innate immune system can successfully inhibit liver metastasis and proliferative action in colon cancer cells.

Withania somnifera. *Withania somnifera* familiar as "ashwagandha" or "Indian ginseng" is belongs to the family of Solanaceae. It exhibits antioxidant, anti-inflammatory, anti-stress, immunomodulatory, adaptogenic, chemo preventive effects, anti-cancer activity. The rhizome contains two main bioactive anticancer components, Withanolide and Withaferin A. *W. somnifera* is a promising therapeutic agent for a broad range of cancers. It showed cytotoxicity against four human cancer cell lines such as prostrate DU-145, colon HCT-15, lung A-549 and neuroblastoma IMR-32. Several studies demonstrated that Withaferin A reduced the side effects of some cancer chemotherapeutic agents, viz. cyclophosphamide and paclitaxel without interfering with the cancer-reducing actions of the drugs. Withaferin A inhibited cell cycle, angiogenesis, proteasomes and tumor growth in the prostate. Withaferin A showed the best binding affinity against Protein kinase C and NF-KB. Furthermore, enzyme ligand binding affinities have also been noted against Tyrosine-protein kinase JAK1, Mitogen-activated protein kinase P38, Glutathione Reductase and Glutathione S-Transferases.

Blumea lacera. *Blumea lacera* frequently known as "kakronda" is associated in the family of Asteraceae. It possesses antioxidant, anti-ulcer, anti-diarrheal, hepatoprotective, antiviral activities. It contains phenolics, glycoalkaloids and essential oils. *B. lacera* leaves have shown non-selective cytotoxic activity against

MDA-MB-435S, BBC-1/KMC, B16F10 cells. It exhibited a broad spectrum of anti-leukemic activity and strong anti-HSV activity.

Rumex vesicarius. *Rumex vesicarius* also known as "amlabet" is belongs to the family of Polygonaceae. It is used in the treatment of tumors, liver diseases, cardiovascular disease, asthma, bronchitis and nausea. It possessed a promising anticancer potential against MCF-7 and WRL68 cell lines and HCC induced hepatic carcinoma model. It showed potent antiangiogenic and antiproliferative activities.

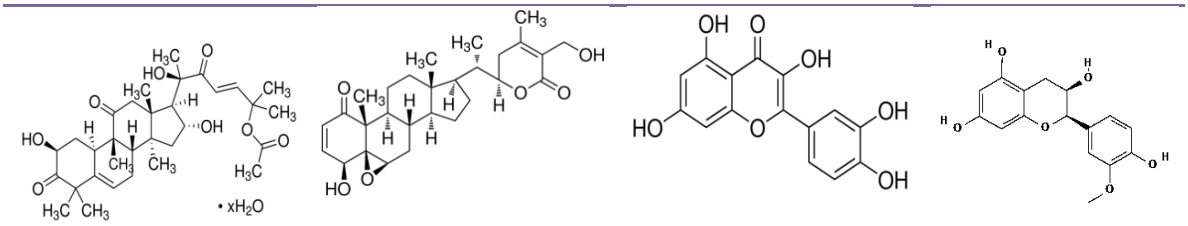
Rubia cordifolia. *Rubia cordifolia* commonly known as "manjishtha" or "Indian maddar" is belongs to the family of Rubiaceae. It contains anthraquinones, glycosides, terpenes and carboxylic acid groups of compounds such as mollugin, furomollugin, dehydro-α lactone, 1-hydroxytectoquinone and manjisthin. The active constituent, Mollugin, exhibited considerable activity against P338 lymphoid leukemia. It has radioprotective action. Aqueous root extract of *R. cordifolia* exhibited cytotoxcity on HeLa cells. Moreover, 1-hydroxytectoquinone isolated from *R. cordifolia* cytotoxic has an effect against A375 human malignant melanoma. The methanolic extract of *Rubia cordifolia* demonstrated antiproliferative and apoptotic properties on HEp-2 (human laryngeal carcinoma) cell line. Furthermore, it showed cytotoxic action on MDA-MB-231, HepG2, BxPC-3 and MCF-7 cancer cells.

Cucumis melo. *Cucumis melo* or "madhuphala" is belongs to the family of Cucurbitaceae. Cucurbitacin B is a tetracyclic-triterpenes present in *Cucumis melo*. The anticancer activity of Cucurbitacin B in human leukemia cells has been observed. It restrains STAT3 activation and the Raf/MEK/ERK pathway in K562 leukemic cells. It is also used as a liver protection medicine in curing hepatic lesions and liver cancer. Cucurbitacin B also inhibited multiple myeloma cells in the G2/M phase. *Cucumis melo* exhibited cytotoxicity against PC3, HCT116, HeLa, and Jurkat cell lines.

Symplocos racemosa. *Symplocos racemosa* or "Lodhra" is associated with the family of Symlocaceae. It has several bioactive glycosides such as symplocomoside, symponoside, benzoyl salireposide, salireposide etc. *Symplocos racemosa* bark showed cytotoxic action on Hep3B hepatocellular carcinoma cells. It has cytotoxicity activity against HeLa cell line.

Table 2. Anticancer Ingredients of Body Revival®

Ingredients / Parts	Extract/ Active component	Anticancer action
Aegle marmelos (fruit)	extract marmelin	○ apoptosis ○ antiproliferative activity ○ cytotoxicity: MCF-7, HEp-2, PC3, A549, CoLo-05, THP-1
Acorus calamus (rhizome)	extract β-asarone	○ cytotoxicity: MDA-MB-435S, HeLa, LoVo ○ down-regulate mitochondrial membrane potential ○ down regulate VEGF mRNA expression ○ down regulate Bcl-2/Bax ratio ○ up regulate caspase-9 and caspase-3 cascades
Withania somnifera (root)	extract withaferin A withanolide withanone quercetin	○ cytotoxicity: DU-145, HCT-15, A-549, IMR-32, A375 ○ inhibit cancer cell G2/M cycle ○ inhibit angiogenesis ○ inhibit tumor growth ○ activate TRIM16 expression ○ inhibits JAK1, MAP kinase P38, Bcl-xL
Blumea lacera (fruit)	extract glycoalkaloids	○ cytotoxicity: MDA-MB-435S, BBC-1/KMC, B16F10 ○ anti-leukemic activity ○ anti-HSV activity
Rumex vesicarius (whole plant)	extract	○ cytotoxicity: MCF-7 and WRL68 ○ inhibits angiogenesis ○ inhibit tumors
Rubia cordifolia (root)	extract mollugin furomollugin	○ cytotoxicity: HEp-2, HepG2, HeLa, BxPC-3, U937 ○ protect radiation
Cucumis melo (seed)	extract cucurbitacin B	○ apoptosis ○ antiproliferative activity ○ cytotoxicity: K562, PC3, HCT116, HeLa, Jurkat ○ inhibits STAT3 activation ○ inhibit Raf/MEK/ERK pathway
Symplocos racemosa (bark)	extract glycosides symconoside	○ apoptosis ○ antiproliferative activity ○ cytotoxicity: Hep3B
Honey	polyphenols methylglyoxal	○ apoptosis ○ antiproliferative activity ○ cytotoxicity: MCF-7, MDA-MB-231, HepG2 ○ suppress angiogenesis ○ arrest cell cycle ○ inhibit tumor growth ○ down regulate ATP production in cancer cells ○ protect against mutagen-induced DNA damage ○ protect from harmful effect of radiation



Cucurbitacin B	Withaferin A	Quercetin	Symplocomoside

Fig 4. Major Anticancer Compounds in Body Revival®

Honey. Honey is composed of sugars, amino acids, proteins, enzymes, vitamins, flavonoids, phenolic acids and other compounds. Bioactive polyphenolic compounds such as kaempferol, quercetin, chrysin, luteolin, apigenin, naringenin etc are present in honey. Honey has potential apoptotic, antiproliferative and immunomodulatory activities. It antagonizes estrogenic activity, restricts cell proliferation, exaggerates apoptosis and reduces mitochondrial membrane potential in the two most widely used breast cancer cell lines, MCF-7 and MDA-MB-231. It inhibits cell proliferation, suppresses angiogenesis, induces apoptosis, protects against mutagen-induced DNA damage in HepG2 liver cancer cells and HT 29 colorectal cancer. Honey contains other anticancer molecules such as methylglyoxal, which inactivates glyceraldehyde-3-phosphate dehydrogenase (GA3PD) and down regulates ATP production in cancer cells and thereby accelerating the death of cancer cells. Hence, honey is potentially helpful to resist cancer via controlling three key steps of carcinogenesis: initiation, proliferation and progression.

2a.2.7 *In vitro* anticancer activity: Body Revival® has been shown in a laboratory investigation to have (a) cytotoxic effects (IC_{50} 34.27µl/ml) on breast cancer cells (MCF-7 cells); (b) restricted cancer cell invasion (26%) and migration (28%); and (c) decreased pro-inflammatory cytokines (IL-6) and matrix metalloproteinase-9 (MMP-9). Additionally, Body Revival® shown chemopreventive or restores/protects normal cells from radiation's detrimental effects. Hence, Body Revival® showed as a powerful multi-target inhibitor of ER- α and HER-2 that has prospective anticancer action without side effects, and may be useful in the therapy management following a successful trial in breast cancer patients (Khan et al, 2023).

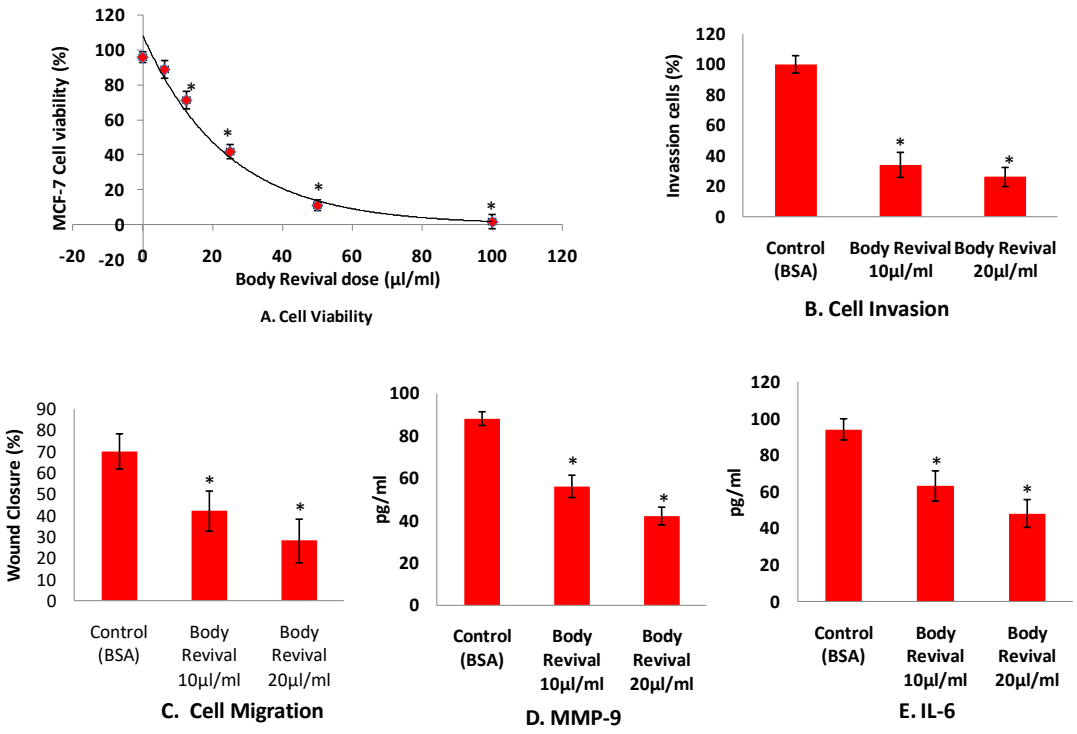


Fig 5. ***In Vitro*** **Anti-Cancer Effects of Body Revival® on MCF-7 Cells**

2a.2.8 ***In silico*** **molecular modeling and docking studies:** Molecular docking studies are performed to gain knowledge on the nature of binding interactions and the amino acid residues that are responsible for inducing the biological activity of a molecule. The purpose of this study was to screen out the ten effective ligands from Body Revival®, such as β-asarone, apigenin, p-coumaric acid, cucurbitacin B, gallic acid, methylglyoxal, quercetin, symconoside A, symconoside B and withaferin, and which may be future ER-α (PDB ID: 5T92) and HER2 (PDB ID: 5JIH) inhibitors and potentially effective drugs to prevent breast cancer.

The result of *in silico* molecular docking analysis of protein-ligands binding is described in Table 3. The binding energy score of cucurbitacin B (-7.8) was the maximum, followed by withaferin (-7.7), symconoside A (-7.2), symconoside B (-6.8) and quercetin (-6.3) with ER-α indicating their strong therapeutic inhibitory properties with the protein ligands binding. Furthermore, the binding energy score of symconoside B (-8.4) was the highest, followed by symconoside A (-7.9),

withaferin A (-7.6), quercetin (-7.5), cucurbitacin B (-6.9), apigenin (-6.9) and gallic acid (-6.4) with HER-2 also.

Table 3. Protein–Ligands Binding Energy of Active Components

Active Components	Protein – Ligands binding energy (kcal/mol)	
	ER-α (5JIH)	HER2 (5T92)
Apigenin	-5.5	-6.9
Cucurbitacin B	-7.8	-6.9
Gallic acid	-5.2	-6.4
Methylglyoxal	-2.8	-3.3
p-Coumaric acid	-5.2	-6.1
Quercetin	-6.3	-7.5
Symconoside A	-7.2	-7.9
Symconoside B	-6.8	-8.4
Withaferin A	-7.7	-7.6
β-asarone	-4.5	-4.9

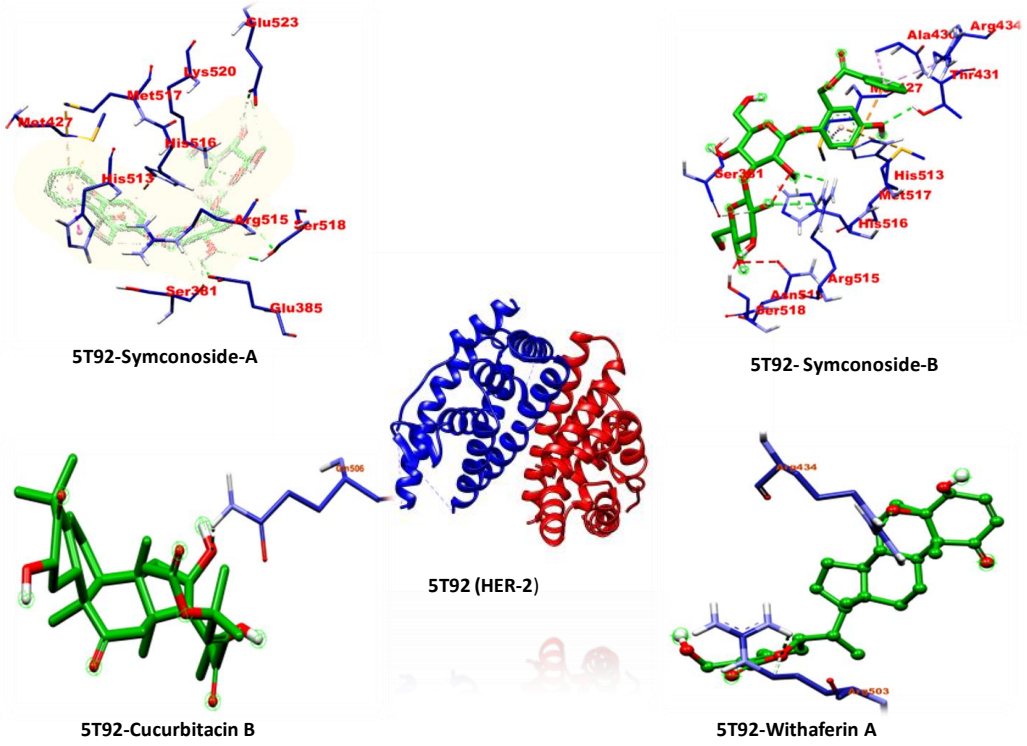


Fig 6. HER-2 Receptor Binding Sites of Most Active Components of BR

The four most active ingredients, symconoside A, symconoside B, curcurbitacin, and withaferin A with HER-2, are shown in Fig. 6 as protein-ligand binding sites with amino acid consequences. Figures showed **symconoside A** binds with **10** amino acids: Ser_381, Glu_385, Met_427, His_513, Arg_515, His_516, Met_517, Ser_518, Lys_520 and Glu_525 of HER-2; **symconoside B** binds with **11** amino acids: Ser_381, Met_427, Ala_430, Thr_431, Ala_434, His_513, Arg_515, His_516, Met_517, Ser_518 and Arg_519 of HER-2; **cucurbitacin B** binds with **1** amino acid: Gln_506 of HER-2; and **withaferin A** binds with **2** amino acids: Arg_434 and Arg_503.

2a.2.9 *In silico* pharmacokinetic, bioavailability and toxicological studies: In order to predict preclinical toxicological endpoints, clinical side effects, and ADME characteristics of these substances, *in silico* approaches are explored. Table 4 shown the *in silico* predicted pharmacokinetic, bioavailability and toxicity evaluations of the four major interacting molecules found in BR, including symconoside A, symconoside B curcurbitacin B, and withaferin A.

Table 4. Pharmacokinetic, Bioavailability and Toxicological Properties

Properties	Symconoside A	Symconoside B	Curcurbitacin B	Withaferin A
Molecular formula	$C_{26}H_{32}O_{14}$	$C_{26}H_{32}O_{14}$	$C_{32}H_{46}O_8$	$C_{28}H_{38}O_6$
Molecular weight (g/mol)	568.52	568.52	558.7	470.6
H-bond donor	14	8	3	6
H-bond acceptor	8	14	8	2
Lipinski violation	3	3	1	0
Skin permeation (LogKp)	-2.73	-2.73	-3.50	-3.02
Aqueous solubility (LogS)	-2.606	-2.79	-4.28	-4.46
Bioavailability score	0.17	0.17	0.55	0.55
Human intestinal absorption	32.58	30.24	79.86	86.31
Caco-2 permeability	-0.651	-0.261	0.582	-0.651
Blood Brain Barrier	-1.45	-1.52	-1.17	-0.03
CYP2C9 inhibitor	No	No	No	No
AMES Toxicity	No	No	No	No
Rat Oral Chronic Toxicity (log mg/kg bw/day)	5.42	5.53	1.66	0.95
Rat Oral Acute Toxicity (LD_{50}) log mg/kg bw	2.50	2.71	3.82	2.78
Maximum tolerable dose (human) log mg/kg/day	-0.008	-0.194	-0.77	-0.41

The strongest H-bond donor is symconoside A, although symconoside B also has the ability to act as an H-bond acceptor. Withaferin A has the greatest aqueous solubility, whereas symconosides is poorly soluble. The Lipinski rule is only not broken by withaferin A. Since withaferin A adheres to all five of Lipinski's principles, it may be termed orally bioavailable than other three components. Withaferin A and cucurbitacin B both has a 0.55 bioavailability score. The Caco-2 human colon cancer cell line is an example of an experimental screen used in drug discovery to measure membrane permeability and estimate human oral absorption. The most rapid rate of oral absorption and Caco-2 permeability is found in withaferin A (0.885 cm/sec). Withaferin A has an intestine absorption rate of 86.32, followed by cucurbitacin B at 79 and symconosides at 30 to 32. The blood-brain barrier (BBB) has been described as a dynamic interface that regulates the passage of substances between the blood and the brain to maintain the best possible circumstances for neuronal and glial activity. BBB prevents the entry of harmful substances into the brain. BBB can be more easily crossed by withaferin A than by the other three substances.

The Ames test is typically used in predicted toxicity models to assess potential carcinogenic/mutagenic effects of substances. The Ames test revealed that none of the bioactive components are carcinogenic. Moreover, Cytochrome P450 2C9 (CYP2C9) enzyme in liver is involved in drug metabolism and excretion. CYP2C9 inhibition may lead to toxic drug accumulation and hazardous drug-drug interactions in the body. The components present in BR did not have any role in CYP2C9 inhibition. Symconoside B, cucurbitacin B, and withaferin A all has human tolerated doses (log mg/kg/day) of -0.194, -0.77, and -0.412, respectively, demonstrating their non-toxic nature. Hence, they failed to exhibit oral acute and chronic toxicity in animal models, and they are categorized as class V according to the poisonous class of the Globally Harmonized System of classification of chemical labels.

2a.2.10 Clinical data on cancer patients: ***only published data***

#Report 1. An exploratory survey (case series) on quality of life has been conducted among cancer patients who used Body Revival® for more than 3 months and were diagnosed to be in Stage I–IV of any cancer and had undergone radiotherapy, chemotherapy, surgery, or a combination. In this case series, out of 38 patients, 61.2% of the males had an average age of 59 years, and 50% of them

had a low BMI. The majority of them had suffered from cancer for more than 12 years, including 27.8% affected by prostate cancer and 35% by breast cancer. Chemotherapy was used in 44.4% of male and 65% of female patients. There was significant ($p<0.001$) improvement in QoL for both male (48.38±4.66; 95% CI: 46.06-50.70) and female (48.75±5.98; 95% CI: 45.95-51.54) cancer patients who were using the Body Revival® supplement. Overall, both men and women had average QoL scores; however, 55.5% of men and 60% of women reported good QoL. Body Revival® supplements improved both the physical and mental domains of QoL. The pain and fatigue scores were significantly lowered, while physical activity and cognitive scores were moderately enhanced (Joshi et al., 2023).

#Report 2. Five breast cancer patients who willingly underwent Body Revival® treatment for about six months were the subjects of a case study. Three patients had Stage II and two had Stage IV with metastases; the average age was 48.6 years (range, 35-64 years). Three patients had surgery, four have chemotherapy, and one has neither chemotherapy nor surgery. They all utilized Body Revival® for an average of 13.2 months. Body Revival® significantly increased ($p<0.001$) the QoL of all patient complaints. It enhanced both the psychological and physical aspects of daily living, either by lessening the side effects of routine cancer treatments or by boosting the body's vital energy (Joshi et al., 2023).

#Report 3. Enlargement of the liver, or hepatomegaly, occurs due to fatty liver disease, liver abscess, hepatitis, liver fibrosis, and carcinoma. Clinical diagnosis and PET CT scan revealed hepatomegaly with abscess in a 60-year-old male patient with a history of left laparoscopic radial nephrectomy due to cancer. The patient's blood contained somewhat elevated levels of hepatic enzymes, including gamma glutamyl transferase (γ-GT), alkaline phosphatase (AKP) and alanine transaminase (ALT), which were indicative of damage to the liver cells. Diabetes, high blood pressure, obesity, and viral hepatitis were not reported. For a period of 12 weeks, the patient consumed oral Body Revival® at a dose of 5 ml on alternate days. Physical, clinical, and laboratory examinations were conducted every four weeks. The patient's liver enzymes were found to be within normal range following a 12-week course of BR treatment, and a CT scan examination showed that the patient's liver had neither a confluent nor an abscess. At that time, there were no signs of liver abscess, hepatomegaly or NAFLD. The patient had a full recovery after receiving Body Revival® (Khan et al., 2023b).

2b. Specific objectives or hypotheses

Hypothesis/key questions

A. Does Body Revival® adjunct therapy enhance the Quality of Life (QoL) of breast cancer patients?

B. Does Body Revival®'s adjuvant therapy improve breast cancer patients' progression-free survival (PFS)?

C. Does Body Revival®'s adjunct therapy helps breast cancer patients who have side effects from their standard treatment plan?

D. Do patients with breast cancer benefit in any way from Body Revival®'s adjunct therapy?

Primary objective(s):

To assess the effect of selected dose of Body Revival® on breast cancer patients in combination with/or without regular therapeutic regimen (such as chemotherapy, radiotherapy or surgery) to improve quality of life (QoL) and progression free survival (PFS) and counteract the affirmed side effects.

Secondary objective(s):

A. To assess the effect of Body Revival® on subject reported on Quality of Life (QoL)
B. To assess the effect of Body Revival® on Karnofsky Performance
C. To assess the effect of Body Revival® on CA-15.3 defined PFS and serologic response, based on Krebs et al (1987) criteria
D. To assess the effect of Body Revival® on complete blood haemogram
E. To assess the safety and tolerability of Body Revival®
F. To assess the effect of Body Revival® on adverse events, based on CTCAE v.5 criteria

Exploratory objective(s):

Examinations of serological, biochemical and radiological markers as a surrogate for interventive therapeutic response

Methods

3. Trial design

3a. Description of trial design

This was a single center, open label, randomized, case-control, longitudinal, cross sectional cohort study.

The selected participants were randomized into four groups or arms:

- Arm I: CT - Control
- Arm II: CT - Body Revival
- Arm III: RAD - Control
- Arm IV: RAD - Body Revival

3b. Important changes to methods after trial commencement

There were no changes to methods after trial commencement.

4. Participants

The study includes adult female patients with breast cancer (stage II-IV) who have had a remission (treatment-free interval) for no more than 6 months after their initial course of chemotherapy, radiotherapy, or surgery.

Subjects were -

- 18 years of age or older
- With a histologically or cytologically confirmed diagnosis of breast cancer (stage II–IV)
- Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months
- Not relapsed during recruitment
- Subjects may not have received Body Revival® or any herbal medicine

4a. Eligibility criteria for participants

The selection criteria were as follows:

Inclusion criteria

Each subject must met the following criteria to enrolled in this study

- Female subjects ≥ 18 years
- A histologically confirmed diagnosis of breast cancer (stage II–IV)
- Or, must have history of measurable disease by CT or MRI scan
- Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months
- Must have no report of relapsed
- Life expectancy of ≥12 months as estimated by the Investigators
- Other significant medical conditions must be well-controlled and stable in the opinion of the Investigators for at least 30 days prior to Study Day 1
- Subjects must provide written informed consent and be able to comply with the protocol procedures

Exclusion Criteria

Each subject must met the following criteria to enrolled in this study

- Clinically significant CNS, hepatic, cardio-respiratory or immunogenic problems
- Pregnant woman and lactating mother
- Subjects have received Body Revival® or any herbal medicine

4b. Settings and locations where the data were collected

The study was conducted from the Research Unit, Department of Kayachikitsa, J.B. Roy State Ayurvedic Medical College and Hospital under Department of Health & Family Welfare (AYUSH), Govt. of West Bengal, Kolkata, India.

The Study Team:

Principal Investigator:	Prof. (Dr.) Srikanta Pandit, MD (Ay.), Ph.D
Associate Investigators:	Prof. (Dr.) Tuhin Kanti Biswas, MD (Ay.), Ph.D
	Prof. (Dr.) Utpalendu Jana, MD (Ay.), Ph.D
Consultant Oncologist:	Prof. (Dr.) Himangsu Roy, M.D., M.S.
Associate Member(s):	Dr. Baidyanath Debnath, MD (Ay.)
Contact Personnel:	Prof. (Dr.) Srikanta Pandit, MD (Ay.), Ph.D
Trial Coordinator:	Dr. Tapas Kumar Sur, MSc, Ph.D

The study plan was reviewed and approved by the Institutional Ethics Committee (JBR/IEC/06/2023 dated July 4, 2023). The enrollment of the study participants was started after staff recruitments. The approved protocol was registered in *Clinical Trials Registry of India* (CTRI/2023/11/059465 dated November 2, 2023).

The study was performed in compliance with "Good Clinical Practice for Clinical Trials", ICMR, Govt. of India (2017) and relevant SOPs of Institutional Ethics Committee of J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata for research involving human subjects. Institutional Ethics Committee was reviewed the project work in due time.

The confidentiality of the identification of all participants was maintained. Security and confidentiality of study data was assured and not disclose to any unauthorized parties.

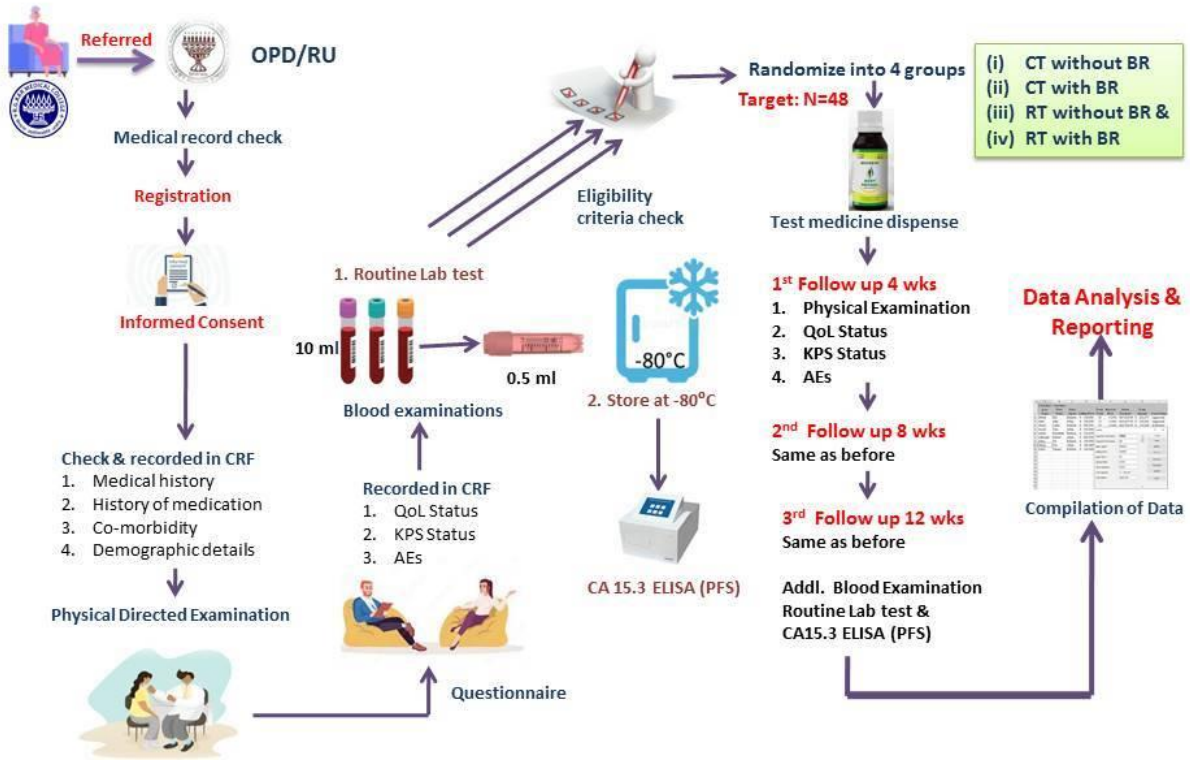


Fig 7. SOP of Clinical Trial

5. Interventions

The breast cancer participants, who were referred from other hospitals and those who met the primary eligible criteria, were recruited for consenting.

Written consent: Prior to any study-specific screening evaluation, each participant was informed in detail about the study agent to be administered and the nature of clinical investigation with its risks and discomforts to be expected. The participant was also instructed that they were free to withdraw their consent and discontinue their participation in the clinical trial at any time without prejudice. Finally, written informed consent was obtained from each participant involved in the clinical trial.

Medical history: At screening, a thorough medical history was taken within 30 days before the test article's initial dosage. The CRF's Medical History part contained the participant's medical history.

Physical examination: A complete physical examination was performed at Screening within 30 days prior to randomization.

Vital signs, body weight and height: Vital signs (blood pressure, heart rate, temperature, and respiratory rate) and body weight was measured prior randomization.

Quality of life (QoL) Status: QoL status was measured and recorded before randomization.

Karnofsky performance status (KPS): KPS was measured and recorded before randomization.

Progression free survival status (PFS): CA-15.3 in blood was determined and checked before enrollment and randomization.

Complete blood haemogram (CBC): CBC was assessed and checked before enrollment and randomization.

Clinical laboratory tests: Liver function and renal function tests were performed and checked before enrollment and randomization.

Side effects/adverse events (AEs): Conventional cancer treatment associated side effects or Adverse Events (AEs) and any untoward hypersensitivity was measured by CTCAE v.5 criteria and recorded in the CRF before enrollment and randomization.

Enrollment: After all scheduled examinations in the screening procedures, eligibility criteria were reviewed and enrolled. All recruited participants were blindly randomized into any of the four arms of the treatment and control groups.

Treatment groups: 6 ml or one teaspoon of Body Revival® was given orally in every sixth day gap before going to bed (preferably in night) for 12 weeks. Hence, 14±1 doses of Body Revival® were administered to the selected participants during treatment (12 weeks/84 days).

Control groups: No interventive medicine was given.

Study activities: Visit time points were intended as targets, variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Schedule visits were as follows:

- At the Screening Visit
- 1st Follow-up: 4 wk after randomization (± 5days)
- 2nd Follow-up: 4 wk after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wk after 2nd Follow-up (± 5days)

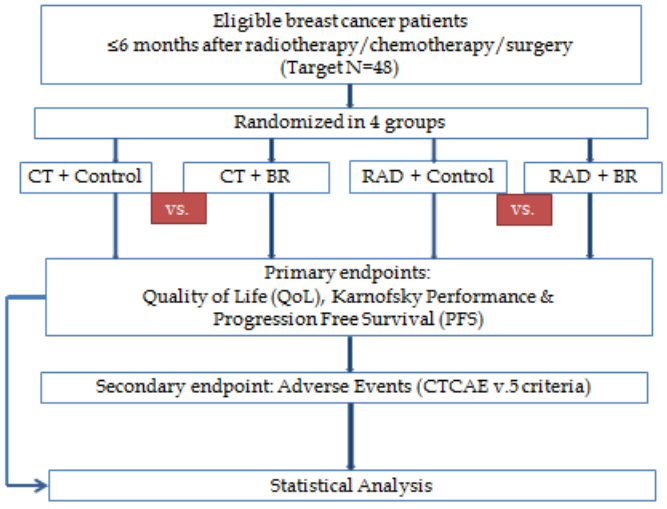


Fig 8. Intervention Overview

6a. Outcomes

Study outcomes were as follows:

Follow-up 1: 4 wk after randomization (± 5days)
The following procedures were performed:
- Physical examination
- Vital Signs and Body Weight
- QoL assessments
- KPS score
- Record any adverse events
- Concomitant medications record

Follow-up 2: 4 wk after 1st Follow-up (± 5days)
The following procedures were performed:
- Physical examination
- Vital Signs and Body Weight
- QoL assessments
- KPS score
- Record any adverse events
- Concomitant medications record

Follow-up 3: 4 wk after 2nd Follow-up (± 5days)
The following procedures were performed:
- Physical examination
- QoL assessments
- KPS score
- Radiological assessments
- Blood CA-15.3
- Hematological and clinical laboratory tests
- Record any adverse events
- Concomitant medications record

Blood sample: Maximum 10 ml of blood was withdrawn by vein puncture in fasting condition, kept into different vials (EDTA/Clot) and preserved until use. All these examinations were done in NABL accredited clinical and diagnostic laboratory.

Clinical laboratory tests

Hematology	
• Hematocrit	Automated Cell Counter, (HORIBA-PENTRA ES 60)
• Hemoglobin	Automated Cell Counter, (HORIBA-PENTRA ES 60)
• Platelet count	Automated Cell Counter, (HORIBA-PENTRA ES 60)
• Red blood cell count	Automated Cell Counter, (HORIBA-PENTRA ES 60)
• White blood cell count	Automated Cell Counter, (HORIBA-PENTRA ES 60)
• Neutrophil	Microscopic, Olympus
• Lymphocyte	Microscopic, Olympus
• Monocytes	Microscopic, Olympus
• Eosinophil	Microscopic, Olympus
• Basophil	Microscopic, Olympus
Serum Chemistry	
• CA-15.3	ELISA (BIOBASE-EL10A)
• Total protein	Automated Analyzer (ADVIA, Siemens)
• Albumin	Automated Analyzer (ADVIA, Siemens)
• Alkaline phosphatase	Automated Analyzer (ADVIA, Siemens)
• Alanine aminotransferase	Automated Analyzer (ADVIA, Siemens)
• Aspartate aminotransferase	Automated Analyzer (ADVIA, Siemens)
• Blood urea nitrogen	Automated Analyzer (ADVIA, Siemens)
• Creatinine	Automated Analyzer (ADVIA, Siemens)

Adverse events (AEs): Regular conventional cancer treatment related side effects or Adverse Events (AEs) and any untoward hypersensitivity were measured by CTCAE v.5 criteria.

Assessing Severity of AEs	
Mild or Grade I	Transient or mild discomfort, no limitation in activity; no medical intervention/therapy required
Moderate of Grade II	Mild to moderate limitation in activity, some assistance may be needed; no or minimum medical intervention/therapy required
Severe or Grade III	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible
Life threatening or Grade IV	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care possible
Death or Grade V	Death

The Principal Investigator (PI) was the responsible person to supervise the safety of the study at his site. This safety monitoring was include careful assessment and appropriate reporting of the conventional cancer treatment related side effects at baseline and adverse events as noted above as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring was included a regular assessment of the number and type of serious adverse events (SAEs). Study Coordinator were explained demonstrated and discussed the every study related events and closely involved with the Investigators and their team.

6b. Any changes to trial outcomes after the trial commenced, with reasons

There were no changes to trial outcomes.

7. Sample size

The target sample size was 48 (including dropouts) and equally distributed into 4 arms. The minimum sample number in each group was considered 10. Total 44 participants completed the trial with minimum expected 10 in each group.

7a. Sample size determination

Epidemiological data were used to guide sample size decisions. The overall breast cancer incidence was 12.5%. There were no trustworthy reports on the incidence of breast cancer in Kolkata. As a result, it was believed that an overall type I error rate of 0.05 had at least 70% power for a 12.5% population proportion.

Confidence interval	Margin of error	Population proportion	Sample size
95%	5%	12.5%	169
90%	5%	12.5%	120
85%	5%	12.5%	91
80%	5%	12.5%	72
70%	5%	12.5%	48

The sample size was determined to be 48. To achieve a 70% confidence level that the real value was within ±5% of the measured value, at least 48 measurements were required. Hence, maximum 12 and minimum 10 in each arm was considered. In this study, the total randomization was done on 44 participants; 12 each in Arm I and Arm II and 10 each in Arm III and Arm IV.

7b. When applicable, explanation of any interim analyses and stopping guidelines

Not applicable.

8. Randomization

8a. Sequence generation

Randomization was stratified by 1:1 treatment vs. case control of selected four arms. The arms were:

- Arm I: CT - Control (N=12)
- Arm II: CT - Body Revival (N=12)
- Arm III: RAD - Control (N=10)
- Arm IV: RAD - Body Revival (N=10)

8b. Type of randomization

Randomization was stratified by 1:1 treatment vs. case control, which means that two separate treatment groups received the same dose of interventive medicine, while their respective control groups received no medicine. AB:BA between chemotherapy control and treatment, then CD:DC between radiation control and treatment.

9. Allocation concealment mechanism

After screening, the participants were randomized and dispensed 1 bottle of 100ml Body Revival® at baseline (Visit 1) by the principal investigator. The participants were returned the bottle at the 4-week, and the investigator team found the residual content. Participants were further returned this bottle at the 8-week follow-up visit, and the investigator team found the residual content.

Finally, participants were returned the bottle at the 12-week follow-up. Adherence was determined by measuring the amount and by response to the question, "On how many days, approximately, did you miss your study medication?"

10. Implementation:

The principal investigator created random allocation sequences; the research fellow physician enrolled participants; and one of the associate investigators assigned them to interventions.

The visit schedule of study and assessment was as follows:

	Screening/ Visit-1	Visit-2 4 week	Visit-3 8 week	Visit-4 12 week
Review and signed ICF	√			
Review inclusion/exclusion criteria	√			
Medical history	√			
Physical examination	√	√	√	√
QoL assessments	√	√	√	√
KPS score	√	√	√	√
Radiological assessments	√			√
PFS (CA-15.3)	√			√
Hematological examination	√			√
Clinical laboratory tests	√			√
Randomization	√			
Dispensing of study medicine	√			
Adverse events (AEs/SEs)*	√	√	√	√

11. Blinding

Not applicable.

12. Statistical methods

12a. Statistical methods used to compare groups for primary and secondary outcomes

All the data were captured and/or transcribed into paper CRF - including clinical data and laboratory data. Clinical efficacies were assessed by examining the improvement score at treatment endpoint. All other efficacy and safety outcomes were assessed in completer analyses because imputation of missing data in these contexts would be scientifically meaningless. Intent-to-Treat Population (ITT), defined as all randomized subjects. This is the primary analysis population for all efficacy endpoints. Evaluable population defined as all randomized subjects who have baseline and at least one on-treatment assessment performed.

For the primary efficacy analyses, multiplicity for the comparison of Body Revival vs. control group was adjusted so that the study level type I error rate controlled to be lower than 0.05 significance level.

Categorical data between the baseline and post treatment were compared with the $\chi 2$ test, and continuous data were analyzed by ANOVA with post-hoc Friedman's Chi-Square test, paired t-test and 95% CI was applied wherever applicable. Alpha for statistical significance will be set at $p<0.05$.

12b. Methods for additional analyses, such as subgroup analyses and adjusted analyses

Safety Analysis Set (SAS), defined as all randomized subjects who was received at least one dose of study drug and who has at least one safety assessment following the first follow up, analyzed by the treatment received. Co-relation was done using Pearson's Correlation Reliability was checked by Cronbach's Alpha. P-value adjusted at less than 0.05 significant levels.

13. Results

The present investigation was conducted from October 2023 to November 2024 by the Research Unit, Department of Kayachikitsa, J.B. Roy State Ayurvedic Medical College and Hospital, Department of Health & Family Welfare (AYUSH), Government of West Bengal, Kolkata, India. The primary eligibility criteria were determined by reviewing the patients' medical records, medication history, treatment protocols, surgical duration, and signed consent to participate in the current study cohort. The study cohort of participants is presented in the following diagram.

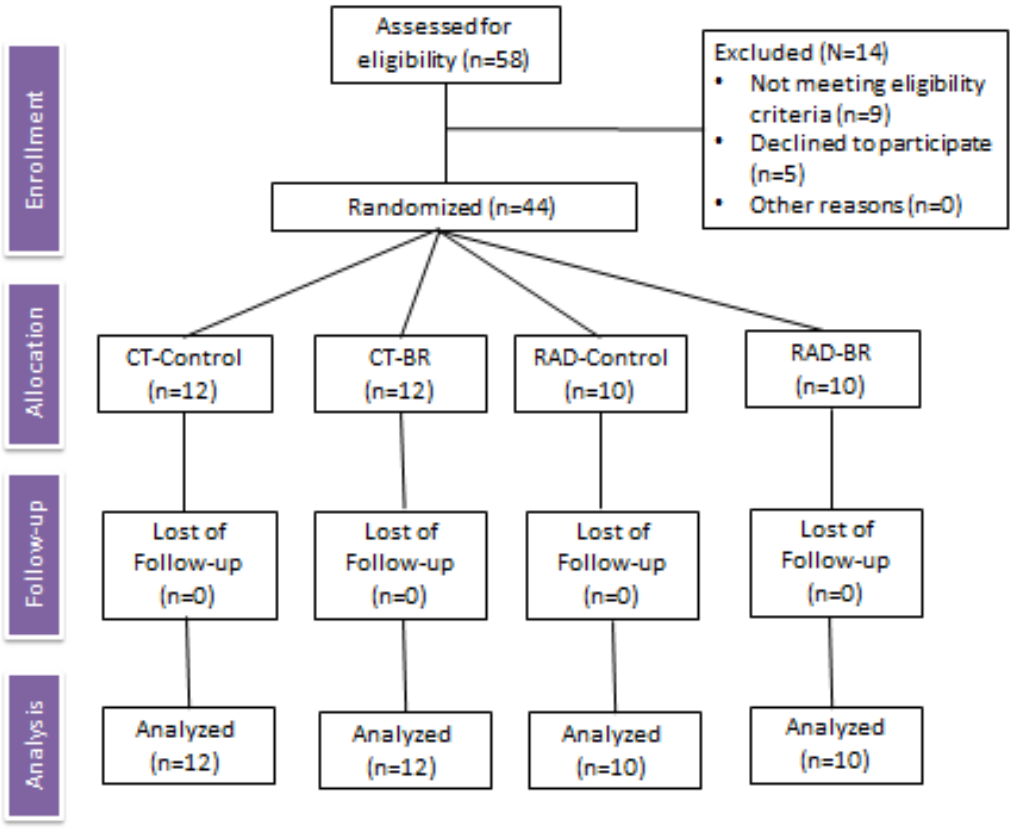


Fig 9. Flow Diagram of Participants

14. Recruitment

In this study, 58 post-operative breast cancer participants were screened. The prime recruitment criteria were adult female patients with breast cancer (stage II–IV) who had experienced a remission (treatment free interval) of not more than six months following their initial course of chemotherapy, radiation, or surgery. Ultimately, 44 individuals were chosen and enlisted to take part in the research. After their written consent all participants were randomized in four groups. The subjects were broadly segregated into two main categories: those who received chemotherapy and those who were treated by radiation in their conventional treatment procedure. A pre-fixed block rule (AB::BA) was used to randomly assign the control and treatment groups.

The participants' distribution was as follows: Group I or CT-control (N=12) without intervention medicine, Group II or CT with intervention medicine (N=12), Group III or RAD-control (N=10) without intervention medicine and Group IV or RAD with intervention medicine (N=10). The intervention medicine was Body Revival®. The dose-duration of Body Revival® was 6 ml (preferably at bedtime) in every sixth alternative day up to 12 weeks. The control group received no interventive medicine, but regular treatments (if any) were not interfered with and were recorded in the CRF.

15. Baseline data

Demographic data was also recoded and presented in **Table 5**. All recruited participants finished the trial. The average age among all participants was 53.73 years (range 36 to 69 years). The average age in Group I was 51.75 years, Group II was 58 years, Group III was 53 years, and Group IV was 51.7 years. 56% of the participants had completed high school. The majority of participants (88.6%) were married. 81.8% were homemakers. The household income of 70.5% of participants was middle income (INR 25,000-50,000), with only 15.9% being upper income (above INR 50,000). The study did not include any smokers; however 34% of participants chewed tobacco.

Table 5. Demographic Details

	Total	CT-Control	CT-BR	RAD-Control	RAD-BR
Number of participants	44	12	12	10	10
Age (years)	53.73±7.69	51.75±7.32	58±5.93	53±8.41	51.70±8.26
Education					
Primary school	13	3	2	4	4
High School	26	8	8	6	4
Graduate	5	1	2	0	2
Marital status					
Unmarried	0	0	0	0	0
Married	39	11	11	10	7
Widow	5	1	1	0	3
Occupation					
Business	0	0	0	0	0
Agriculture	0	0	0	0	0
Home-maker	36	10	9	9	8
Service/retired	8	2	3	1	2
Total family income (INR)					
<25000	7	1	2	2	2
25000-50000	31	10	8	6	7
Above 50000	6	1	2	2	1
Smoking habit					
Never smoke	44	12	12	10	10
Smoker/ex-smoker	0	0	0	0	0
Tobacco chewing habit					
Never use	29	7	9	6	7
Presently use/ex- use	15	5	3	4	3

The comorbidity of the selected participants is presented in **Table 6**. GI and liver complications were reported by 79.5% of breast cancer participants. The GI and liver problems were 83% in Group I, 75% in Group II, and 80% in Groups III and IV. Anemia and hypertension were present in 38.6% of participants.

Table 6. Comorbidities of Participants

Groups	Hypertension	Diabetes	Ischemic heart disease	Anemia	Asthma	Thyroidisms	GI & Liver problems	Renal problems	Neuropsychiatric disease	Anxiety/ Depression
Total (N=44)	17	6	4	17	0	0	35	0	0	0
CT-Control (N=12)	5	1	0	4	0	0	10	0	0	0
CT-BR (N=12)	3	2	2	4	0	0	9	0	0	0
RAD-Control (N=10)	2	1	0	7	0	0	8	0	0	0
RAD-BR (N=10)	7	2	2	2	0	0	8	0	0	0

Close physical examinations of patients revealed that 41 of 44 had skin problems (swelling, rash, cracking, itching, dryness and peeling, pruritus). Aside from that, they suffered musculoskeletal concerns (40 of 41), gastrointestinal troubles (33 of 44), and HEENT problems (27 of 44). There were only two participants with mild CVDs (**Table 7**). No individuals were complaining about urogenital, neurological, or respiratory problems.

Table 7. Physical Directed Examinations

	Total (N=44)	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
HEENT	27	8	7	8	4
Respiratory	0	0	0	0	0
Cardiovascular	4	0	2	0	2
Abdominal	33	9	9	8	7
Genitourinary	0	0	0	0	0
Musculoskeletal	40	11	10	10	9
Neurological	0	0	0	0	0
Extremities	0	0	0	0	0
Lymph nodes	0	0	0	0	0
Dermatologic	41	10	11	10	10

The baseline vital indicators are shown in **Table 8**. The average body weight was 56.93 kg (range: 46–64 kg). The average height was 159.20 cm (range: 153-165 cm). The average BMI was 22.14 (range 18.2–25.7). Blood pressure was moderately across the usual range.

Table 8. Vital Signs Assessments

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
Body weight (kg)	57.16 ± 4.62	57.08 ± 3.44	57.2 ± 4.84	56.2 ± 6.01
Height (cm)	60 ± 4.00	159.3 ± 3.55	159 ± 2.49	158.3 ± 3.05
BMI	21.92 ± 1.98	22.24 ± 1.70	22.2 ± 1.99	22.19 ± 2.43
Pulse rate (bpm)	82.50 ± 3.72	82.08 ± 4.35	80.6 ± 5.16	81.6 ± 4.59
Blood pressure (Systole) mm Hg	131.92 ± 19.2	127.75 ± 13.05	128.3 ± 12.61	137.9 ± 15.57
Blood pressure (Diastole) mm Hg	86.25 ± 6.74	83.91 ± 5.14	84.6 ± 3.50	90.3 ± 4.13

Results are mean ± standard deviation

Table 9 presents the baseline clinical evaluation of physical performance status after chemotherapy and radiotherapy of selected breast cancer patients. The majority of the selected patients needed significant to sporadic help and regular medical attention, as shown by the average baseline KPS score of 51.67 to 54.

Table 9. Karnofsky Performance Scale (KPS) Assessments

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
KPS Score (%)	51.67±3.89	52.50±4.52	53±4.83	54±5.16

Results are mean ± standard deviation

Blood tumor marker CA-15.3 was used to assess progression-free survival in patients with post-operative breast cancer (**Table 10**). In general, a serum level of CA-15.3 ≥30 is considered risky. The baseline CA-15.3 serum levels in all groups in this investigation were below the risk of illness progression. According to ELISA reports, the lowest CA-15.3 was 7 U/ml of blood, while the highest was 22 U/ml.

Table 10. Blood Tumor Marker CA-15.3 Assessments

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
Blood CA-15.3 (U/ml)	16.17±4.59	15.67±3.55	16.30±3.02	16.50±3.69

Results are mean ± standard deviation

Table 11. Quality of Life Score (QoL) Assessments

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
Total Score (176)	94.17±3.83	94.50±2.58	79.30±4.90	78.10±2.33
General Domain (32)	16.92±1.44	16.83±1.47	13.50±1.35	14.50±1.43
Physical Domain (40)	22.17±3.41	22.67±2.06	17.30±2.50	16.20±1.14
Psychological Domain (32)	17.42±1.56	16.92±1.88	14.40±1.90	14.50±1.78
Familial Domain (28)	16.67±1.44	16.33±1.61	12.40±1.26	12.20±1.40
Cognitive Domain (8)	3.67±0.65	4±0.74	3.80±0.79	3.60±0.70
Economic Domain (12)	6.17±0.83	6±0.85	6.50±0.71	6±0.67
Optimism Domain (8)	4.50±0.80	4.33±1.15	4.70±0.82	4.50±0.53
Informational Domain (8)	4.17±0.58	4.42±0.67	3.90±0.99	4.20±1.32
Physician Relationship Domain (4)	1.17±0.39	1.42±0.51	1.20±0.42	1.10±0.32
Body Imaging Domain (4)	1.33±0.49	1.58±0.51	1.60±0.52	1.40±0.52

Results are mean ± standard deviation

Table 11 shows the baseline total score of QoL in selected breast cancer patients. The average score for the selected chemotherapy patients was 94 (53%) out of 176, while radiation groups was 78 (44%), indicating very low QoL. The general domain score ranged from 13.50 (42%) in to 16.92 (52.8%). The physical domain score in chemotherapy groups was 22.17 (55.4%) and 22.67 (56.6%), whereas in radiation groups it was 17.3 (43.2%) and 16.2 (40.5%). The average score in the psychological category was 17.42 (54.4%) and 16.92 (52.8%) in the chemotherapy groups, and 14.4 (45%) and 14.5 (45%) in the radiation groups. The average score of these major domains showed a poor quality of life in selected patients.

Table 12. Safety Assessments - Blood Profiles

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
Hct (%)	35.2±2.70	35±1.95	33.7±2.31	35.9±1.91
Hb (g%)	9.9±1.20	10.1±1.17	9.4±1.27	10.6±1.18
RBC (10^6/cc)	3.59±0.23	3.61±0.23	3.52±0.26	3.68±0.28
WBC (10^3/cc)	5.15±0.23	5.21±0.24	4.90±0.26	5.11±0.28
Platelet (10^5/cc)	2.11±0.33	2.15±0.23	1.95±0.25	2.04±0.30
Neutrophil (%)	31.83±5.93	29.42±5.72	25.1±4.95	29.9±4.58
Lymphocyte (%)	57.16±6.60	60.16±6.43	64.2±5.88	59.4±4.42
Monocyte (%)	4.25±1.05	4.417±1.24	4.8±1.29	4.7±4.70
Eosinophil (%)	5.83±1.02	5.4167±1.08	5.5±1.17	5.4±0.84
Protein (g/dl)	5.58±0.42	5.50±0.37	5.62±0.38	5.45±0.45
Albumin (g/dl)	3.23±0.32	3.10±0.31	3.09±0.40	3.17±0.38
ALP (IU/L)	117.4±37.97	121.3±37.42	132.5±42.95	114.8±38.63
AST (U/dl)	60.16±18.58	55.5±16.79	62.5±18.44	61.9±19.12
ALT (U/dl)	50.67±12	46.16±11.55	45.40±9.62	48.50±6.45
BUN (mg/dl)	12.33±2.22	12.42±2.99	13±1.94	12.9±2.72
Creatinine (mg/dl)	0.858±0.12	0.891±0.13	0.920±0.23	0.96±0.16

Results are mean ± standard deviation

The baseline blood profiles of all subjects are shown in **Table 12**. Chemotherapy and radiation drastically affect the blood profile, indicating adverse effects.

According to CTCAE version 5, blood hemoglobin levels were considerably reduced (Grade II AEs) in all groups. Blood protein and albumin levels were also below normal.

Apart from that, chemotherapy and radiation-related adverse events on the physiological system and overall health were recorded (**Table 13**). Most post-operative breast cancer patients had muscle weakness, dizziness, and fatigue. Anorexia, nausea, and vomiting were prevalent among all. They also complained of hot flushes. Rash, dry skin, pruritus, and hair loss were all common symptoms in these patients.

Table 13. Adverse Events Assessments

	CT-Control (N=12)	CT-BR (N=12)	RAD-Control (N=10)	RAD-BR (N=10)
1. Anorexia	10	12	10	10
2. Constipation	8	10	8	7
3. Diarrhoea	4	2	2	3
4. Dizziness	12	12	10	10
5. Dry skin	10	10	10	10
6. Fatigue	12	12	10	10
7. Hot flashes/flushes	12	12	10	10
8. Muscle weakness	10	10	10	10
9. Nausea	12	10	8	10
10. Pruritus/itching	8	9	8	9
11. Rash	9	6	8	9
12. Vomiting	10	5	8	10

Results are mean ± standard deviation

16. Numbers analyzed

A total of 44 subjects completed the trial, and all data were statistically analyzed. Group I had 12 participants; Group II had 12; Group III had 10; and Group IV had 10. There were no reported cases of dropouts.

17. Outcomes and estimation

Table 14 presents the changes in vital signs after a 12-week treatment with Body Revival®. Body weights decreased marginally in all groups, but significantly in both control groups. BMI was significantly lower in chemotherapy and radiation therapy control groups, but higher in the Body Revival® treated radiation group. The BMI of individual participants before and after treatment in all groups is shown in a dot diagram (**Fig. 9**). Other vital indicators, such as pulse and blood pressure, were unchanged following therapy compared to their baseline data.

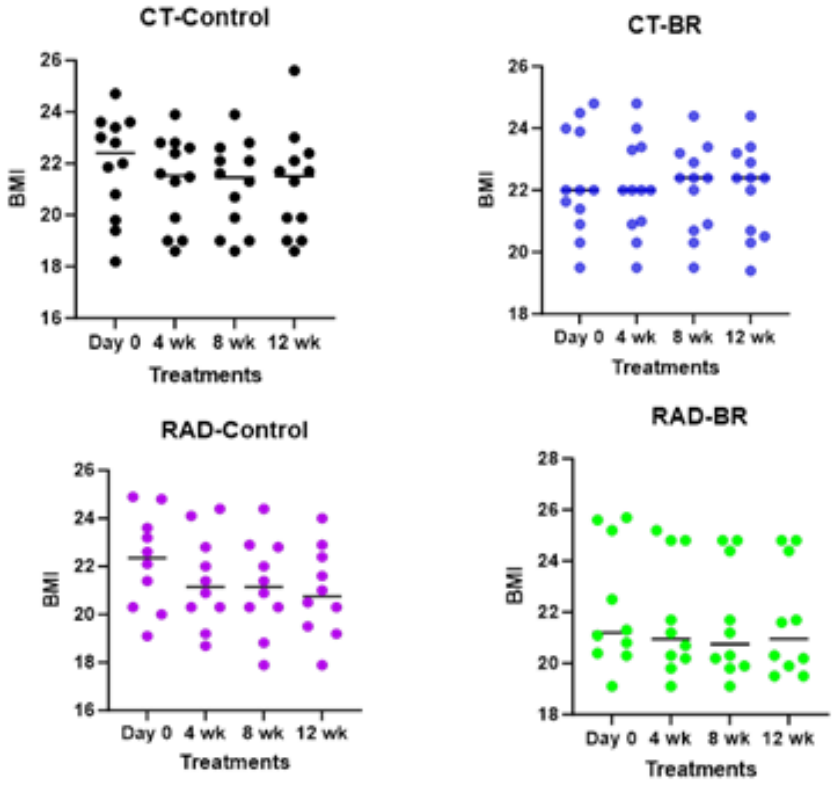


Fig 10. Dot Diagram of BMI

Table 15 shows the physical guided assessments of participants after 12 weeks of treatment. Body Revival therapies provided total recovery from regular general health concerns and complaints. Abdominal obstacles, dermatological problems, and muscular weakening symptoms had all been relieved.

Table 14. Vital Signs: After Treatment

	CT-Control (N=12)				CT-BR (N=12)				RAD-Control (N=10)				RAD-BR (N=10)			
	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
Body weight (kg)	57.16 ± 4.62	55.25 ± 4.90[a*]	54.8 ± 4.72[a*]	54.08 ± 4.66[a*]	57.08 ± 3.44	56.58 ± 3.63	56.67 ± 3.60	56.41 ± 3.52	57.2 ± 4.84	55.4 ± 5.03[a*]	54.8 ± 5.41[a*]	54.5 ± 5.16[a*]	56.2 ± 6.01	55 ± 5.59[a*]	54.4 ± 5.56[a*]	54.1 ± 5.52[a*]
Height (cm)	60 ± 4.00	–	–	–	159.3 ± 3.55	–	–	–	159 ± 2.49	–	–	–	158.3 ± 3.05	–	–	–
BMI	21.92 ± 1.98	21.28 ± 1.76[a*]	21.13 ± 1.70[a*]	21.18 ± 2.02	22.24 ± 1.70	22.1 ± 1.55	22.04 ± 1.42	22 ± 1.47	22.2 ± 1.99	21.41 ± 1.92[a*]	21.17 ± 1.96[a*]	20.93 ± 1.84	22.19 ± 2.43	21.78 ± 2.29	21.62 ± 2.22[a*]	21.67 ± 2.20[a*]
Pulse rate (bpm)	82.50 ± 3.72	82.08 ± 3.17	82.33 ± 3.05	82.75 ± 2.73	82.08 ± 4.35	77.03 ± 4.31	82 ± 4.95	82.42 ± 4.93	80.6 ± 5.16	81.4 ± 4.52	81.6 ± 4.11	80.6 ± 3.89	81.6 ± 4.59	81.3 ± 4.21	81.8 ± 5.22	82.3 ± 4.05
Blood pressure (Systole)	131.92 ± 19.2	131.5 ± 17.42	131.91 ± 16.65	133 ± 16.41	127.75 ± 13.05	127.25 ± 11.35	127.42 ± 9.13	126.75 ± 9.81	128.3 ± 12.61	126.2 ± 14.10	128.5 ± 12.28	128.8 ± 12.18	139.1 ± 15.57	137.9 ± 15.57	137.6 ± 15.08	140.8 ± 13.76
Blood pressure (Diastole)	86.25 ± 6.74	85.92 ± 5.40	84.8 ± 4.78	83.5 ± 5.68	83.91 ± 5.14	83.17 ± 3.32	83.5 ± 4.30	82.66 ± 3.55	84.6 ± 3.50	83.9 ± 3.60	84.1 ± 3.51	83.9 ± 4.06	90.3 ± 4.13	89.5 ± 5.03	88.4 ± 5.54	88 ± 4.80

Paired sample t test; a* denoted $p<0.05$ when compared to Day 0;

Table 15. Physical Directed Examinations: After Treatment

	CT-Control (N=12)				CT-BR (N=12)				RAD-Control (N=10)				RAD-BR (N=10)			
	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
HEENT	8	7	4	2	7	5	2	0	8	8	8	6	4	4	2	0
Respiratory	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular	0	0	0	0	2	2	2	2	0	0	0	0	2	2	2	2
Abdominal	9	9	8	6	9	6	2	0	8	8	6	2	7	7	1	0
Genitourinary	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal	11	10	8	7	10	5	2	0	10	10	9	6	9	9	3	0
Neurological	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Extremities	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymph nodes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermatologic	10	9	8	7	11	8	3	0	10	10	9	8	10	10	3	0

Table 16. Karnofsky Performance Scale (KPS): After Treatment

Groups	Day 0	4 wk	8 wk	12 wk	% change (Day 0-12 wk)	Cronbach's Alpha	X^2	Friedman's Test p-value
CT-Control (N=12)	51.67±3.89	57.50±4.52	62.50±7.54	67.50±6.22	30.6	0.783	26.798	<0.001
CT-BR (N=12)	52.50±4.52	65±5.22	79.17±6.69	90.83±7.93	73	0.819	33.960	<0.001
RAD-Control (N=10)	53±4.83	57±6.75	62±6.32	64±5.16	20.7	0.886	21.143	<0.001
RAD-BR (N=10)	54±5.16	62±6.32	74±6.99	83±8.23	53.7	0.856	27.249	<0.001
CT-CONTROL vs. CT-BR p-value	0.655	<0.01	<0.01	<0.01				
RAD-CONTROL vs. RAD-BR p-value	0.705	0.096	<0.01	<0.01				

Table 17. Quality of Life (QoL) - Total Score: After Treatment

Total Score (176)	Group-I CT-Control	Group-II CT-BR	Friedman's Chi-Square p-Value	Group-III RAD-Control	Group-IV RAD-BR	Friedman's Chi-Square p-Value
Screening (Day 0)	94.17±3.83	94.50±2.58	0.079 0.778	79.30±4.90	78.10±2.33	0.911 0.340
Follow-up 1 (4 wk)	95.67±4.14 (1.59)	101.92±3.32 (7.99)	6.860 <0.01	81.90±4.72 (3.27)	84±2.91 (7.55)	1.909 0.167
Follow-up 2 (8 wk)	98.42±3.48 (4.51)	115.58±2.61 (22.62)	11.414 <0.001	86.44±4.33 (8.7)	96.50±3.50 (23.56)	8.746 <0.01
Follow-up 3 (12 wk)	104.25±3.47 (10.7)	133.00±2.80 (41.1)	11.840 <0.001	93.90±3.67 (18.41)	117.50±3.60 (50.48)	9.580 <0.01
Cronbach's Alpha	0.952	0.697		0. .977	0.445	
Friedman's Chi-Square	32.455	35.420		28.959	29.094	
p-Value	<0.001	<0.001		<0.001	<0.001	

Parentheses represent percent change compared to Day 0

Table 18. Quality of Life (QoL) - General Domain Score: After Treatment

Total Score (32)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	16.92±1.44	16.83±1.47	0.827	13.50±1.35	14.50±1.43	0.140
Follow-up 1 (4 wk)	17.17±1.53	17.83±1.64	0.144	14±1.49	15.50±1.51	0.063
Follow-up 2 (8 wk)	17.42±1.62	21.92±1.16	<0.001	14.56±1.24	17.60±1.17	<0.01
Follow-up 3 (12 wk)	19.25±1.22	25.92±1.16	<0.001	18.20±1.14	22.20±1.75	<0.01
Cronbach's Alpha	0.953	0.792		0.902	0.682	
Friedman's Chi-Square	27.947	34.243		27.171	27.027	
p-Value	<0.001	<0.001		<0.001	<0.001	

Table 19. Quality of Life (QoL) - Physical Domain Score: After Treatment

Total Score (40)	Group-I CT-Control	Group-II CT-BR	Friedman's Chi-Square p-Value	Group-III RAD-Control	Group-IV RAD-BR	Friedman's Chi-Square p-Value
Screening (Day 0)	22.17±3.41	22.67±2.06	0.581	17.30±2.50	16.20±1.14	0.166
Follow-up 1 (4 wk)	22.17±3.41	24.50±1.57	<0.05	17.90±2.28	17.60±1.35	0.691
Follow-up 2 (8 wk)	22.42±3.32	27.33±1.67	<0.01	18.56±2.30	20.90±2.02	<0.05
Follow-up 3 (12 wk)	23.33±2.27	32.92±1.62	<0.01	18.80±2.10	28.90±1.10	<0.01
Cronbach's Alpha	0.981	0.925		0.978	0.661	
Friedman's Chi-Square	11.628	34.815		16.091	28.863	
p-Value	<0.01	<0.001		<0.001	<0.001	

Table 20. Quality of Life (QoL) - Psychological Domain Score: After Treatment

Total Score (32)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	17.42±1.56	16.92±1.88	0.439	14.40±1.90	14.50±1.78	0.782
Follow-up 1 (4 wk)	18±1.60	19.08±2.35	0.138	14.70±1.83	16.10±1.52	<0.05
Follow-up 2 (8 wk)	18.92±1.56	22.67±1.50	<0.001	16±1.41	19.5±2.72	<0.01
Follow-up 3 (12 wk)	19.83±1.03	26.42±1.08	<0.001	16.50±1.27	22.50±1.35	<0.01
Cronbach's Alpha	0.900	0.786		0.950	0.872	
Friedman's Chi-Square	23.468	33.157		20.854	27.368	
p-Value	<0.001	<0.001		<0.001	<0.001	

Table 21. Quality of Life (QoL) - Familial Domain Score: After Treatment

Total Score (28)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	16.67±1.44	16.33±1.61	0.516	12.40±1.26	12.20±1.40	0.655
Follow-up 1 (4 wk)	16.75±1.36	17.58±1.73	0.181	12.70±1.16	13±1.49	0.532
Follow-up 2 (8 wk)	17±1.13	18.58±1.93	<0.05	13.22±1.20	14.50±1.84	0.085
Follow-up 3 (12 wk)	17.33±0.98	19.67±1.72	<0.05	14.60±0.84	17.40±1.43	<0.01
Cronbach's Alpha	0.973	0.946		0.929	0.759	
Friedman's Chi-Square	14.091	28.623		23.566	24.383	
p-Value	<0.01	<0.001		<0.001	<0.001	

Table 22. Quality of Life (QoL) - Cognitive Domain Score: After Treatment

Total Score (8)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	3.67±0.65	4±0.74	0.346	3.80±0.79	3.60±0.70	0.480
Follow-up 1 (4 wk)	3.75±0.75	4.58±0.51	<0.05	4.10±0.74	4.20±0.79	0.739
Follow-up 2 (8 wk)	3.92±0.51	5±0.43	<0.01	4.33±0.50	4.40±0.52	0.564
Follow-up 3 (12 wk)	4.17±0.39	5.25±0.45	<0.01	4.50±0.53	4.80±0.42	0.182
Cronbach's Alpha	0.874	0.340		0.897	0.842	
Friedman's Chi-Square	10.500	19.846		12.840	18.750	
p-Value	<0.05	<0.001		<0.01	<0.001	

Table 23. Quality of Life (QoL) - Economic Domain Score: After Treatment

Total Score (12)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	6.17±0.83	6±0.85	0.655	6.50±0.71	6±0.67	0.096
Follow-up 1 (4 wk)	6.08±0.79	6.50±0.71	0.808	6.4±0.70	5.90±0.74	0.132
Follow-up 2 (8 wk)	6.41±0.79	6.42±0.67	0.988	6.78±0.67	6.50±0.85	0.317
Follow-up 3 (12 wk)	6.58±0.80	6.67±0.49	0.739	6.90±0.57	6.60±0.70	0.180
Cronbach's Alpha	0.962	0.903		0.896	0.826	
Friedman's Chi-Square	12.000	14.471		8.429	10.571	
p-Value	<0.01	<0.01		NS	<0.05	

Table 24. Quality of Life (QoL) - Optimism Domain Score: After Treatment

Total Score (8)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	4.50±0.80	4.33±1.15	0.637	4.70±0.82	4.50±0.53	0.564
Follow-up 1 (4 wk)	4.57±0.79	4.58±0.90	0.996	4.90±0.57	4.50±0.53	0.157
Follow-up 2 (8 wk)	4.75±0.75	5.17±0.72	0.132	5.11±0.78	4.80±0.63	0.366
Follow-up 3 (12 wk)	4.92±0.79	5.58±0.51	<0.05	5.58±0.51	5.40±0.84	0.994
Cronbach's Alpha	0.958	0.880		0.889	0.738	
Friedman's Chi-Square	10.412	20.700		11.889	13.500	
p-Value	<0.05	<0.001		<0.01	<0.01	

Table 25. Quality of Life (QoL) - Informational Domain Score: After Treatment

Total Score (8)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	4.17±0.58	4.42±0.67	0.366	3.90±0.99	4.20±1.32	0.317
Follow-up 1 (4 wk)	4.17±0.58	4.42±0.67	0.365	3.80±0.79	4.20±1.32	0.206
Follow-up 2 (8 wk)	4.17±0.58	4.58±0.51	0.059	4.22±0.97	4.70±0.95	0.248
Follow-up 3 (12 wk)	4.50±0.67	5.67±0.65	<0.01	4.70±0.82	5.30±0.82	0.109
Cronbach's Alpha	0.952	0.737		0.905	0.902	
Friedman's Chi-Square	12.000	22.663		11.478	13.297	
p-Value	<0.01	<0.001		<0.01	<0.01	

Table 26. Quality of Life (QoL) – Physician Relationship Domain: After Treatment

Total Score (4)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	1.17±0.39	1.42±0.51	0.180	1.20±0.42	1.10±0.32	0.564
Follow-up 1 (4 wk)	1.67±0.49	1.75±0.45	0.705	1.60±0.52	1.70±0.48	0.655
Follow-up 2 (8 wk)	2.08±0.67	2.33±0.49	0.180	2±0.50	2.20±0.63	0.414
Follow-up 3 (12 wk)	2.50±0.52	2.83±0.39	0.102	2.40±0.52	2.60±0.70	0.527
Cronbach's Alpha	0.470	0.573		0.167		
Friedman's Chi-Square	21.935	26.154		17.143		
p-Value	<0.001	<0.001		<0.001		

Table 27. Quality of Life (QoL) – Body Imaging Domain: After Treatment

Total Score (4)	Group-I	Group-II	Friedman's Chi-Square	Group-III	Group-IV	Friedman's Chi-Square
	CT-Control	CT-BR	p-Value	RAD-Control	RAD-BR	p-Value
Screening (Day 0)	1.33±0.49	1.58±0.51	0.180	1.60±0.52	1.40±0.52	0.414
Follow-up 1 (4 wk)	1.33±0.49	1.58±0.51	0.180	1.60±0.52	1.40±0.52	0.414
Follow-up 2 (8 wk)	1.33±0.49	1.58±0.51	0.180	1.67±0.50	1.40±0.52	0.414
Follow-up 3 (12 wk)	1.83±0.39	2.08±0.67	0.257	1.90±0.32	1.80±0.42	0.564
Cronbach's Alpha	0.899	0.934		0.920	0.914	
Friedman's Chi-Square	18.000	18.000		9.000	12.000	
p-Value	<0.001	<0.001		<0.05	<0.01	

Table 28. Blood Tumor Marker CA-15.3: After Treatment

	Blood CA-15.3 (U/ml)				
Groups	**Day 0**	**12 wk**	**% change**	**95% CI**	**p-value**
CT-Control	16.17±4.59	14.67±3.75	-9.27	-0.30 to 0.30	0.095
CT-BR	15.67±3.55	8.92±2.07	-43.07	4.30 to 9.19	<0.001
RAD- Control	16.30±3.02	18.90±2.56	15.95	-3.77 to -1.42	<0.001
RAD-BR	16.50±3.69	11.40±1.84	-30.90	2.75 to 7.44	<0.001
CT-CONTROL vs. CT-BR	0.716	<0.01			
RAD-CONTRO vs. RAD-BR	0.856	<0.01			

Table 29. Safety Assessments – Hematological Profiles: After Treatment

	CT-Control		CT-BR		RAD- Control		RAD-BR	
	Day 0	**12 wk**	**Day 0**	**12 wk**	**Day 0**	**12 wk**	**Day 0**	**12 wk**
Hct (%)	35.2 ±2.70	35.7 ±2.56 <0.01	35 ±1.95	37.58 ±1.24 <0.001	33.7 ±2.31	35.1 ±1.37 <0.01	35.9 ±1.91	38.2 ±1.39 <0.001
Hb (g%)	9.9 ±1.20	10.2 ±1.06 <0.01	10.1 ±1.17	11.1 ±0.88 <0.001	9.4 ±1.27	10 ±1.18 <0.001	10.6 ±1.18	11.7 ±0.91 <0.001
RBC (10^6/cc)	3.59 ±0.23	3.65 ±0.17 <0.05	3.61 ±0.23	3.77 ±0.13 <0.01	3.52 ±0.26	3.62 ±0.11 0.067	3.68 ±0.28	3.86 ±0.12 <0.05
WBC (10^3/cc)	5.15 ±0.23	5.25 ±0.17 <0.01	5.21 ±0.24	5.64 ±0.13 <0.01	4.90 ±0.26	5.16 ±0.11 <0.001	5.11 ±0.28	6.05 ±0.12 <0.001
Platelet (10^5/cc)	2.11 ±0.33	2.36 ±0.28 <0.001	2.15 ±0.23	2.79 ±0.19 <0.001	1.95 ±0.25	2.21 ±0.22 <0.001	2.04 ±0.30	2.89 ±0.14 <0.001
Neutrophil (%)	31.83 ±5.93	35.66 ±4.22 <0.001	29.42 ±5.72	38.91 ±1.97 <0.001	25.1 ±4.95	31.9 ±2.96 <0.001	29.9 ±4.58	40.1 ±1.45 <0.001
Lymphocyte (%)	57.16 ±6.60	54.75 ±5.01 <0.05	60.16 ±6.43	54.16 ±2.40 <0.01	64.2 ±5.88	58.8 ±2.93 <0.01	59.4 ±4.42	52.5 ±1.08 <0.001
Monocyte (%)	4.25 ±1.05	3.91 ±0.79 0.368	4.41 ±1.24	3.58 ±0.66 0.101	4.8 ±1.29	3.8 ±0.42 <0.05	4.7 ±4.70	3.9 ±3.90 0.070
Eosinophil (%)	5.83 ±1.02	5.25 ±0.86 <0.05	5.4167 ±1.08	2.91 ±0.51 <0.001	5.5 ±1.17	5.2 ±0.78 0.434	5.4 ±0.84	3.2 ±0.63 <0.001

Paired sample t test; compared to baseline (day 0);

Table 30. Safety Assessments – Biochemical Profiles: After Treatment

	CT-Control		CT-BR		RAD-Control		RAD-BR	
	Day 0	**12 wk**	**Day 0**	**12 wk**	**Day 0**	**12 wk**	**Day 0**	**12 wk**
Protein	5.58	5.89	5.50	6.50	5.62	5.88	5.45	6.2
(g/dl)	±0.42	±0.25	±0.37	±0.23	±0.38	±0.28	±0.45	±0.24
		<0.01		<0.001		<0.001		<0.001
Albumin	3.23	3.49	3.10	3.77	3.09	3.34	3.17	3.67
(g/dl)	±0.32	±0.25	±0.31	±0.16	±0.40	±0.30	±0.38	±0.11
		<0.001		<0.001		<0.001		<0.001
Alkaline	117.4	110.9	121.3	92.3	132.5	118.6	114.8	99.1
phosphatase	±37.97	±28.99	±37.42	±29.53	±42.95	±33.70	±38.63	±30.29
(IU/L)		0.068		<0.001		<0.01		<0.01
AST	60.16	53.58	55.5	46.16	62.5	56.2	61.9	44.8
(U/dl)	±18.58	±14.26	±16.79	±8.78	±18.44	±13.71	±19.12	±6.39
		<0.01		<0.01		<0.01		<0.01
ALT	50.67	45.58	46.16	46.83	45.40	44.10	48.50	41.4
(U/dl)	±12	±9.71	±11.55	±4.57	±9.62	±8.30	±6.45	±2.45
		<0.01		<0.01		0.346		<0.001
BUN	12.33	12.417	12.42	10.5	13	12.6	12.9	11.1
(mg/dl)	±2.22	±1.78	±2.99	±0.99	±1.94	±1.42	±2.72	±1.52
		0.795		<0.05		0.309		<0.01
Creatinine	0.858	0.808	0.891	0.875	0.920	0.93	0.96	0.9
(mg/dl)	±0.12	±0.29	±0.13	±0.10	±0.23	±0.19	±0.16	±0.09
		0.546		0.504		0.798		0.111

Paired sample t test;

Table 16 demonstrates the improvement in physical health condition and daily tasks following Body Revival® treatment, as measured by the Karnofsky Performance Scale (KPS). Body Revival® treatment improved KPS scores by 73% in chemotherapy and 53.7% in radiation therapy participants when compared to baseline data. ANOVA with Chi-square and post-hoc Friedman's test revealed that the changes were highly significant. The remarkable improvement in KPS score is graphically represented (**Fig. 10**).

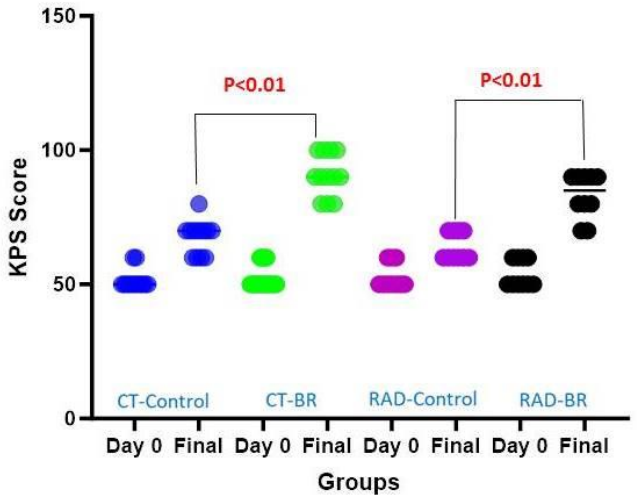


Fig 11. Dot Diagram of KPS

Table 17 highlighted the overall improvement of Body Revival® treatment on Quality of Life on post-operative breast cancer patients who had received chemotherapy and radiation therapy. Total score of QoL is based on all domains. Body Revival® treatment significantly improved the total score 22.62% at 8 week and 41.9% at 12 week of chemotherapy patients, whereas it improved 23% at 8 week and 50.48% at 12 week in radiation therapy patients. However, only a 10.7% and 18.41% improvement in quality of life was recorded in chemotherapy patients and radiation therapy patients who did not get Body Revival® treatment. Furthermore, ANOVA with Chi-square and post-hoc Friedman's test demonstrated very significant differences both within and between groups. Cronbach's alpha was 0.952 in CT-Control, 0.697 in CT-BR, 0.977 in RAD-Control, and 0.445 in the RAD-BR groups. The substantial improvement in total QoL score is graphically illustrated in **Fig. 11**.

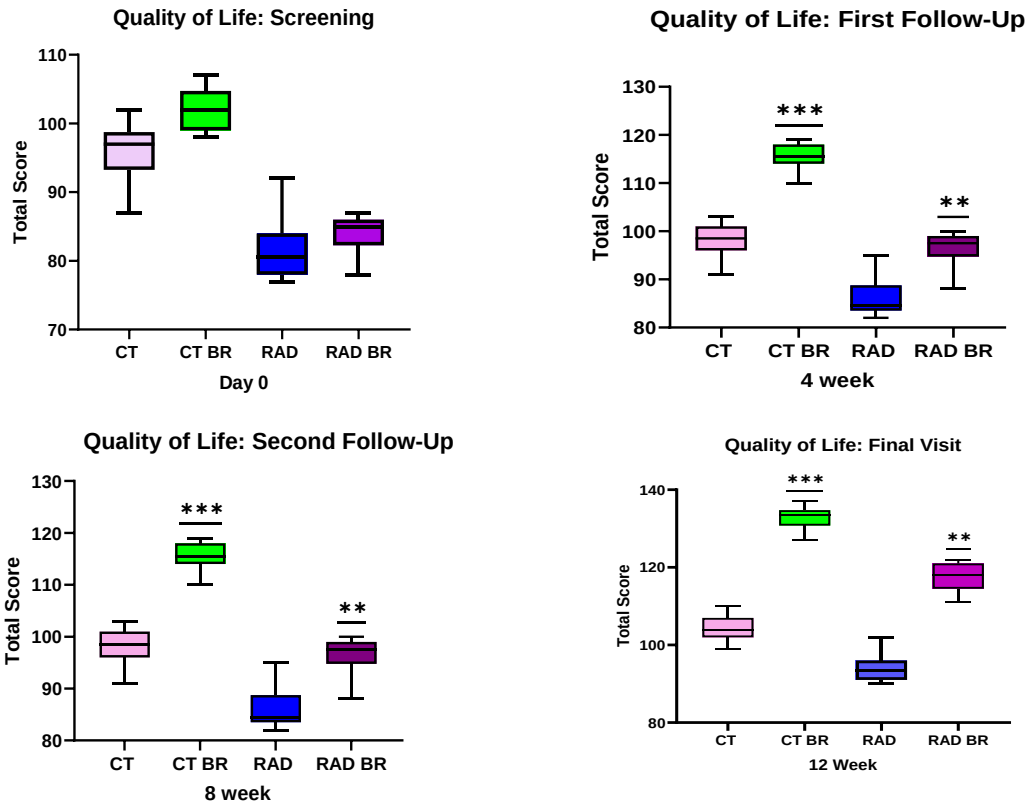


Fig 12. Total Score of QoL

Table 18 and **Fig. 12** show QoL in the general domain. Body Revival® treatment enhanced general domain score (maximum 32) from 16.83 to 25.92 in chemotherapy ($p<0.001$) and 14.50 to 22.20 in radiation ($p<0.01$).

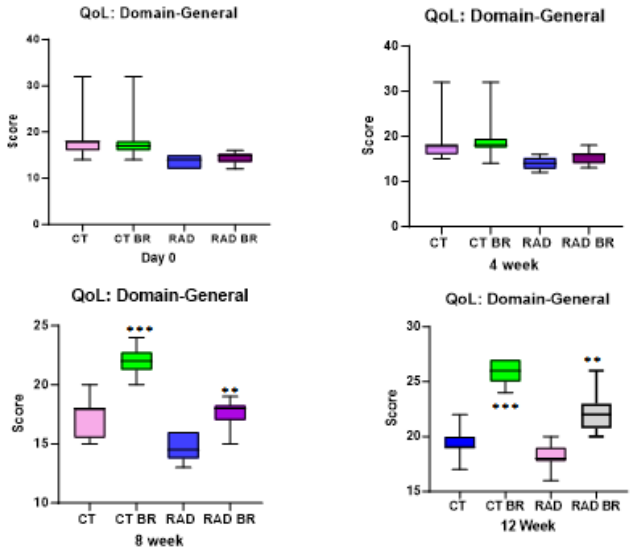


Fig 13. General Domain Score of QoL

Table 19 and **Fig. 13** exhibit QoL in the physical domain. Within 12 weeks, Body Revival® treatment increased the physical domain from 22.67 to 32.92 (45.2%) in the chemotherapy group and 16.20 to 28.90 (78.3%) in the radiation therapy group, out of a maximum score of 40.

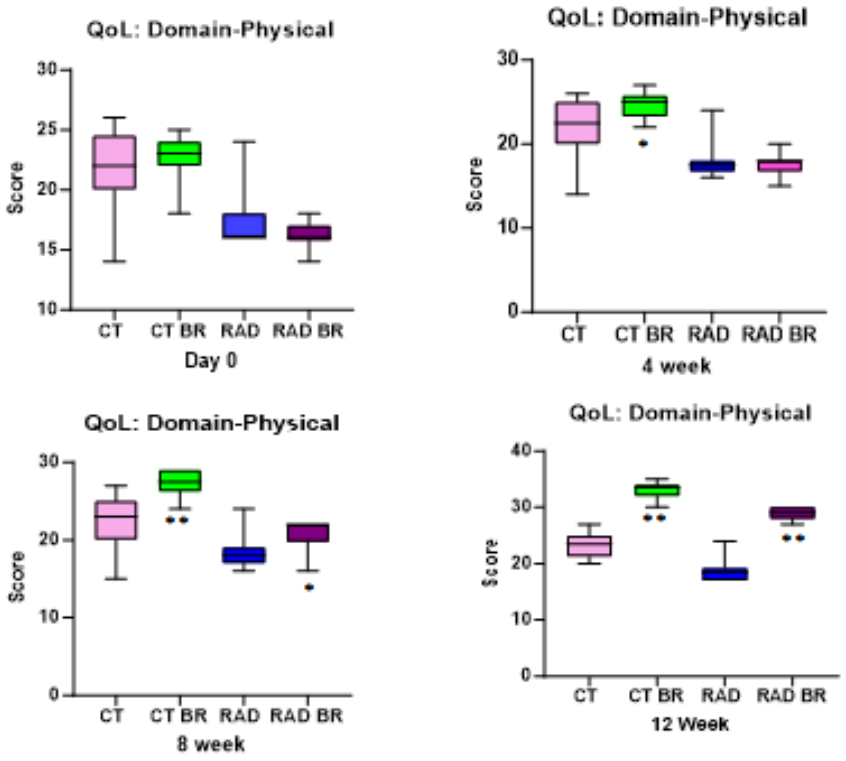


Fig 14. Physical Domain Score of QoL

The psychological domain of QoL is presented in **Table 20** and **Fig. 14**. This domain consists with maximum 32 points. Body Revival® treatment enhanced the psychological domain score from 16.92 at baseline to 19.08 in 4 weeks, 22.67 in 8 weeks, and 26.42 in 12 weeks in the post-operative chemotherapy group. The improvement was 56%. Similarly, Body Revival® treatment improved 55% in the radiation therapy group. In contrast, the psychological domain score in chemotherapeutic control became from 17.42 to 19.83 (13.8%), and in radiation control from 14.40 to 16.50 (14.5%). Cronbach's alpha values were 0.9 in CT-Control, 0.786 in CT-BR, 0.95 in RAD-Control, and 0.872 in the RAD-BR group.

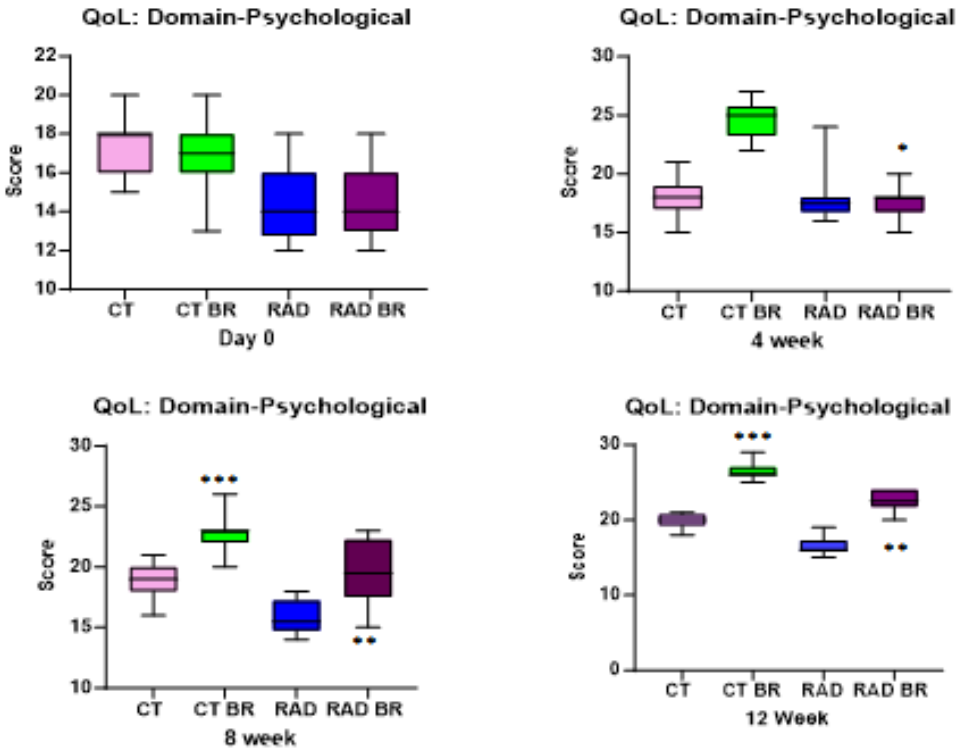


Fig 15. Psychological Domain Score of QoL

The Body Revival® treatment also significantly enhanced the Familial Domain (**Table 21**). The chemotherapy group reported a 20% improvement, whereas the radiation therapy group showed a 42.6% rise.

Table 22 shows the Cognitive Domain of QoL. The test medication considerably improved cognitive functioning exclusively in the chemotherapy group.

Table 23 covers the Economic Domain of Quality of Life. There were no significant changes observed in this domain following test medication therapy.

The Body Revival® treatment only significantly changed the Optimism Domain (**Table 24**) and the Informational Domain of QoL (**Table 25**) of the chemotherapy group at the 12 week, but had no effect on the radiation group.

In the Physician Relationship Domain (**Table 26**) and Body Imaging Domain (**Table 27**) of QoL, the test medication had no effect on either the chemotherapy or radiation groups.

Table 28 shows CA-15.3, a tumor marker for breast cancer growth and development, in serum. CA-15.3 levels were significantly lower in both groups following Body Revival® treatment. Body Revival® decreased CA-15.3 by 43% in the chemotherapy group (95% CI: 4.30 to 9.19) and 30.9% in the radiation group (95% CI: 2.75 to 7.44). However, in the radiation control group, blood CA-15.3 was 15.9% increased, despite remaining within the permissible limit. **Fig. 15** shows blood CA-15.3 levels in all groups.

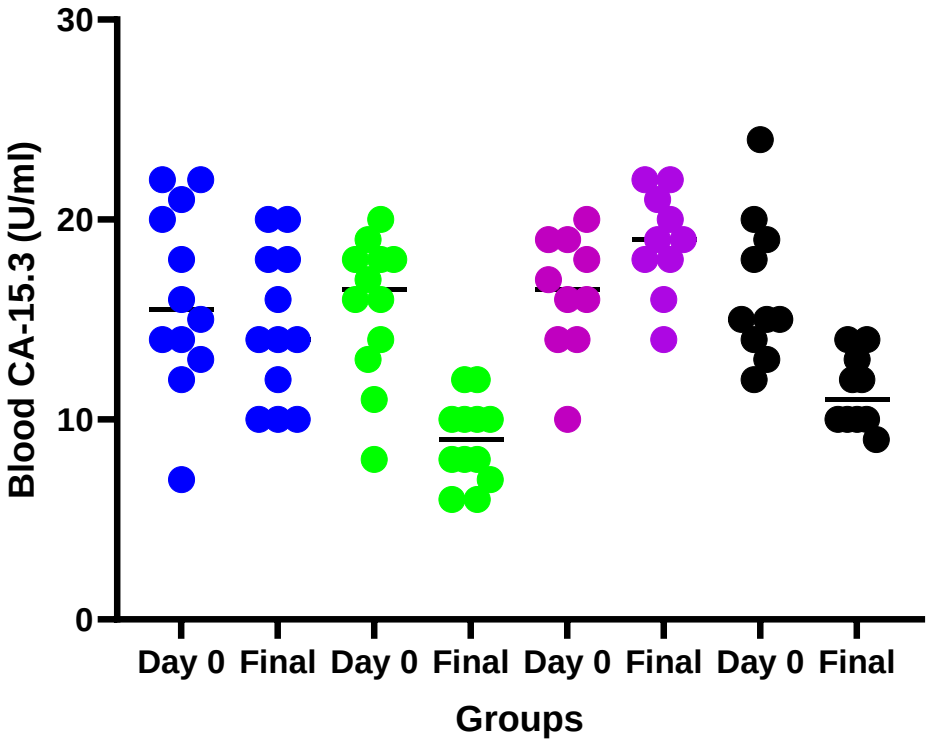


Fig 16. Dot Diagram of Blood CA-15.3

Table 29 demonstrates the hematological safety assessment of Body Revival® treatment for the suggested groups. The baseline hemoglobin concentrations were 9.9 gm% in the CT-Control group, 10.1 gm% in the CT-BR group, 9.4 gm% in the RAD-Control group, and 10.6 gm% in the RAD-BR group. Following therapy, it was 10.2 gm%, 11.1 gm%, 10.2 gm%, and 11.7 gm% (**Fig. 16**). As a result, Body Revival® significantly increased blood hemoglobin concentrations in breast cancer chemotherapy and radiation therapy patients. It also increased hematocrit levels and red blood cell count. Furthermore, Body Revival® treatment increased the number of white blood cells, lymphocytes, and neutrophils.

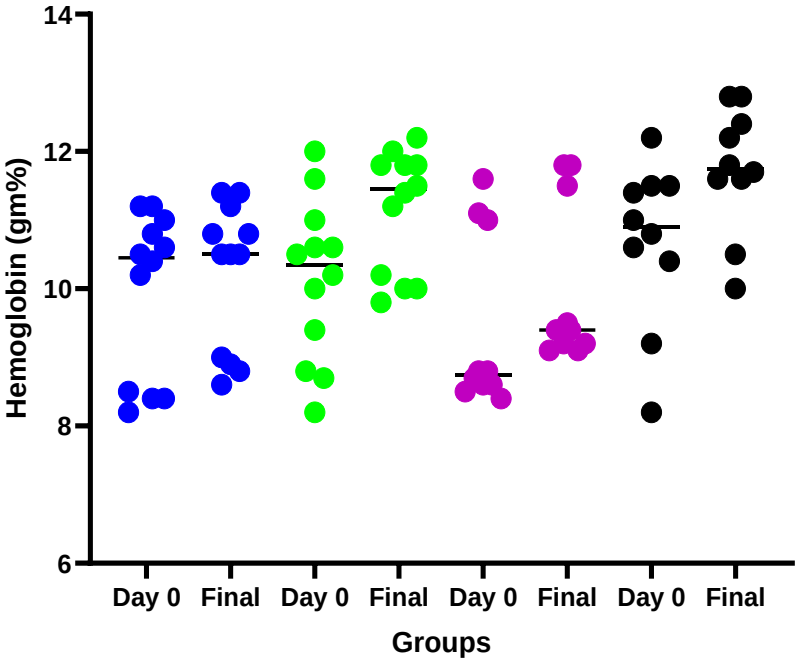


Fig 17. Dot Diagram of Blood Hemoglobin

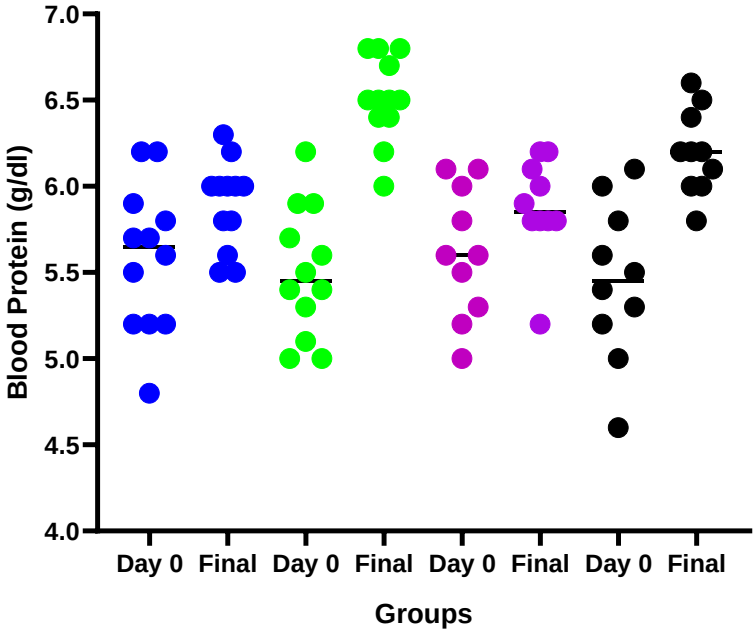


Fig 18. Dot Diagram of Blood Protein

Table 30 displays the biochemical blood profiles following Body Revival® treatment in all groups. Body Revival® significantly ($p < 0.001$) boosted total

protein levels from 5.5 to 6.5 g/dl in the chemotherapy group, and 5.45 to 6.2 g/dl in radiation group in the 12-week period (**Fig. 17**). It also considerably increases albumin concentrations in both groups.

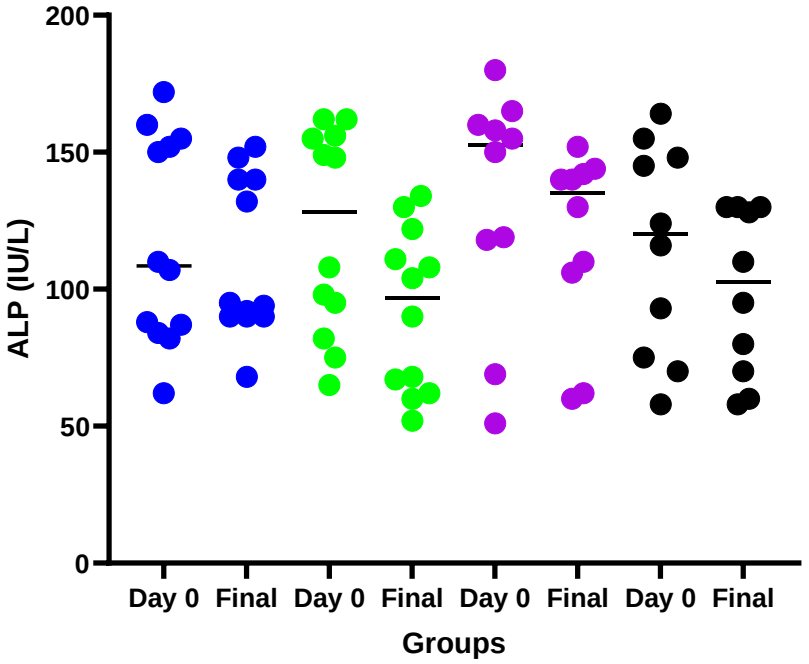


Fig 19. Dot Diagram of Blood Alkaline Phosphatase

Baseline data reveal that conventional chemotherapy and radiation therapy increased the liver enzymes ALT, AST, and ALP in blood (**Table 30**). Body Revival® treatment significantly lowered all of these enzymes in the blood. ALP levels were lowered to 92.3 from 121.3 IU/L (24%) in chemotherapy patients and 99.1 from 114.8 IU/L (13.6%) in radiation therapy patients after surgery (**Fig. 18**). However, BUN and Creatinine levels did not change.

Consequently, according to CTCAE version 5, Body Revival® treatment substantially enhanced hematocrit, hemoglobin, and RBC count to combat anemia. It additionally elevates the number of white blood cells, lymphocytes, and neutrophils, thereby recovering from chemotherapy and radiation-induced immune suppression. Furthermore, after therapy, participants' protein and albumin levels raised while liver enzymes (AST, ALT, and ALP) were reduced. Body Revival® treatment totally relieves muscle weakness, dizziness, and fatigue. It also alleviated symptoms of anorexia, nausea, and vomiting.

18. Ancillary analyses

The reliability was checked statistically in the using instruments (QoL and KPS) by Cronbach's alpha. Cronbach's alpha is a measure of internal consistency, or how closely linked an array of components (variance, covariance) is as a whole. Cronbach's alpha measures the level of agreement on a standardized 0–1 scale (**Table 31**). High Cronbach's alpha values suggest that each participant's response values throughout a series of questions are consistent. If Cronbach's alpha ≥0.9 then Internal consistency is excellent; and so, 0.9 ≥ 0.8 is good; 0.8 ≥ 0.7 acceptable; 0.7 ≥ 0.6 questionable; 0.6 ≥ 0.5 poor and 0.5 > unacceptable.

Table 31. Reliability of KPS Score and QoL Score

	Cronbach's Alpha			
Instruments	CT-Control	CT-BR	RAD-Control	RAD-BR
KPS	0.783	0.819	0.886	0.856
QoL Total Score	0.952	0.697	0.977	0.445
QoL General Domain	0.953	0.792	0.902	0.682
QoL Physical Domain	0.981	0.925	0.978	0.661
QoL Psychological Domain	0.900	0.786	0.950	0.872
QoL Familial Domain	0.973	0.946	0.929	0.759
QoL Cognitive Domain	0.874	0.340	0.897	0.842
QoL Economic Domain	0.962	0.903	0.896	0.826
QoL Optimism Domain	0.958	0.880	0.889	0.738
QoL Informational Domain	0.952	0.737	0.905	0.902
QoL Body Imaging Domain	0.899	0.934	0.920	0.914

In statistics, the Pearson's correlation coefficient is a correlation coefficient that measures linear correlation between two sets of data. It is used to determine the relationship between two dichotomous quantitative variables. Actually, the Pearson correlation assesses the strength of a linear relationship between two variables. It has a value between -1 to 1, with a value of -1 meaning a total negative linear correlation, 0 being no correlation, and + 1 meaning a total positive correlation. Values between ±0.50 and ±1 suggest a strong correlation. Moderate Degree: Values between ±0.30 and ±0.49 indicate a moderate correlation. Low Degree: Values below +0.29 are considered a weak correlation. No Correlation: a value of zero implies any relationship. **Table 32** presents the Pearson's correlation between BR treatment groups and treatment durations in

QoL of post-operative breast cancer patients. A significant, robust, and positive linear connection was observed between the control and treatment groups.

Table 32. Correlation between Treatment Groups and Durations in QoL

	Pearson Correlation			
	Day 0	4 Week	8 Week	12 Week
CT-Control	1	0.960**	0.908**	0.667**
CT-BR	1	0.793**	0.399	0.240
RAD-Control	1	0.985**	0.929**	0.905**
RAD-BR	1	0.566*	0.007	-0.563*

** Correlation is significant at the 0.01 level; * Correlation is significant at the 0.05 level

19. Harms

Other terminologies that are frequently used in regulatory studies to describe hazards are adverse events and adverse medication responses. There was no one report of hyper-reactivity after consuming test drug, Body Revival®. Potentially Body Revival® counteracts chemotherapy and radiation therapy-related frequent adverse events per CTCAE version 5 (**Table 33**).

Table 33. Chemotherapy and Radiation Therapy Related Complaints

	CT-Control - DAY 0	CT – Control - 12 WK	CT -BR - DAY 0	CT- BR - 12 WK	RAD –Control - DAY 0	RAD- Control - 12 WK	RAD- BR - DAY 0	RAD- BR - 12 WK
1. Anorexia	10	8	12	1	10	8	10	2
2. Constipation	8	8	10	1	8	7	7	2
3. Diarrhoea	4	0	2	0	2	0	3	0
4. Dizziness	12	10	12	1	10	8	10	1
5. Dry skin	10	7	10	2	10	8	10	1
6. Fatigue	12	9	12	1	10	7	10	2
7. Hot flashes/flushes	12	9	12	0	10	8	10	1
8. Muscle weakness	10	7	10	1	10	8	10	1
9. Nausea	12	9	10	0	8	5	10	0
10. Pruritus/itching	8	6	9	0	8	5	9	0
11. Rash	9	5	6	0	8	5	9	1
12. Vomiting	10	7	5	0	8	6	10	1

20. Discussion

According to JAMA Oncology (2024), 5.94 million cancer deaths were prevented for breast, cervical, colorectal, lung, and prostate cancers combined. Cancer prevention and screening activities prevented eight out of ten of these fatalities. Screening helped to save 25% of breast cancer deaths (Goddard et al., 2024). Despite certain similarities to western populations, the breast cancer profile in India differs significantly from that of other developed or developing countries in terms of epidemiology, clinic-pathology, and clinical therapeutic techniques. Although women of various socioeconomic backgrounds are affected, young (mid-forties) premenopausal urban women appear to be at a higher risk. The lack of understanding among Indian women about disease signs, screening modalities, self-breast examination, and/or routine mammographic screening has been ascribed to neglect, resulting in a costly delay in diagnosis and treatment. Several studies indicated risk factors such as early menarche, late menopause, nulliparity, delayed age of childbirth, and longer length of breast feeding as protective against breast cancer (Das et al., 2012; NIH, 2023; CDC, 2023; ACS, 2023).

Micrometastatic and macrometastatic disease are currently treated using three broad systemic approaches: chemotherapy, targeted therapy, and immunotherapy, often in combination. While cytotoxic chemotherapy remains the backbone of metastatic treatment and is now the sole option for many cancers subtypes, medications that target tumor-driving oncoproteins, or 'targeted therapy', are improving results in many cancers (Ganesh and Massague, 2023, Ruidas et al., 2024). Different treatment options in breast cancers, such as chemotherapy, biological agents, and hormone therapy, are chosen based on disease stage, receptor status, menopausal status, other factors such as prognosis or prediction, as well as the compliance, tolerance, feasibility, and cost-benefit aspects of each approach individually (ACS, 2021).

Radiotherapy is an important component of the multidisciplinary management of breast cancer patients. For node-positive breast cancer patients, locoregional radiation after mastectomy improves local control, reduces distant metastases, and increases survival rates. Traditionally, post-mastectomy patients have

received radiation treatment using a standard radiotherapy regimen based on clinical landmarks (Azam et al., 2023).

An aggressive multi-agent treatment is used to cure cancer, but it has serious side effects such as nausea, vomiting, exhaustion, hair loss, peripheral neuropathy, cognitive impairment, and so on. Women with breast cancer who get chemotherapy experience decreased sexual function and premature menopause. Chemotherapy also impairs the central nervous system. Although there are several unpleasant effects associated with cancer therapy, knowing the mechanism behind them will help to improve the management of these adverse effects, so improving cancer patient survival and thus QoL (Langeh et al., 2023).

The treatment technique of complementary and alternative medicine has recently become common in Western society. It has been suggested that two-thirds of adult cancer patients seek complementary therapy during and after standard treatment. The use of this therapy in breast cancer women has been widely accepted. Breast cancer women have been reported to use herbal and Ayurvedic medicine to manage cancer and its treatment-related symptoms (Lee et al., 2000; Boon et al, 2000; Hann et al., 2005; Lengacher et al., 2006; Ruidas et al., 2020; Ruidas et al., 2022; Khan et al, 2022)

The nine natural ingredients of Body Revival® are *Aegle marmelos* (Indian Bael) fruit pulp powder, *Acorus calamus* (Vacha) rhizome, *Withania somnifera* (Ashwagandha) root, *Blumea lacera* (Kukrondha) fruit, *Rumex vesicarius* (Chukrika) whole plant, *Rubia cordifolia* (Manjishtha) root, *Cucumis melo* (Muskmelon) seed, *Symplocos racemosa* (Lodhra) stem bark and honey. Previous research has shown that Body Revival® improves the immune system, detoxifies toxic body toxins and gut microorganisms, repairs damaged tissues, and rejuvenates healthy cells, as well as helping to improve QoL and disease-free longevity in cancer patients over the previous 25 years (Sur & Khan, 2016; Khan et al., 2022; Joshi et al., 2023a; Joshi et al., 2023b; Khan et al., 2023a; Khan et al., 2023b; Sur & Pandit, 2024). It showed as a powerful multi-target inhibitor of ER-α and HER-2 that has prospective anticancer action without side effects, and may be useful in the therapy management following a successful trial in breast cancer patients (Khan et al., 2023a). Body Revival® has a therapeutic index greater than 10, indicating that it is both safe and effective against cancer. Moreover, the current study definitely and undoubtedly demonstrated that Body Revival®

reduced chemotherapy and radiation therapy-induced side effects and adverse occurrences in cancer patients (Sur & Pandit, 2024).

The current study (NCT:CTRI/2023/11/059465) was carried out in a single center on post-operative breast cancer patients to determine the efficacy and safety of test drug – Body Revival® in improving physical performance and quality of life as disease-free life progresses.

Living longer is the ultimate desire for cancer patients, and the time when the disease does not progress is significant when combined with improved quality of life and no further treatment harm. Participants considered that increased or sustained QoL is a relevant endpoint, which is consistent with existing literature (Reed et al., 2012; von Itzstein et al., 2020). Even though breast cancer is still incurable, many patients' prognosis has gradually improved due to changes in treatment, particularly for HER2+ and ER + subtypes. Patients want treatments that improve their quality of life and help them live longer (Mertz et al., 2022).

Breast cancer is also recognized as diverse at various levels, including molecular, morphological, and clinical, which has significant implications for diagnosis and treatment. Current breast cancer surveillance guidelines advocate regular mammography and physical examinations, as well as additional symptom-related laboratory tests and imaging tests, such as computed tomography or positron emission tomography (Smith et al., 2013). Serum tumor markers are routinely utilized and, when combined with imaging, provide a cost-effective technique to aid in the diagnosis of breast cancer as well as monitor the disease's response to therapy. The most often used tumor markers in breast cancer are CA15.3, CEA, and cancer antigen 27.29 (CA27.29), all of which are recommended for use in breast cancer by the American Society of Clinical Oncology (Duffy et al., 2000; Harris et al., 2007; Gaughran et al., 2020; Ryu et al., 2023). In the present clinical trial, Body Revival® significantly decreased the serum tumor marker CA15.3 (**Table 28**), indicating its potential for breast cancer treatment. As a result, it is possible that Body Revival® treatment contributes to progression-free survival rates for breast cancer patients.

The Karnofsky Performance Scale Index measures functional disability. It can be used to compare the efficacy of various therapies and to determine the prognosis for particular patients. In most major illnesses, the lower the Karnofsky score, the less likely the patient would survive (Schag et al., 1984). KPS is mostly beneficial

for assessing overall physical quality of life. Breast cancer patients reported higher levels of fatigue than those without a history of cancer. These changes were noticeable before and after the patients began chemotherapy and radiation treatment. In addition, patients' fatigue exacerbated once treatment began. More severe fatigue before to treatment was associated with lower performance status and the occurrence of fatigue-related symptoms, e.g., sleep issues and muscle weakness. Increased fatigue after starting chemotherapy was linked to the recurrence of fatigue-related symptoms as well as the development of chemotherapy side effects, such as nausea and mouth sores (Jacobsen et al., 1999; de Jong et al., 2002; Bower et al., 2006). In the present clinical trial, lower physical performance scores were connected with lower KPS scores. Body Revival® substantially raised the KPS score of breast cancer chemotherapy and radiation therapy patients while also reversing fatigue and related problems (**Table 16**). In addition, it was noticed KPS as a promising predictive factor for assessing the therapeutic impact of Body Revival®.

Myelosuppression is the primary dose-limiting effect of systemic cancer treatment. Cyclophosphamide is a frequently used anticancer medication with a high therapeutic index and a broad antitumor action. Furthermore, cyclophosphamide promotes dose-limiting suppression of growing hematopoietic progenitor cells, resulting in significant neutropenia, however dose decreases may alter therapy success (Emadi et al., 2009; Gramajo Lopez et al, 2021). Earlier preliminary investigations revealed that Body Revival® can help minimize myelosuppression following cyclophosphamide induced chemotherapy (Khan et al., 2020). In the present clinical trial, Body Revival® significantly increased blood hemoglobin concentrations, hematocrit levels and red blood cell count in breast cancer chemotherapy and radiation therapy patients and combat anemia. Furthermore, Body Revival® treatment increased white blood cell, lymphocyte, and neutrophil counts, which supported previous findings (**Table 29)**.

Radiotherapy is the most common treatment for many malignancies; however it can harm healthy tissues in the short and long term. According to the most recent data, more than 70% of patients with malignant tumors require radiation therapy. Radiation-induced skin reactions are one of the most serious side effects, affecting quality of life and the progression of cancer treatment. Chronic radiation-induced reactions include ulcers and sores, fibrosis, telangiectasias, secondary skin cancer, and radiation-induced keratosis. Inflammation begins

immediately after radiation therapy and lasts for months or years, also contributes to the development of radiation-induced fibrosis. TNF-a, IL-6, and IL-1 contribute to inflammation, while TGF-β and platelet-derived growth factor stimulate fibroblast activity and extracellular matrix protein formation (Straub et al., 2015; Peter, 2015; Wei et al., 2018). Previous studies on Body Revival® found that it had cytotoxic effects (IC_{50} 34.27µl/ml) on breast cancer cells (MCF-7 cells) via suppressing pro-inflammatory cytokines (IL-6) and matrix metalloproteinase-9 (Khan et al., 2023). According to the current study, Body Revival® reduces the frequency of chemotherapy and radiation therapy-related adverse events, including dermatologic complaints, as per CTCAE version 5 (**Table 33)**.

Quality of life (QoL) is now viewed as a main endpoint metric for oncology management and care since it reflects patients' perceptions of how cancer diagnosis and treatment affect their daily lives. It is a significant factor both when cancer is diagnosed and after it has been treated. Patients' quality of life following cancer therapy may differ based on the physical and psychological repercussions. Furthermore, better QoL has been associated to a higher survival rate in cancer patients (Latha et al, 2011; Nayak et al., 2017; Alam et al, 2020; Mertz et al., 2022; Javan Biparva et al., 2024). Thus, research into the components that influence QoL may provide insights into how to improve the QoL of breast cancer patients and, as a result, increase their survival. In fact, a breast cancer diagnosis has major physical, mental, and economic effects for patients and their families, necessitating a significant shift in a person's natural lifestyle as well as the dynamism of family members.

The present study used the reliable and accepted QoL tools in Indian cancer patients (Latha et al, 2011). This tool had useful domains that addressed all aspects of life challenges (Indian cultural context) such as general well-being, physical well-being, psychological well-being, familial relationships, cognitive well-being, optimism and belief, economic well-being, informational support, and body image. The observations after treatment with Body Revival® and comparison to their respective case control in selected domains are reported in the result section (**Table 17-Table 27**). Furthermore, the reliability was examined of treatment groups and validated (**Table 32**). Although the study was limited to a single institution and only included post-operative breast cancer patients, it was nevertheless a sensitive instrument for QoL. The current findings clearly demonstrated that Body Revival® considerably improved the QoL of breast

cancer patients in all essential dimensions, including general well-being, physical well-being, psychological well-being, familial relationships, and cognitive well-being. In an exploratory survey of cancer patients diagnosed in Stages I–IV, Body Revival® treatment for three months greatly enhanced physical and mental areas of QoL. The pain and exhaustion scores were substantially decreased, but physical activity and cognition scores were marginally improved (Joshi et al., 2023a). In another study, Body Revival® significantly boosted the QoL of five patients with complaints, three of whom had surgery, four of whom received chemotherapy, and one who did not have either (Joshi et al., 2023b). From non-invasive breast cancer to finishing treatment or even receiving palliative care in patients with advanced cancer, the primary domains of QoL are disease symptoms, negative psychological effects such as anxiety, stress, fear, and depression, a decreased level of perceived life expectancy, and the potential adverse side effects of the disease. In the current study, financial restrictions were recognized as the major challenge among both patients and family caregivers, making it the common barrier to symptom treatment and having a greater influence on both parties' QoL. A similar finding was observed in research by Nayak et al., 2017; Alam et al., 2020; and Islam et al., 2023.

21. Generalizability

Body Revival® is an herbal Ayurvedic medicine (M/s Health Reactive, Mumbai, India) to support the concept of Ayurvedic oncology. Ayurvedic Oncology is a comprehensive approach to cancer therapy that integrates traditional Ayurvedic principles with modern cancer treatments to improve patient results and quality of life. The significance of Ayurvedic Oncology is based on its ability to (i) integrate complementary therapies (combines Ayurvedic treatments like herbal medicines with standard cancer treatments), (ii) address cancer prevention (prevention through lifestyle changes, diet, and stress management), (iii) improve quality of life (alleviating cancer symptoms, side effects, and emotional distress, thereby improving patients' overall well-being), and (iv) reduce treatment side effects (reducing chemotherapy and radiation side effects, improving patients' comfort and tolerance).

A substantial study report says that it can be used to increase immune function and overcome the health risks associated with conventional cancer treatment. Every experiment conducted in this study complied with national and

international cancer research standards. Global standards were also followed in verifying and checking the trustworthiness of the tools and data collected. In the present study, Body Revival® enhances cancer patients' quality of life by lowering disease recurrence and associated hazardous events while also enhancing physical performance. Hence, Body Revival® can aid with cancer therapy and management.

22. Interpretation

- Body Revival® treatment enhanced QoL for patients with breast cancer in terms of general well-being, physical well-being and psychological well-being.
- Body Revival® improved physical performance in daily life.
- Body Revival® lowered the breast cancer tumor biomarker CA-15.3 in blood and thereby reducing the chances of recurrence of disease.
- Body Revival® reduced the side effects of chemotherapy and radiation in cancer patients.
- Body Revival® treatment enhanced appetite, physical stamina and endurance while reduced nausea, constipation, muscle weakness, dizziness and fatigue in cancer patients.
- Body Revival® decreased liver enzymes and enhanced protein and hemoglobin levels in blood.
- Body Revival® improved WBC and neutrophil count and immunological function in chemotherapy-induced cancer patients.
- The treatment outcome of chemotherapy group showed better than the radiation group.
- Body Revival® can alleviate chemotherapy and radiation-related adverse effects in cancer patients.
- Body Revival® can help with cancer therapy and management.

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Other information

23. Registration

The study protocol, ICF, CRF and other documents that pertain to subject information, recruitment methods etc. were reviewed and approved by the Institutional Ethics Committee (JBR/IEC/06/2023, dt. July 4, 2023). The copy of approval letter is attached in **Appendix-X**.

The study protocol was also submitted to the ICMR Clinical Trial Registration portal for approval through the national clinical trial registration process. CTRI registration was obtained on November 2, 2023. The CTRI NCT is CTRI/2023/11/059465. A copy of the permission letter is given in **Appendix-XI**.

24. Protocol

The study protocol is attached in **Appendix-VIII**.

25. Funding

The sponsoring organization assumed financial responsibility for research personnel salary, patients' trial investigation charges, and any study-related logistical support. The sponsor's name and address for this study are as follows:

M/s Health Reactive,
Excellency Bldg, 1st Floor, Opp. MTNL
4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053
Office Tel: 26399871-85 (15 Lines)
Office Email: info@healthreactive.com
www.bodyrevival.in

Appendix

Project Title: 12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Study Sponsor: Health Reactive, Mumbai & Rajasthan, India

Appendix-I

PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM TO PARTICIPATE IN THE RESEARCH STUDY "BODY REVIVAL IN BREAST CANCER PATIENTS"

Principal Investigator: Dr. Srikanta Pandit
Subject Number:

Project Title: 12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Study Sponsor: Health Reactive, Mumbai & Rajasthan, India
Protocol No.: HR-BR-BC0523; Version 1.0 dated June 6, 2023

1. What is the study about?

Breast cancer is the leading cause of deaths in women. Early detection and proper treatment can save more lives. In most of the cases, the conventional therapy of breast cancer produces toxicities and severe side effects that lower the quality of life of the patient. To reduce the treatment related side effects and to improve the quality of life with progression free survival, the present study will be conducted with a complementary treatment of Ayurvedic medicine (Body Revival). This medicine may be helpful to lower the side effects of your regular cancer treatment. We are invited you to participate in such a study as volunteer. To ensure your safety and protect your rights this study is being approved by Institutional Ethics Committee.

2. What will you have to do?

If you agree to participate, we would take a written consent for this purpose. For screening purpose we would take your medical history and conduct your physical check up by taking weight, height pulse and blood pressure. We also assess your other health condition by asking some specific questions related to your regular physical performances and mental conditions and also any treatment related side effects you feel recently. Other than that routine blood examinations (CBC, LFT and RF tests) will be performed for checking your present health condition. If you select for trial, then you will be advised to follow the direction of taking test medicine for 12 weeks (3 month). All test medicine will be given to you without any cost. If you are a participant then you would to be come to this hospital after 1 month (4 weeks), 2 month (8 weeks) and 3 month (12 weeks) for physical check up, questionnaire and other reporting. In that time we would like to advice you for other health related problems also. The blood examination will be done in two time, i.e., during your first visit and after completion of your treatment. Maximum 1 h would be required for your study related examinations in every visit. The following visits/schedule and purposes you have to be follow:

	Screening/ Visit-1	**Visit-2 4 week**	**Visit-3 8 week**	**Visit-4 12week**
Physical check-up	√	√	√	√
Questionnaire/Interview for your health	√	√	√	√
Blood tests	√			√
Dispensing medicine	√	√		

3. Are there any risks?

The product may be benefit to you or maybe not, but there is no risk by participating in this study.

4. Can I leave the study?

Your participation in this study is completely voluntary. You can choose to leave from the study at any time. Your decision to leave the study will not affect your medical care or relationship with your doctor or hospital facilities.

5. What is the cost of the study?

All the tests will be free of charge.

INFORMED CONSENT

SUBJECT'S NAME ..... ID ..... AGE .....

Please tick if you agree

1. I confirmed that I have read and understood the information sheet for the above study dated ..... and have had the opportunity to ask questions. ☐
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without having to give a reason, and without my rights and privileges being affected. ☐
3. I understand the my data would be kept confidential but individuals authorized by the Principal Investigator, the ethics committee of the institute where the study will be conducted and government regulatory authority will have access to my records both in respect of the current study and further research that may be conducted in relation to it. Even if I withdraw, I agree to this access. However, I understand that my identity will not be revealed and confidentiality of information will be maintained. ☐
4. I agree not to restrict the use of any data or results that arise from this study for the academic purpose. ☐
5. I agree to voluntarily take part in the above study. ☐

Signature / Thumb impression of the subject ..... Date: .....

Signatory's name: .....

Study Investigator's Signature: ..... Date: .....

Study Investigator's Name: .....

Principal Investigator: Dr. Srikanta Pandit (9831723650)
Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Sponsor: Health Reactive, Mumbai & Rajasthan, India
Protocol No. & Version: HR-BR-BC0523; Version 1.0 dated June 6, 2023

Appendix-II
CASE RECORD FORM

Project Title: 12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Principal Investigator: Dr. Srikanta Pandit
Study Sponsor: Health Reactive, Mumbai & Rajasthan, India
Protocol Number & Version: HR-BR-BC0523; Version 1.0 dated June 6, 2023

Informed Consent Information:

Date and time the ICF procedure started:	Date: Time:
Date and time the ICF procedure ended:	Date: Time:
Time when patient gave the consent:	
Language in which ICF was obtained:	English / Hindi / Bengali
ICF explained and obtained by:	PI / Co-PI
One set of signed ICF given to patient:	Yes / No

Hospital Registration No. & Date:			
Patient ID:			
Complete name:			
Complete address:			
District:		**PIN:**	
Contract number(s).			
Age (yrs.):		**Sex:**	Female
Religion:	Hindu/Muslim/Others	**Caste:**	Gen/ST/SC/OBC

Medical history cancer:

Last hospital visit (date/months):		
Hospital name:		
Disease confirmed (month/year):		
Diagnosis process:	Radiography / Ultrasonography / Needle biopsy / Biopsy / IHC / Others	
Treatment process:	Radiotherapy received?	Yes / No (if yes, describe in blank space)
	Chemotherapy received?	Yes / No (if yes, describe in blank space)
	Both RT & CT received?	Yes / No (if yes, describe in blank space)
Surgery process:	Surgery done?	Yes / No (if yes, comments below)

Date of Surgery:
Type of Surgery: Lumpectomy/ Mastectomy / Sentinel node biopsy / Axillaries lymph node dissection
Surgery Side: Left / Right / Both
Area of tumor: UOQ / LOQ / UIQ / LIQ / CENTRAL / UNSPECIFIED
Tumor Size (cm):
Grade: 0 / I / II / III / IV
Any other:

History of medication: (last 6 months)

Co-morbidity: (last 6 months)

	Y	N	Stable	Unstable		Y	N	Stable	Unstable
Hypertension					Thyroidisms				
Diabetes					GI & Liver problems				
Ischemic heart disease					Renal problems				
Anemia					Neuropsychiatric disease				
Asthma					Anxiety/ Depression				

Demographic details:

No. of family members	≤4 / ≤ 6 / ≥ 6
Education	Illiterate / primary school/high school / collegiate / university
Marital status	Married /unmarried/widow/divorced
Occupation	Business / agriculture / Home maker/ service / retired / unemployed
Total family income (INR)	< 25000 / 25000-50000 / 50000-100000 / above 100000
Smoking habit	Smoker / ex-smoker / never smoke
Tobacco chewing habit	Presently use / ex-use / never use
Alcohol drinking habit	Regularly / occasionally / ex-use / never use
LMP (if any)	
Child bearing condition	Presently pregnant / lactating / NA

Physical directed examination:

Parameters	Screening Visit	Follow up 1 (4 wk)	Follow up 2 (8 wk)	Follow up 3 (12 wk)
	Date:	Date:	Date:	Date:
HEENT				
Respiratory				
Cardiovascular				
Abdominal				
Genitourinary				
musculoskeletal				
Neurological				
Extremities				
Lymph nodes				
Dermatologic				
Weight (kg):				
BMI:				
Pulse (btm):				
Blood pressure (mm Hg):				
Height (cm):				

Quality of Life (QoL) status

Domains	Screening Visit	Follow up 1 (4 wk)	Follow up 2 (8 wk)	Follow up 3 (12 wk)
	Date:	Date:	Date:	Date:
General well-being				
Physical well-being				
Psychological well-being				
Familial relationship				
Cognitive well-being				
Economic well-being				
Optimism and belief				
Informational support				
Patient physician relationship				
Body image				

Karnofsky Performance Scale (KPS) status

	Screening Visit	Follow up 1 (4 wk)	Follow up 2 (8 wk)	Follow up 3 (12 wk)
	Date:	Date:	Date:	Date:
Score (0-100%)				

Progression Free Survival (PFS) status

	Screening Visit	Follow up 3 (12 wk)
	Date:	Date:
Blood CA-15.3		
CT Scan / USG		

Laboratory examinations

	Screening Visit	Follow up 3 (12 wk)
	Date:	Date:
Hematocrit (Hct)		
Hemoglobin		
Platelet count		
Red blood cell count		
White blood cell count		
Neutrophil		
Lymphocyte		
Monocytes		
Eosinophil		
Basophil		
Total protein		
Albumin		
Alkaline phosphatase		
Alanine aminotransferase		
Aspartate aminotransferase		
Blood urea nitrogen		
Creatinine		

Adverse Events (AEs) status

	Screening Visit	Follow up 1 (4 wk)	Follow up 2 (8 wk)	Follow up 3 (12 wk)
	Date:	Date:	Date:	Date:
1. Albumin, serum-low				
2. Alkaline phosphatase				
3. Allergic reaction/hypersensitivity				
4. Allergic rhinitis				
5. ALT, SGPT				
6. Anemia (Haemoglobin)				
7. Anorexia				
8. Ascites (non-malignant)				
9. AST, SGOT				
10. Burn				
11. Colitis				
12. Constipation				
13. Creatinine				
14. Diarrhoea				
15. Distension/bloating, abdominal				
16. Dizziness				
17. Dry mouth/salivary gland (xerostomia)				
18. Dry skin				
19. Dysphagia (difficulty swallowing)				
20. Edema: Head/neck/trunk/viscera				
21. Fatigue (asthenia, lethargy, malaise)				
22. Fever				
23. Gastritis (including bile reflux gastritis)				
24. Hair loss/alopecia				
25. Hematoma				
26. Hot flashes/flushes				
27. Hyperpigmentation				
28. Hypertension				
29. Insomnia				
30. Muscle weakness				
31. Nausea				
32. Otitis, external / middle ear				
33. Pain				
34. Palpitations				
35. Photosensitivity				
36. Pruritus/itching				
37. Rash: erythema multi-form				
38. Seizure				
39. Syncope (fainting)				
40. Tremor				
41. Ulceration				
42. Vomiting				
43. Weight gain				
44. Weight loss				
45. Wound complication, non-infectious				

CTCAE v.5 criteria: Grade 1 Mild AE; Grade 2 Moderate AE; Grade 3 Severe AE; Grade 4 Life-threatening or disabling AE; Grade 5 Death related to AE

Randomization and test medicine dispensing

Eligibility criteria checked?	Yes / No	date:
Selected for study?	Yes / No	date:
Randomized?	Yes / No	date:
Study medicine dispensed?	Yes / No	date:

Dt. of dispensed	Amount dispensed	Units dispensed	Dt. of returned	Actual amount returned	Expected amount returned	Reason for difference between actual amount & expected amount returned

Concomitant medication record (Follow-up 1 to Follow-up 3)

Sl. No.	Medication	Strength	Frequency	Reason for Use	Start Date	Stop Date

Exit Page

- ☐ Subject completed the study.
- ☐ Subject did not meet the eligibility criteria.
- ☐ Subject failed in the screening process.
- ☐ Subject withdrew consent.
- ☐ Subject exited due to an AE / SAE.
- ☐ Subject lost to follow-up.
- ☐ Subject was withdrawn as per Investigator's discretion.
- ☐ Subject was non-compliant to the study drug.

Investigator's Signature

I confirm that I reviewed the data in this Case Report for this patient. All information entered by myself or the best of my knowledge, complete and accurate, as of the date below.

_____

Investigator's signature & Date

Appendix-III

Karnofsky Performance Scale

Description	Scale (%)
1. Normal, no complaints, no evidence of disease	100
2. Able to carry on normal activity; minor symptoms of disease	90
3. Normal activity with effort; some symptoms of disease	80
4. Cares for self; unable to carry on normal activity or active work	70
5. Requires occasional assistance but is able to care for needs	60
6. Requires considerable assistance and frequent medical care	50
7. Disabled; requires special care and assistance	40
8. Severely disabled; hospitalization is indicated, death not imminent	30
9. Very sick, hospitalization necessary, active treatment necessary	20
10. Moribund, fatal processes progressing rapidly	10
11. Dead	0

Ref. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Ed MacLeod CM. New York: Columbia University Press; 1949:191–205.

Appendix-IV

CA-15.3 PFS (Krebs Criteria)

Tumor marker CA-15.3 is considered as an important concern in realm of breast cancer oncology. Generally, CA-15.3 serum level ≥30 is deemed as a risk. Progression will be defined based on CA-15.3 levels in blood (Krebs Criteria, 1987) as described in the table below:

Criteria	**State of Disease**	**Reference Value**
CA-15.3 in serum level (ELISA/CIA methods)	Normal	≤ 25 IU/ml
	Risks	≥ 30 IU/ml
	Progression of disease	≥ 50 IU/ml

Ref. Krebs BP, Pons-Anicet DMG, Mira R, Namer M. Value of CA 15:3 in the follow-up of breast cancer patients. British Journal of Cancer 1987; 55(5): 567-569. https://doi.org/10.1038/bjc.1987.115

Appendix-V

Quality of Life (QoL) Assessment

The quality of life (QoL) is one of the most concerning health issues for oncology patients. To evaluate the QoL of cancer patients in an Indian context, the majority of researchers employed the QoL questionnaire version II, which are created and validated by Latha *et al.* (2011). The valid QoL for breast cancer patients, which will be followed, is given below:

Questionnaire	**Very much (4)**	**Moderate (3)**	**A little (2)**	**Not at all (1)**
General well-being				
1. How do you rate your overall quality of life during the past week?				
2. How would you rate your overall physical conditioning during the past week?				
3. Do you feel you are physically performing less than what you want to do?				
4. Do you feel confident about managing your financial needs at any situation?				
5. Do you get the kind of support you need from your friends and relatives?				
Physical well-being				
1. Do you experience any pain at present?				
2. Does your pain interfere in your day-to-day activity?				
3. Is your appetite normal?				
4. Do you have any problem in sleep?				
5. Do you feel you need more rest?				
6. Do you feel fatigued?				
7. Are you able to move around (physical) as usual?				
8. Do you have problems in passing urine?				
9. Do you have problems in passing motion?				
10. Are you satisfied with your working capacity?				
Psychological well-being				
1. Do you feel depressed?				
2. Does your feeling of sadness or depression interfere with your everyday functioning?				
3. Are you comfortable attending social functions as usual?				
4. Do you feel that you have too much time, nothing important to do?				
5. Do you have a fear of recurrence?				
6. Do you have a fear of functional disability?				
7. Do you have a fear of rejection and losing social status?				
8. Do you feel very lonely or remote from other people?				
Familial relationship				
1. How satisfied are you about your relationship with your family?				
2. Do you feel free to share your problems with your family members?				
3. Do you get the kind of support you need from your spouse and family members?				
4. Are you confident that you are able to fulfill your family needs?				
5. Sexual and personal ability				
6. Are you satisfied with your present sex life?				
7. Do you need any assistance to do your day-to-day activities?				

Questionnaire	Very much (4)	Moderate (3)	A little (2)	Not at all (1)
Cognitive well-being				
1. Do you have difficulty in remembering things?				
2. How dependent are you on medication?				
Economic well-being				
1. Do you feel that your physical condition has resulted in reduced economic status?				
2. How important do you feel about yourself at present?				
3. Are you satisfied with the responsibilities you have already fulfilled?				
Optimism and belief				
1. To what extent do your personal beliefs/religious faith gives you the strength to face the difficulties?				
2. Do you expect always good things to happen?				
Informational support				
1. Are you able to get the required information from your doctors?				
2. How much of information do you want about your disease/treatment?				
Patient physician relationship				
1. Do you feel your doctor is cooperative?				
Body image				
2. Are you satisfied with the way your body looks?				

Instructions

- Out of 41 items, 39 items are 4-point scale that rated on a response scale of "not at all" (1) to "very much" (4).
- The remaining two items are in 10-point semantic scale.
- For item 40 (on overall physical condition) and 41 (an overall QoL), the response option ranged from "very poor" (1) to "excellent" (10) and the period is during the past 2 weeks.
- The total score of the whole tool consists of a maximum score of 176 and a minimum score of 41.
- The higher score indicates better QoL among the cancer patients.
- The total score categorized into five:
  1. Above 165- very high QoL
  2. 147–165 - high QoL
  3. 118–146-- average QoL
  4. 99–117 - low QoL, and
  5. Below 99 - very low QoL

Ref. Latha VE, Rakannan R, Mani CS, Muthuvel R, Surendren V, Paul JFU. Validation of cancer institute quality of life questionnaire version II for cancer patients in India. Indian J Cancer 2011; 48(4):500-506

Appendix-VI

Common Terminology Criteria for Adverse Events v5.0 (CTCAE)
Publish Date: November 27, 2017

An Adverse Event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

Grades: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.
- A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

CTCAE Category AE	Grade I	Grade II	Grade III	Grade IV	Grade V
Albumin, serum-low	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Allergic reaction/hypersensitivity	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death

Allergic rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
ALT, SGPT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Anemia (Haemoglobin)	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
Ascites (non-malignant)	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
AST, SGOT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy	Life-threatening consequences (e.g., hemodynamic collapse)	Death

		compared to baseline; not interfering with ADL	output compared to baseline; interfering with ADL		
Distension/bloating, abdominal	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
Dry mouth/salivary gland (xerostomia)	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Dysphagia (difficulty swallowing)	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death

Fatigue (asthenia, lethargy, malaise)	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
Gastritis (including bile reflux gastritis)	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
Hair loss/alopecia	Thinning or patchy	Complete	—	—	—
Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Hot flashes/flushes	Mild	Moderate	Interfering with ADL	—	—
Hyperpigmentation / Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may beindicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—

Muscle weakness	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Otitis, middle ear	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death
Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
Rash: erythema multi-form	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus,	Death

				intractable epilepsy)	
Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death

Appendix-VII

Original Data Sheet

Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Study Sponsor: Health Reactive, Mumbai & Rajasthan, India
Protocol No.: HR-BR-BC0523; Version 1.0 dated June 6, 2023

1. Enrollment

Sl. No	Patient ID	Age	Religion	District (WB)	Disease Confirmed	Treatment Procedure	Date of Surgery	Date of Enrollment	Randomization	Status
1	BC-01	53	H	N-24 PGS	16/8/2022	CT	6/11/2023	6/11/2023	BR	COMPLETE
2	BC-02	45	H	S-24 PGS	3/2/2022	CT	14/11/2023	14/11/2023	Control	COMPLETE
3	BC-03	52	H	KOLKATA	4/9/2022	CT+RT	20/11/2023	20/11/2023	BR	COMPLETE
4	BC-04	54	H	KOLKATA	1/6/2022	CT	23/11/2023	23/11/2023	BR	COMPLETE
5	BC-05	62	H	KOLKATA	10/2/2022	CT	2/12/2023	2/12/2023	Control	COMPLETE
6	BC-06	60	H	KOLKATA	21/2/2022	CT	4/12/2023	4/12/2023	BR	COMPLETE
7	BC-07	51	H	NADIA	10/5/2022	CT+RT	5/12/2023	5/12/2023	Control	COMPLETE
8	BC-08	55	M	HOOGHLY	26/05/2022	CT	9/12/2023	9/12/2023	Control	COMPLETE
9	BC-09	49	M	E-MEDINIPUR	28/05/2022	CT+RT	21/12/2023	21/12/2023	BR	COMPLETE
10	BC-10	47	H	N-24 PGS	11/6/2022	CT+RT	4/1/2024	4/1/2024	Control	COMPLETE
11	BC-11	58	H	N-24 PGS	15/6/2022	CT	8/1/2024	8/1/2024	BR	COMPLETE
12	BC-12	60	H	N-24 PGS	23/06/2022	CT+RT	16/1/2024	16/1/2024	BR	COMPLETE
13	BC-13	52	H	KOLKATA	30/6/2022	CT	19/1/2024	19/1/2024	Control	COMPLETE
14	BC-14	51	H	NADIA	7/7/2022	CT	22/1/2024	22/1/2024	BR	COMPLETE
15	BC-15	62	H	N-24 PGS	23/7/2022	CT+RT	3/2/2024	3/2/2024	Control	COMPLETE
16	BC-16	44	M	NADIA	13/10/2022	CT+RT	12/2/2024	12/2/2024	BR	COMPLETE

17	BC-17	55	M	N-24 PGS	14/10/2022	CT+RT	17/2/2024	17/2/2024	Control	COMPLETE
18	BC-18	47	H	N-24 PGS	20/10/2022	CT	18/3/2024	18/3/2024	Control	COMPLETE
19	BC-19	63	M	N-24 PGS	21/10/2022	CT	20/4/2024	20/4/2024	BR	COMPLETE
20	BC-20	44	H	NADIA	29/10/2022	CT+RT	26/4/2024	26/4/2024	BR	COMPLETE
21	BC-21	47	M	N-24 PGS	5/11/2022	CT	29/4/2024	29/4/2024	Control	COMPLETE
22	BC-22	58	H	KOLKATA	14/10/2022	CT+RT	9/5/2024	9/5/2024	Control	COMPLETE
23	BC-23	42	H	KOLKATA	8/6/2022	CT+RT	13/5/2024	13/5/2024	BR	COMPLETE
24	BC-24	61	M	N-24 PGS	15/7/2022	CT	17/5/2024	17/5/2024	BR	COMPLETE
25	BC-25	47	H	HOWRAH	12/6/2022/	CT	20/5/2024	20/5/2024	Control	COMPLETE
26	BC-26	64	M	HOOGHLY	5/8/2022	CT	24/5/2024	24/5/2024	BR	COMPLETE
27	BC-27	48	M	N-24 PGS	10/12/2022	CT+RT	27/5/2024	27/5/2024	Control	COMPLETE
28	BC-28	52	H	N-24 PGS	6/1/2023	CT+RT	29/5/2024	29/5/2024	BR	COMPLETE
29	BC-29	49	H	S-24 PGS	12/2/2023	CT	3/6/2024	3/6/2024	Control	COMPLETE
30	BC-30	55	H	N-24 PGS	16/1/2023	CT+RT	6/6/2024	6/6/2024	Control	COMPLETE
31	BC-31	46	H	N-24 PGS	8/3/2023	CT	10/6/2024	10/6/2024	BR	COMPLETE
32	BC-32	62	M	HOOGHLY	7/6/2022	CT	12/6/2024	12/6/2024	Control	COMPLETE
33	BC-33	56	H	HOWRAH	9/12/2022	CT+RT	14/6/2024	14/6/2024	BR	COMPLETE
34	BC-34	36	H	N-24 PGS	1/4/2023	CT+RT	15/6/2024	15/6/2024	Control	COMPLETE
35	BC-35	62	H	N-24 PGS	19/3/2022	CT	19/6/2024	19/6/2024	BR	COMPLETE
36	BC-36	60	M	N-24 PGS	30/4/2023	CT	22/6/2024	22/6/2024	Control	COMPLETE
37	BC-37	49	H	W-MEDINIPUR	16/5/2022	CT+RT	24/6/2024	24/6/2024	BR	COMPLETE
38	BC-38	58	H	HOWRAH	26/9/2022	CT	29/6/2024	29/6/2024	BR	COMPLETE
39	BC-39	52	M	N-24 PGS	10/5/2023	CT+RT	1/7/2024	1/7/2024	Control	COMPLETE
40	BC-40	56	M	N-24 PGS	1/6/2023	CT	3/7/2024	3/7/2024	Control	COMPLETE
41	BC-41	66	H	KOLKATA	8/7/2023	CT+RT	19/8/2024	19/8/2024	BR	COMPLETE
42	BC-42	69	H	KOLKATA	1/9/2023	CT+RT	2/8/2024	2/8/2024	BR	COMPLETE
43	BC-43	66	H	S-24 PGS	21/11/2023	CT	2/8/2024	2/8/2024	Control	COMPLETE
44	BC-44	39	H	S-24 PGS	10/2/2024	CT	12/8/2024	12/8/2024	Control	COMPLETE

2. Demographic Information

Sl. No	Patient ID	Education	Marital status	Occupation	Total family income (INR)	Smoking habit	Tobacco chewing habit	Alcohol drinking habit	LMP (if any)	Child bearing condition
1	BC-01	3	1	3	3	0	0	0	NA	0
2	BC-02	2	1	3	2	0	1	0	NA	0
3	BC-03	3	1	4	2	0	0	0	NA	0
4	BC-04	2	1	3	2	0	0	0	NA	0
5	BC-05	1	2	3	1	0	0	0	NA	0
6	BC-06	2	1	3	2	0	1	0	NA	0
7	BC-07	2	1	3	2	0	0	0	NA	0
8	BC-08	2	1	3	2	0	0	0	NA	0
9	BC-09	1	2	3	2	0	1	0	NA	0
10	BC-10	1	1	3	1	0	0	0	NA	0
11	BC-11	2	1	3	2	0	0	0	NA	0
12	BC-12	3	1	4	1	0	0	0	NA	0
13	BC-13	3	1	4	2	0	1	0	NA	0
14	BC-14	1	2	3	2	0	0	0	NA	0
15	BC-15	1	1	3	3	0	0	0	NA	0
16	BC-16	2	1	3	2	0	0	0	NA	0
17	BC-17	1	1	3	2	0	0	0	NA	0
18	BC-18	2	1	3	2	0	0	0	NA	0
19	BC-19	3	1	4	2	0	1	0	NA	0
20	BC-20	2	2	3	2	0	0	0	NA	0
21	BC-21	2	1	4	2	0	0	0	NA	0
22	BC-22	2	1	3	1	0	1	0	NA	0
23	BC-23	1	1	3	1	0	0	0	NA	0
24	BC-24	2	1	3	1	0	0	0	NA	0

25	BC-25	1	1	3	2	0	0	0	NA	0
26	BC-26	2	1	4	1	0	1	0	NA	0
27	BC-27	2	1	3	2	0	0	0	NA	0
28	BC-28	1	2	3	3	0	1	0	NA	0
29	BC-29	2	1	3	2	0	0	0	NA	0
30	BC-30	2	1	3	3	0	1	0	NA	0
31	BC-31	2	1	3	2	0	0	0	NA	0
32	BC-32	2	1	3	2	0	1	0	NA	0
33	BC-33	2	1	3	2	0	0	0	NA	0
34	BC-34	2	1	4	2	0	0	0	NA	0
35	BC-35	2	1	3	2	0	0	0	NA	0
36	BC-36	2	1	3	3	0	1	0	NA	0
37	BC-37	2	1	3	2	0	0	0	NA	0
38	BC-38	2	1	4	2	0	0	0	NA	0
39	BC-39	1	1	3	2	0	1	0	NA	0
40	BC-40	2	1	3	2	0	1	0	NA	0
41	BC-41	2	1	3	2	0	1	0	NA	0
42	BC-42	1	1	3	2	0	1	0	NA	0
43	BC-43	1	1	3	3	0	0	0	NA	0
44	BC-44	1	1	3	2	0	0	0	NA	0

3. Comorbidities

Patient ID	Hypertension	Diabetes	Ischemic heart disease	Anemia	Asthma	Thyroidisms	GI & Liver problems	Renal problems	Neuropsychiatric disease	Anxiety/ Depression
BC-01	0	0	0	1	0	0	0	0	0	0
BC-02	0	0	0	0	0	0	0	0	0	0
BC-03	1	1	1	1	0	0	0	0	0	0
BC-04	0	0	0	1	0	0	0	0	0	0
BC-05	1	0	0	0	0	0	0	0	0	0
BC-06	1	1	0	0	0	0	0	0	0	0
BC-07	0	0	0	1	0	0	0	0	0	0
BC-08	0	0	0	0	0	0	0	0	0	0
BC-09	1	0	0	0	0	0	0	0	0	0
BC-10	0	0	0	1	0	0	0	0	0	0
BC-11	0	0	0	0	0	0	0	0	0	0
BC-12	1	0	0	0	0	0	0	0	0	0
BC-13	0	0	0	0	0	0	0	0	0	0
BC-14	1	1	0	0	0	0	0	0	0	0
BC-15	0	0	0	1	0	0	0	0	0	0
BC-16	0	0	0	0	0	0	0	0	0	0
BC-17	0	0	0	1	0	0	0	0	0	0
BC-18	1	0	0	0	0	0	0	0	0	0
BC-19	0	0	0	0	0	0	0	0	0	0
BC-20	1	0	0	0	0	0	0	0	0	0
BC-21	0	0	0	0	0	0	0	0	0	0
BC-22	0	0	0	0	0	0	0	0	0	0
BC-23	0	0	0	0	0	0	0	0	0	0
BC-24	0	0	0	1	0	0	0	0	0	0

BC-25	1	0	0	0	0	0	0	0	0	0
BC-26	0	0	0	0	0	0	0	0	0	0
BC-27	0	0	0	1	0	0	0	0	0	0
BC-28	1	1	0	0	0	0	0	0	0	0
BC-29	0	0	0	1	0	0	0	0	0	0
BC-30	1	0	0	0	0	0	0	0	0	0
BC-31	0	0	0	0	0	0	0	0	0	0
BC-32	0	0	0	1	0	0	0	0	0	0
BC-33	0	0	0	0	0	0	0	0	0	0
BC-34	0	0	0	1	0	0	0	0	0	0
BC-35	0	0	0	0	0	0	0	0	0	0
BC-36	1	1	0	0	0	0	0	0	0	0
BC-37	1	0	0	0	0	0	0	0	0	0
BC-38	0	0	0	1	0	0	0	0	0	0
BC-39	0	0	0	0	0	0	0	0	0	0
BC-40	0	0	0	1	0	0	0	0	0	0
BC-41	1	1	0	1	0	0	0	0	0	0
BC-42	1	0	0	1	0	0	0	0	0	0
BC-43	1	0	0	0	0	0	0	0	0	0
BC-44	1	0	0	1	0	0	0	0	0	0

4. Physical Examination

4.1 Group: CT-Control

Patient ID	Body Weight (kg)				Ht (cm)	BMI				PULSE (bpm)				BP (SYSTOLE)				BP (DIASTOLE)			
	Day 0	4 wk	8 wk	12 wk	Day 0	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
BC-02	60	58	58	59	162	23.4	22.6	22.6	23	88	88	87	87	118	110	120	122	88	85	80	78
BC-05	60	59	59	58	165	22	21.6	21.6	21.7	82	80	80	82	148	145	148	152	92	92	92	92
BC-08	52	50	50	49	162	19.8	19	19	18.6	78	76	76	78	116	118	115	115	76	75	78	75
BC-13	60	59	58	57	162	22.8	22.4	22.1	21.7	80	82	82	82	116	118	119	122	78	80	82	80
BC-18	62	60	58	58	162	23.6	22.8	22.1	22.1	86	84	86	86	155	150	152	150	88	85	86	88
BC-21	58	56	56	53	153	24.7	23.9	23.9	25.6	86	82	83	84	116	120	118	122	82	85	80	82
BC-25	54	50	50	50	153	23	21.3	21.3	21.3	80	80	82	84	150	148	145	150	92	94	90	90
BC-29	56	55	53	51	160	21.85	21.48	20.7	19.9	80	82	83	82	115	118	116	118	90	89	88	85
BC-32	62	60	60	59	162	23.6	22.8	22.8	22.4	84	85	85	84	116	119	118	120	78	82	80	76
BC-36	50	48	48	48	155	20.8	19.9	19.9	19.9	80	82	80	82	154	150	152	155	94	90	90	90
BC-40	62	60	60	59	162	18.2	18.6	18.6	19	88	85	84	84	119	122	125	120	82	84	84	84
BC-44	50	48	48	48	162	19.4	19	19	19	78	79	80	78	160	160	155	150	95	90	88	82

4. Physical Examination

4.2 Group: CT-BR

Patient ID	Body Weight (kg)				Ht (cm)	BMI				PULSE (bpm)				BP (SYSTOLE)				BP (DIASTOLE)			
	Day 0	4 wk	8 wk	12 wk	Day 0	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
BC-01	64	64	64	63	160	19.5	19.5	19.5	19.4	80	80	78	78	110	116	118	115	80	80	84	82
BC-04	55	55	56	56	158	22	22	22.4	22.4	78	78	78	78	122	120	122	124	82	80	80	80
BC-06	52	52	53	53	160	20.3	20.3	20.7	20.7	84	20.3	86	86	152	148	145	146	95	90	90	90
BC-11	56	55	55	55	153	23.9	23.4	23.4	23.4	76	76	78	78	121	119	122	120	86	85	84	82
BC-14	54	55	55	55	158	21.63	22	22	22	84	84	82	82	150	148	145	146	90	88	88	86
BC-19	60	60	61	61	165	22	22	22.4	22.4	88	86	88	88	120	128	125	124	78	82	75	76
BC-24	60	60	58	58	158	24	24	23.2	23.2	84	85	84	86	124	120	122	119	82	80	78	82
BC-26	59	56	55	55	155	24.5	23.3	22.9	22.9	75	78	75	75	122	118	124	126	83	82	85	80
BC-31	60	60	61	61	165	22	22	22.4	22.4	80	82	80	82	126	128	125	120	85	84	84	84
BC-35	55	55	55	54	162	20.9	20.9	20.9	20.5	88	90	92	92	119	122	122	125	78	80	82	82
BC-38	55	52	52	52	160	21.4	21	20.3	20.3	86	85	84	84	125	122	124	126	80	82	84	82
BC-43	55	55	55	54	158	24.8	24.8	24.4	24.4	82	80	79	80	142	138	135	130	88	85	88	86

4. Physical Examination

4.3 Group: RAD-Control

Patient ID	Body Weight (kg)				Ht (cm)	BMI				PULSE (bpm)				BP (SYSTOLE)				BP (DIASTOLE)			
	Day 0	4 wk	8 wk	12 wk	Day 0	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
BC-07	56	55	55	54	155	24.8	24.4	24.4	24	88	88	86	86	128	125	128	129	84	82	85	82
BC-10	50	48	47	48	158	20	19.2	18.82	19.2	86	86	86	84	126	120	125	122	85	84	85	84
BC-15	58	55	55	54	160	22.6	21.4	21.4	21	86	86	84	84	112	115	112	118	82	84	80	80
BC-17	60	58	55	55	155	24.9	24.1	22.9	22.9	78	82	82	80	124	120	122	124	84	80	85	82
BC-22	49	48	46	46	160	19.1	18.7	17.9	17.9	78	76	78	78	115	116	120	118	80	85	78	80
BC-27	58	55	55	54	162	22.1	20.9	20.9	20.5	80	82	86	84	124	122	128	125	80	82	82	82
BC-30	55	52	52	52	160	21.4	20.3	20.3	20.3	76	78	76	76	150	150	152	152	90	90	90	90
BC-34	62	60	60	59	162	23.6	22.8	22.8	22.4	72	74	75	74	126	115	124	126	86	82	84	85
BC-39	60	60	61	61	158	23.2	22	22	21.6	78	80	82	80	128	125	126	124	85	80	84	82
BC-41	64	63	62	62	160	20.3	20.3	20.3	19.5	84	82	81	80	150	154	148	150	90	90	88	92

4. Physical Examination
4.4 Group: RAD-BR

Patient ID	Body Weight (kg)				Ht (cm)	BMI				PULSE (bpm)				BP (SYSTOLE)				BP (DIASTOLE)			
	Day 0	4 wk	8 wk	12 wk	Day 0	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk	Day 0	4 wk	8 wk	12 wk
BC-03	58	56	55	55	155	25.7	24.8	24.4	24.4	84	82	82	83	140	138	135	138	92	95	95	90
BC-09	54	53	52	52	160	21.09	20.7	20.3	20.3	84	80	82	84	145	146	145	145	93	92	90	90
BC-12	49	48	48	47	155	20.4	19.8	19.8	19.5	72	70	70	72	142	145	146	145	92	90	90	90
BC-16	52	52	51	51	160	20.3	20.3	19.9	19.9	80	82	84	82	119	112	120	122	89	85	84	80
BC-20	58	55	55	55	165	21.3	20.2	20.2	20.2	84	82	84	84	160	155	156	185	92	90	90	90
BC-23	63	62	62	62	158	25.2	24.8	24.8	24.8	82	84	86	84	120	122	118	120	84	80	78	82
BC-28	46	46	46	47	155	19.1	19.1	19.1	19.5	82	84	84	85	142	142	140	145	92	94	92	94
BC-33	64	63	62	62	158	25.6	25.2	24.8	24.8	76	81	75	79	117	119	120	118	82	84	82	84
BC-37	56	55	53	51	158	20.8	21.2	21.2	21.6	84	84	85	85	148	145	146	145	95	95	95	94
BC-42	62	60	60	59	159	22.5	21.7	21.7	21.7	88	84	86	85	158	155	150	145	92	90	88	86

5. KPS Score

5.1 Group: CT-Control

SL. No.	Patient ID	CT CONTROL	Day 0	4 wk	8 wk	12 wk
2	**BC-02**	**CT-CONTROL**	60	60	60	70
5	**BC-05**	**CT-CONTROL**	50	50	60	60
8	**BC-08**	**CT-CONTROL**	50	50	50	60
13	**BC-13**	**CT-CONTROL**	50	60	60	70
18	**BC-18**	**CT-CONTROL**	50	50	50	60
21	**BC-21**	**CT-CONTROL**	50	60	70	70
25	**BC-25**	**CT-CONTROL**	60	60	70	70
29	**BC-29**	**CT-CONTROL**	50	60	60	60
32	**BC-32**	**CT-CONTROL**	50	60	70	70
36	**BC-36**	**CT-CONTROL**	50	60	60	70
40	**BC-40**	**CT-CONTROL**	50	60	70	70
44	**BC-44**	**CT-CONTROL**	50	60	70	80

5. KPS Score

5.2 Group: CT-BR

SL. No.	Patient ID	CT-Body Rev	Day 0	4 wk	8 wk	12 wk
1	BC-01	CT-BODY REV	50	70	80	100
4	BC-04	CT-BODY REV	50	60	70	80
6	BC-06	CT-BODY REV	60	70	80	100
11	BC-11	CT-BODY REV	50	60	70	80
14	BC-14	CT-BODY REV	50	60	70	90
19	BC-19	CT-BODY REV	60	70	80	90
24	BC-24	CT-BODY REV	50	60	80	90
26	BC-26	CT-BODY REV	60	70	90	100
31	BC-31	CT-BODY REV	50	70	90	100
35	BC-35	CT-BODY REV	50	70	80	80
38	BC-38	CT-BODY REV	50	60	80	90
43	BC-43	CT-BODY REV	50	60	80	90

5. KPS Score
5.3 Group: RAD-Control

SL. No.	Patient ID	RAD-Control	Day 0	4 wk	8 wk	12 wk
7	**BC-07**	**RAD-CONTROL**	60	70	70	70
10	**BC-10**	**RAD-CONTROL**	50	50	60	60
15	**BC-15**	**RAD-CONTROL**	60	60	70	70
17	**BC-17**	**RAD-CONTROL**	50	50	60	60
22	**BC-22**	**RAD-CONTROL**	50	50	60	60
27	**BC-27**	**RAD-CONTROL**	50	50	50	60
30	**BC-30**	**RAD-CONTROL**	50	60	60	60
34	**BC-34**	**RAD-CONTROL**	60	60	60	70
39	**BC-39**	**RAD-CONTROL**	50	60	60	60
41	**BC-41**	**RAD-CONTROL**	50	60	70	70

5. KPS Score

5.4 Group: RAD-BR

SL. No.	Patient ID	RAD-BRl	Day 0	4 wk	8 wk	12 wk
3	**BC-03**	**RAD-BODY REV**	50	60	70	90
9	**BC-09**	**RAD-BODY REV**	60	60	70	80
12	**BC-12**	**RAD-BODY REV**	50	70	80	90
16	**BC-16**	**RAD-BODY REV**	60	70	80	90
20	**BC-20**	**RAD-BODY REV**	50	60	70	70
23	**BC-23**	**RAD-BODY REV**	50	50	60	70
28	**BC-28**	**RAD-BODY REV**	60	60	80	90
33	**BC-33**	**RAD-BODY REV**	50	60	70	80
37	**BC-37**	**RAD-BODY REV**	60	70	80	90
42	**BC-42**	**RAD-BODY REV**	50	60	80	80

6. PFS

6.1 Group: CT-Control

CT CONTROL				Blood CA-15.3	
				U/ml	U/ml
			Age	Day 0	12 wk
2	**BC-02**	**CT-CONTROL**	45	16	14
5	**BC-05**	**CT-CONTROL**	62	15	10
8	**BC-08**	**CT-CONTROL**	55	7	10
13	**BC-13**	**CT-CONTROL**	52	13	14
18	**BC-18**	**CT-CONTROL**	47	22	18
21	**BC-21**	**CT-CONTROL**	47	18	20
25	**BC-25**	**CT-CONTROL**	47	21	20
29	**BC-29**	**CT-CONTROL**	49	22	18
32	**BC-32**	**CT-CONTROL**	62	20	16
36	**BC-36**	**CT-CONTROL**	60	14	12
40	**BC-40**	**CT-CONTROL**	56	14	10
44	**BC-44**	**CT-CONTROL**	39	12	14

6. PFS

6.2 Group: CT-BR

CT BR				Blood CA-15.3	
				U/ml	U/ml
			Age	Day 0	12 wk
1	BC-01	CT-BODY REV	53	19	10
4	BC-04	CT-BODY REV	54	8	6
6	BC-06	CT-BODY REV	60	16	10
11	BC-11	CT-BODY REV	58	18	12
14	BC-14	CT-BODY REV	51	17	8
19	BC-19	CT-BODY REV	63	18	10
24	BC-24	CT-BODY REV	61	16	8
26	BC-26	CT-BODY REV	64	20	7
31	BC-31	CT-BODY REV	46	14	6
35	BC-35	CT-BODY REV	62	13	10
38	BC-38	CT-BODY REV	58	18	8
43	BC-43	CT-BODY REV	66	11	12

6. PFS
6.3 Group: RAD-Control

RAD CONTROL				Blood CA-15.3	
				U/ml	U/ml
			Age	Day 0	12 wk
7	**BC-07**	**RAD-CONTROL**	51	10	14
10	**BC-10**	**RAD-CONTROL**	47	14	18
15	**BC-15**	**RAD-CONTROL**	62	14	16
17	**BC-17**	**RAD-CONTROL**	55	19	22
22	**BC-22**	**RAD-CONTROL**	58	17	19
27	**BC-27**	**RAD-CONTROL**	48	19	22
30	**BC-30**	**RAD-CONTROL**	55	18	20
34	**BC-34**	**RAD-CONTROL**	36	16	21
39	**BC-39**	**RAD-CONTROL**	52	20	19
41	**BC-41**	**RAD-CONTROL**	66	16	18

6. PFS

6.4 Group: RAD-BR

RAD BODY REVIVAL				Blood CA-15.3		CT Scan / USG	
				U/ml	U/ml		
			Age	Day 0	12 wk	Day 0	12 wk
3	**BC-03**	**RAD-BODY REV**	52	13	12	0	0
9	**BC-09**	**RAD-BODY REV**	49	12	10	0	0
12	**BC-12**	**RAD-BODY REV**	60	15	14	0	0
16	**BC-16**	**RAD-BODY REV**	44	18	10	0	0
20	**BC-20**	**RAD-BODY REV**	44	19	14	0	0
23	**BC-23**	**RAD-BODY REV**	42	14	10	0	0
28	**BC-28**	**RAD-BODY REV**	52	24	13	0	0
33	**BC-33**	**RAD-BODY REV**	56	20	12	0	0
37	**BC-37**	**RAD-BODY REV**	49	15	9	0	0
42	**BC-42**	**RAD-BODY REV**	69	15	10	0	0

7. QoL: Screening

7.1 Group: CT-Control

ID	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-02	17	14	19	14	4	6	4	5	2	2	87
BC-05	18	20	18	16	4	5	3	4	1	1	90
BC-08	18	23	20	18	3	6	6	4	1	2	101
BC-13	18	22	18	18	4	5	5	4	1	1	96
BC-18	15	26	18	16	4	7	5	4	1	1	97
BC-21	17	25	18	17	3	7	5	4	1	1	98
BC-25	18	26	15	15	3	7	4	5	1	1	95
BC-29	14	25	15	17	3	5	5	4	1	1	90
BC-32	18	20	16	18	5	6	4	3	1	2	93
BC-36	18	23	18	15	3	6	4	4	1	2	94
BC-40	17	20	18	18	4	7	4	4	1	1	94
BC-44	15	22	16	18	4	7	5	5	2	1	95

7. QoL: Screening
7.2 Group: CT-BR

ID	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-01	16	23	17	15	3	5	6	5	2	2	94
BC-04	18	18	19	16	4	7	4	5	2	1	94
BC-06	16	22	20	18	4	5	4	5	1	1	96
BC-11	18	23	13	19	5	7	6	5	2	1	99
BC-14	14	24	16	16	3	5	6	5	1	1	91
BC-19	18	24	16	15	4	5	3	5	1	2	93
BC-24	17	25	17	17	5	7	3	4	2	2	99
BC-26	15	25	16	16	5	6	4	4	2	1	94
BC-31	16	22	18	17	3	6	4	4	1	2	93
BC-35	18	22	18	16	4	6	4	4	1	2	95
BC-38	19	24	15	13	4	6	3	4	1	2	91
BC-43	17	20	18	18	4	7	5	3	1	2	95

7. QoL: Screening
7.3 Group: RAD-Control

ID	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-07	14	16	12	12	3	6	5	5	2	1	76
BC-10	12	24	18	12	4	7	5	6	1	2	91
BC-15	12	16	13	12	5	7	5	4	1	1	76
BC-17	14	16	14	11	3	6	4	4	1	2	75
BC-22	15	16	14	13	3	6	6	3	1	1	78
BC-27	12	17	14	14	5	7	3	3	2	1	78
BC-30	15	18	15	12	4	5	5	3	1	2	80
BC-34	12	18	16	12	4	7	5	4	1	2	81
BC-39	15	16	16	15	3	7	4	4	1	2	83
BC-41	14	16	12	11	4	7	5	3	1	2	75

7. QoL: Screening
7.4 Group: RAD-BR

ID	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-03	15	14	12	12	3	6	5	6	1	1	75
BC-09	15	17	18	10	3	5	5	6	1	1	81
BC-12	15	17	14	10	3	7	4	4	1	2	77
BC-16	15	17	13	12	3	5	4	6	1	1	77
BC-20	16	16	16	13	4	6	4	4	1	1	81
BC-23	16	15	13	12	4	7	5	4	1	2	79
BC-28	15	18	14	14	5	6	4	3	1	1	81
BC-33	12	16	15	13	4	6	5	3	2	2	78
BC-37	12	16	16	14	3	6	5	3	1	2	78
BC-42	14	16	14	12	4	6	4	3	1	1	75

8. QoL: 4 week

8.1 Group: CT-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-02	17	14	19	14	4	6	4	5	2	2	87
BC-05	18	20	18	16	4	5	3	4	1	1	90
BC-08	18	23	21	18	3	6	6	4	1	2	102
BC-13	18	22	18	18	4	5	5	4	2	1	97
BC-18	15	26	19	16	4	7	5	4	2	1	99
BC-21	17	25	18	17	3	7	5	4	2	1	99
BC-25	18	26	15	16	3	7	5	5	1	1	97
BC-29	15	25	16	17	3	5	5	4	2	1	93
BC-32	18	20	17	18	5	6	4	3	1	2	94
BC-36	20	23	19	15	3	6	4	4	2	2	98
BC-40	17	20	19	18	4	7	4	4	2	1	96
BC-44	15	22	17	18	5	7	5	5	2	1	97

8. QoL: 4 week

8.2 Group: CT-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-01	18	25	19	18	4	5	6	5	2	2	104
BC-04	20	22	22	18	5	7	4	5	2	1	106
BC-06	18	24	22	18	5	5	4	5	2	1	104
BC-11	20	25	15	21	5	7	6	5	2	1	107
BC-14	14	25	18	18	4	6	6	5	1	1	98
BC-19	18	26	17	16	5	5	4	5	1	2	99
BC-24	18	27	18	18	5	7	4	4	2	2	105
BC-26	16	26	18	17	5	6	4	4	2	1	99
BC-31	17	24	18	18	4	6	4	4	2	2	99
BC-35	18	23	22	16	4	6	4	4	2	2	101
BC-38	19	25	18	14	5	6	4	4	2	2	99
BC-43	18	22	22	19	4	7	5	3	1	2	103

8. QoL: 4 week

8.3 Group: RAD-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-07	14	18	12	12	3	6	5	5	2	1	78
BC-10	12	24	18	12	4	7	5	5	2	2	91
BC-15	12	17	14	12	5	7	5	4	2	1	79
BC-17	14	17	14	11	4	6	4	4	1	2	77
BC-22	15	16	14	13	4	6	6	3	2	1	80
BC-27	13	18	14	14	5	7	4	3	2	1	81
BC-30	16	18	15	13	4	5	5	3	2	2	83
BC-34	13	18	16	13	5	6	5	4	1	2	83
BC-39	16	17	17	15	3	7	5	4	1	2	87
BC-41	15	16	13	12	4	7	5	3	1	2	78

8. QoL: 4 week
8.4 Group: RAD-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-03	18	15	16	14	3	6	5	6	2	1	86
BC-09	15	18	19	12	4	5	5	6	2	1	87
BC-12	16	18	15	10	3	7	4	4	1	2	80
BC-16	17	18	15	13	4	5	4	6	2	1	85
BC-20	16	18	16	14	5	6	4	4	2	1	86
BC-23	16	18	14	12	5	7	5	4	2	2	85
BC-28	16	20	15	15	5	6	4	3	1	1	86
BC-33	13	18	17	14	4	6	5	3	2	2	84
BC-37	14	16	18	14	4	6	5	3	1	2	83
BC-42	14	17	16	12	5	5	4	3	2	1	79

9. QoL: 8 week

9.1 Group: CT-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-02	18	15	20	15	4	6	4	5	2	2	91
BC-05	18	20	18	17	4	6	4	4	3	1	95
BC-08	18	23	21	18	4	6	6	4	1	2	103
BC-13	19	22	18	18	4	5	5	4	2	1	98
BC-18	15	26	19	17	4	7	6	4	2	1	101
BC-21	18	25	18	17	4	7	5	4	2	1	101
BC-25	18	27	17	16	3	7	5	5	3	1	102
BC-29	15	25	16	17	4	6	5	4	3	1	96
BC-32	18	20	19	18	5	6	4	3	1	2	96
BC-36	20	23	20	15	3	6	4	4	2	2	99
BC-40	17	20	21	18	4	7	4	4	2	1	98
BC-44	15	23	20	18	4	8	5	5	2	1	101

9. QoL: 8 week

9.2 Group: CT-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-01	22	29	23	19	5	6	6	5	2	2	119
BC-04	24	25	22	18	5	7	4	5	3	1	114
BC-06	23	27	22	22	5	5	5	5	2	1	117
BC-11	22	29	20	21	5	7	6	5	2	1	118
BC-14	20	27	23	19	5	6	6	5	3	1	115
BC-19	22	27	23	17	6	6	5	5	2	2	115
BC-24	20	29	23	19	5	7	5	5	3	2	118
BC-26	22	28	21	17	5	6	4	4	2	1	110
BC-31	21	28	22	19	5	6	5	4	2	2	114
BC-35	22	26	24	17	4	7	5	4	2	2	113
BC-38	23	29	23	15	5	7	5	4	3	2	116
BC-43	22	24	26	20	5	7	6	4	2	2	118

9. QoL: 8 week

9.3 Group: RAD-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
7	16	18	14	13	4	6	5	5	2	1	84
10	13	24	18	13	4	7	6	6	2	2	95
15	13	19	14	13	5	7	5	5	2	1	84
17	14	19	15	11	4	6	4	4	3	2	82
22	16	17	16	13	4	6	6	4	2	1	85
27	14	19	16	15	5	7	4	5	2	1	88
30	16	18	15	13	4	6	5	3	2	2	84
34	14	18	17	13	5	7	6	4	1	2	87
39	16	17	18	15	4	8	5	4	2	2	91
41	15	16	15	13	4	7	5	3	2	2	82

9. QoL: 8 week
9.4 Group: RAD-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-03	18	19	18	18	4	6	5	6	3	1	98
BC-09	17	22	22	15	4	6	5	6	2	1	100
BC-12	17	22	16	11	4	7	4	4	1	2	88
BC-16	19	20	19	14	4	5	5	6	2	1	95
BC-20	18	22	20	15	5	6	4	4	2	1	97
BC-23	18	22	19	13	5	7	5	4	2	2	97
BC-28	19	22	15	15	5	6	4	5	2	1	94
BC-33	15	22	23	14	5	7	5	4	2	2	99
BC-37	18	16	23	16	4	7	5	4	3	2	98
BC-42	17	22	20	14	4	8	6	4	3	1	99

10. QoL: 12 week

10.1 Group: CT-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-02	19	20	21	15	4	6	5	5	2	2	99
BC-05	19	22	20	17	4	6	4	5	3	2	102
BC-08	19	24	21	18	4	7	6	4	2	2	107
BC-13	20	24	18	18	4	5	5	5	3	2	104
BC-18	17	26	20	18	5	7	6	5	3	1	108
BC-21	19	25	20	17	4	7	6	4	2	2	106
BC-25	20	27	20	17	4	7	5	5	3	2	110
BC-29	18	25	18	18	4	6	5	5	3	2	104
BC-32	19	20	19	18	5	7	4	3	2	2	99
BC-36	22	23	20	16	4	6	4	4	2	2	103
BC-40	20	21	21	18	4	7	4	4	2	1	102
BC-44	19	23	20	18	4	8	5	5	3	2	107

10. QoL: 12 week
10.2 Group: CT-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-01	24	33	27	20	6	6	6	6	3	3	134
BC-04	27	30	25	18	5	7	5	5	3	2	127
BC-06	24	34	26	22	5	6	6	6	3	1	133
BC-11	26	34	26	22	5	7	6	5	3	2	136
BC-14	25	35	27	20	6	7	6	6	3	2	137
BC-19	26	32	25	20	6	7	6	6	3	2	133
BC-24	25	33	27	21	5	7	5	6	3	3	135
BC-26	27	34	26	20	5	6	5	6	3	1	133
BC-31	27	34	26	19	5	6	5	6	3	3	134
BC-35	26	32	27	18	5	7	5	6	2	2	130
BC-38	27	34	26	16	5	7	6	4	3	2	130
BC-43	27	30	29	20	5	7	6	6	2	2	134

10. QoL: 12 week

10.3 Group: RAD-Control

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-07	20	18	16	14	4	6	5	5	2	2	92
BC-10	18	24	19	14	4	7	6	6	2	2	102
BC-15	16	19	15	15	5	7	5	5	3	1	91
BC-17	17	19	16	14	5	6	5	4	3	2	91
BC-22	19	17	17	15	4	7	6	5	3	2	95
BC-27	18	19	16	16	5	7	5	5	2	2	95
BC-30	18	20	15	15	4	7	5	3	2	2	91
BC-34	19	18	17	15	5	7	6	5	2	2	96
BC-39	19	17	18	15	4	8	6	4	3	2	96
BC-41	18	17	16	13	5	7	5	5	2	2	90

10. QoL: 12 week
10.4 Group: RAD-BR

	General	Physical	Psychological	Familial	Cognitive	Economic	Optimism	Informational	Physician relationship	Body image	Total
	32	40	32	28	8	12	8	8	4	4	176
BC-03	22	29	22	20	5	6	6	6	3	2	121
BC-09	20	28	24	19	5	6	5	6	2	2	117
BC-12	21	30	22	16	4	7	4	4	1	2	111
BC-16	23	30	23	18	5	6	6	6	3	2	122
BC-20	22	30	23	18	5	6	4	4	2	1	115
BC-23	22	29	22	16	5	7	6	6	3	2	118
BC-28	23	28	20	16	5	6	6	5	3	1	113
BC-33	20	30	24	16	5	7	6	6	3	2	119
BC-37	23	28	24	17	4	7	5	5	3	2	118
BC-42	26	27	21	18	5	8	6	5	3	2	121

11. Hematology

11.1 Group: CT-Control

Patient ID	Hct		Hb%		RBC		WBC		Platlet		N		L		M		E	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-02	36	37	10.5	10.8	3.6	3.7	5.5	5.5	2.2	2.4	38	40	50	48	5	6	7	6
BC-05	38	38	10.2	10.5	3.7	3.7	5	5.1	2	2.5	36	40	52	50	5	4	6	5
BC-08	39	40	11	11.2	3.8	3.8	4.6	4.8	1.8	2	38	38	49	54	6	4	5	4
BC-13	37	37	10.4	10.5	3.7	3.8	4.8	5	2.3	2.5	36	40	52	50	4	4	7	6
BC-18	36	36	11.2	11.4	3.9	3.9	6.1	6.2	2.4	2.8	34	35	53	54	5	4	7	6
BC-21	37	37	11.2	11.4	3.9	3.9	4.2	4.5	2.4	2.5	36	38	54	52	3	4	6	6
BC-25	35	36	10.6	10.8	3.6	3.7	4.5	4.6	2.1	2.5	34	38	56	53	3	3	6	6
BC-29	30	31	8.4	8.8	3.2	3.4	5	5	1.7	1.9	24	30	66	59	3	4	6	6
BC-32	33	34	8.2	9	3.5	3.6	5.8	5.7	2.8	2.7	24	30	65	62	5	3	6	5
BC-36	37	37	10.8	10.5	3.5	3.5	5.4	5.5	1.6	2	34	38	58	52	3	4	4	5
BC-40	32	32	8.5	8.6	3.5	3.5	5.7	5.8	2.1	2.2	24	30	66	63	5	3	4	4
BC-44	33	34	8.4	8.9	3.2	3.4	5.2	5.4	2	2.4	24	31	65	60	4	4	6	4

11. Hematology
11.2 Group: CT-BR

Patient ID	Hct		Hb%		RBC		WBC		Platlet		N		L		M		E	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-01	33	37	8.8	10	3.4	3.7	4.5	5	2.5	3	25	36	64	58	4	3	6	3
BC-04	33	38	9.4	10.2	3.4	3.8	4.6	5.1	2.3	2.8	22	38	67	54	6	3	5	3
BC-06	38	38	10.6	11.5	3.7	3.8	5.1	5.6	2.5	3	32	40	58	54	4	3	6	3
BC-11	37	38	10.2	11.8	3.9	3.9	5.2	5.5	2.3	2.8	32	42	54	50	5	4	7	4
BC-14	36	38	10	11.2	3.7	3.9	5.2	5.8	2.1	2.7	32	40	57	53	4	3	6	3
BC-19	35	39	10.5	11.4	3.8	3.8	5.4	5.8	2.3	2.6	38	42	49	51	7	4	4	3
BC-24	31	35	8.2	9.8	3.2	3.5	4.6	5.2	2	2.6	22	38	67	56	5	3	6	3
BC-26	35	39	11	12	3.6	3.8	6.4	6.5	1.8	2.8	34	40	57	54	4	3	5	3
BC-31	36	36	12	12.2	4	4	4.7	5.2	2	2.9	30	38	64	54	2	4	4	3
BC-35	36	37	11.6	11.8	3.7	3.7	4.9	5.4	2.2	3.1	32	38	59	55	4	4	4	3
BC-38	34	37	8.7	10	3.6	3.8	6.3	6.4	1.9	2.4	20	36	71	58	4	4	5	2
BC-43	36	39	10.6	11.8	3.4	3.6	5.7	6.2	1.9	2.8	34	39	55	53	4	5	7	2

11. Hematology

11.3 Group: RAD-Control

Patient ID	Hct		Hb%		RBC		WBC		Platlet		N		L		M		E	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-07	32	34	8.7	9.2	3.4	3.5	4.8	5	1.9	2.2	22	30	67	59	4	4	7	6
BC-10	30	33	8.6	9.1	3.1	3.5	4.5	4.9	2.4	2.5	24	30	66	60	4	4	6	6
BC-15	33	34	8.5	9.4	3.4	3.6	4.6	5	2	2.4	20	28	70	63	4	3	5	6
BC-17	32	35	8.8	9.5	3.4	3.6	5.7	5.8	2	2.2	23	30	67	59	5	4	5	6
BC-22	37	37	11	11.8	3.9	3.7	4.6	5	1.8	2.1	34	35	54	56	4	4	7	5
BC-27	32	34	8.6	9.1	3.4	3.6	4.7	5	2	2.2	22	36	66	55	5	4	7	5
BC-30	35	35	11.6	11.8	3.8	3.8	4.6	4.8	1.6	1.9	30	35	61	56	4	4	4	5
BC-34	35	36	8.4	9.2	3.4	3.5	5.3	5.5	1.7	1.8	22	30	68	62	5	3	5	5
BC-39	37	37	11.1	11.5	3.9	3.8	5.3	5.5	2.3	2.4	32	35	54	56	8	4	5	4
BC-41	34	36	8.8	9.4	3.5	3.6	4.9	5.1	1.8	2.4	22	30	69	62	5	4	4	4

11. Hematology
11.4 Group: RAD-BR

Patient ID	Hct		Hb%		RBC		WBC		Platlet		N		L		M		E	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-03	32	37	9.2	10.5	3.2	3.7	4.2	5	2.1	2.9	20	38	69	53	4	5	6	4
BC-09	39	4	11.5	12.8	3.8	4	6.1	6.8	2	2.8	35	40	54	52	5	4	6	4
BC-12	36	37	10.4	11.6	3.8	3.8	5.5	6.5	1.9	2.6	30	41	61	52	3	4	6	3
BC-16	37	39	11	11.8	3.9	3.9	5.5	6.7	2.1	3	34	40	54	52	6	4	5	3
BC-20	36	38	11.5	12.4	3.7	3.8	5.2	6.3	1.7	2.8	32	42	58	52	5	3	4	3
BC-23	35	37	10.8	11.6	3.8	3.9	4.8	5.9	1.7	2.8	32	41	58	53	5	3	5	3
BC-28	37	4	11.4	12.2	3.9	3.9	4.6	5.5	2.3	3	30	39	61	55	4	3	5	2
BC-33	36	39	12.2	12.8	4	4.1	4.8	5.7	2.3	3	32	42	58	51	4	4	5	3
BC-37	37	39	10.6	11.7	3.5	3.8	5.6	6.4	2.6	3.1	30	40	58	53	6	4	5	3
BC-42	34	36	8.2	10	3.2	3.7	4.8	5.7	1.7	2.9	24	38	63	52	5	5	7	4

12. Biochemistry

12.1 Group: CT-Control

Patient ID	Protein		Albumin		ALP		AST		ALT		BUN		Creatine	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-02	5.2	6	3.8	3.8	160	148	74	70	44	42	8	9	0.9	0.9
BC-05	5.7	6	3.2	3.5	152	140	58	50	74	70	14	13	0.8	0.9
BC-08	4.8	5.5	2.9	3.2	84	90	67	60	50	44	11	12	0.8	0.8
BC-13	5.8	6	3.1	3.4	110	95	72	68	52	45	12	12	0.8	0.9
BC-18	5.2	5.5	3.1	3.5	87	90	92	74	60	50	14	15	0.9	0.8
BC-21	5.6	5.8	3.5	3.7	107	92	56	50	59	40	12	12	0.9	0.9
BC-25	6.2	6.3	3.5	3.6	62	68	34	30	40	42	14	15	1.2	1.3
BC-29	5.5	5.6	2.7	3	88	94	62	58	46	42	11	12	0.8	0.9
BC-32	5.9	6	3	3.2	82	90	21	30	28	30	15	14	0.9	0
BC-36	5.7	6	3	3.5	155	140	56	45	43	40	9	10	0.7	0.8
BC-40	6.2	6.2	3.5	3.7	172	152	72	60	50	48	14	12	0.8	0.8
BC-44	5.2	5.8	3.5	3.8	150	132	58	48	62	54	14	13	0.8	0.7

12. Biochemistry
12.2 Group: CT-BR

Patient ID	Protein		Albumin		ALP		AST		ALT		BUN		Creatine	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-01	5	6	3.1	3.8	162	130	65	55	56	42	12	10	0.8	0.8
BC-04	5.5	6.5	3	3.8	148	122	69	50	62	40	10	12	1	0.9
BC-06	5.9	6.8	3.2	3.9	108	90	67	52	60	45	9	10	0.9	0.8
BC-11	5.3	6.5	3.4	4	95	68	66	54	43	38	14	10	0.8	0.7
BC-14	6.2	6.8	3.6	4	155	104	70	55	40	35	16	12	0.9	0.9
BC-19	5.1	6.4	3.2	3.8	98	67	62	50	57	39	18	12	1.1	1
BC-24	5.7	6.5	3.4	3.9	82	62	29	30	32	30	15	10	0.8	0.9
BC-26	5.4	6.4	2.8	3.7	75	60	30	34	29	34	9	10	1.1	1
BC-31	5	6.2	2.7	3.5	65	52	29	36	34	30	9	9	1	1
BC-35	5.4	6.7	2.5	3.6	156	111	48	40	44	40	14	10	0.7	0.8
BC-38	5.9	6.8	3.2	3.6	162	134	69	50	48	39	12	11	0.8	0.9
BC-43	5.6	6.5	3.1	3.7	149	108	62	48	57	40	11	10	0.8	0.8

12. Biochemistry
12.3 Group: RAD-Control

Patient ID	Protein		Albumin		ALP		AST		ALT		BUN		Creatine	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-07	6.1	6.2	3.1	3.2	155	140	80	70	68	60	12	11	1.2	1.3
BC-10	5	5.2	3.5	3.6	118	106	75	70	50	48	13	12	0.5	0.6
BC-15	6.1	6.2	3.7	3.8	160	142	64	60	47	50	14	14	0.8	0.7
BC-17	5.8	6	3.2	3.5	51	60	32	34	39	44	15	13	1.1	1
BC-22	5.6	5.8	3	3.2	158	140	50	42	43	40	14	12	0.8	0.9
BC-27	5.6	5.9	2.7	3	150	130	56	50	39	42	12	13	0.9	1
BC-30	5.3	5.8	2.5	3	119	110	73	66	38	35	15	15	0.9	1
BC-34	5.5	5.8	2.7	3	69	62	37	40	35	30	15	14	0.7	0.8
BC-39	6	6.1	3.6	3.7	165	144	70	60	52	48	10	11	1.2	1
BC-41	5.2	5.8	2.9	3.4	180	152	88	70	43	44	10	11	1.1	1

12. Biochemistry
12.4 Group: RAD-BR

Patient ID	Protein		Albumin		ALP		AST		ALT		BUN		Creatine	
	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final	Day 0	Final
BC-03	4.6	5.8	2.9	3.5	155	130	82	50	55	45	11	10	1.1	1
BC-09	5.6	6.2	3.5	3.6	93	70	86	46	44	40	8	9	0.9	0.8
BC-12	5.4	6.2	3.2	3.6	58	60	28	32	48	40	11	10	0.7	0.8
BC-16	6	6.5	3.7	3.8	124	110	72	50	52	44	16	12	1.1	1
BC-20	5	6	3.5	3.8	116	95	67	52	62	45	15	10	1.2	1
BC-23	6.1	6.6	3.6	3.7	75	80	64	40	48	40	16	14	1	0.8
BC-28	5.8	6.4	2.6	3.5	164	130	54	45	42	38	10	10	0.8	0.9
BC-33	5.2	6.2	2.8	3.7	70	58	32	38	40	42	14	12	0.9	0.9
BC-37	5.5	6.1	3.1	3.8	148	130	64	45	46	40	14	12	0.8	0.8
BC-42	5.3	6	2.8	3.7	145	128	70	50	48	40	14	12	1.1	1

13. AEs

	CT DAY 0	CT 12 WK	CT BR DAY 0	CT BR 12 WK	RAD DAY 0	RAD 12 WK	RAD BR DAY 0	RAD BR 12 WK
1. Anorexia	10	8	12	1	10	8	10	2
2. Constipation	8	8	10	1	8	7	7	2
3. Diarrhoea	4	0	2	0	2	0	3	0
4. Dizziness	12	10	12	1	10	8	10	1
5. Dry skin	10	7	10	2	10	8	10	1
6. Fatigue	12	9	12	1	10	7	10	2
7. Hot flashes/flushes	12	9	12	0	10	8	10	1
8. Muscle weakness	10	7	10	1	10	8	10	1
9. Nausea	12	9	10	0	8	5	10	0
10. Pruritus/itching	8	6	9	0	8	5	9	0
11. Rash: erythema multi-form	9	5	6	0	8	5	9	1
12. Vomiting	10	7	5	0	8	6	10	1

Appendix-VIII

Clinical Trial Protocol: HR-BR-BC0523

Study Broad Title:	12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Study Brief Title:	12 Weeks Intervention of Body Revival in Breast Cancer Patients
Study Number:	HR-BR-BC0523
Product Name:	Body Revival
Product License:	HP-177-AY
Indication:	Breast Cancer
Sponsor:	Health Reactive Excellency Bldg, 1st Floor, Opp. MTNL 4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053 Office Tel: 26399871-85 (15 Lines) Office Email: info@healthreactive.com Website: www.healthreactive.com
Sponsor Contact:	Mr. Munish Khan CEO, Health Reactive Excellency Bldg, 1st Floor, Opp. MTNL 4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053 Office Tel: 26399871-85 (15 Lines) Office Email: info@healthreactive.com
Trial Site:	Research Unit J. B. Roy State Ayurvedic Medical College & Hospital Dept. of Health & Family Welfare (AYUSH), Govt. of W.B. The West Bengal University of Health Sciences (Affiliated) 170-172 Raja Dinendra Street, Shyambazar, Kolkata 700004 Office Tel: 2554545417 Office Email: jbrsamc_2008@rediffmail.com Website: www.wbhealth.gov.in/contents/jbroy_college wbuhs.ac.in/Affiliated%20Courses/j-b-roy-state-ayurvedic-medical-college-hospital/
Trial Investigators:	Dr. Srikanta Pandit, M.D (Ay.), Ph.D Dr. Tuhin Kanti Biswas, M.D (Ay)., Ph.D Dr. Utpalendu Jana, M.D (Ay).
Protocol No. & Version:	HR-BR-BC0523; Version 1.0
Date:	June 6, 2023

Clinical Trial Study Team:

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Study Team Members:	Trial Personnel (by Contractual Appointment)
Contact Personnel:	Prof. (Dr.) Supriyo Chaudhuri, MD (Ay.), Ph.D Principal, J. B. Roy State Ayurvedic Medical College & Hospital Tel.: 9330814091; Email: chaudhuridrsupriyo@gmail.com
Trial Coordinator:	Dr. Tapas Kumar Sur, MSc, Ph.D Tel.: 8017575428; Email: drtapaskumarsur@gmail.com
Sponsor's Representative:	Mr. Munish Khan, CEO, Health Reactive Office Tel: 26399871-85 (15 Lines) Office Email: info@healthreactive.com

Study Synopsis:

1. **Sponsor:**
   Health Reactive
   Excellency Bldg, 1st Floor, Opp. MTNL
   4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053

2. **Name of the Finished Product:**
   Body Revival

3. **Type of the Product:**
   Ayurvedic formulation

4. **Product License:**
   HP-177-AY

5. **Study Number:**
   HR-BR-BC0523

6. **Study Title:**
   12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study

7. **Brief Title:**
   12 Weeks Intervention of Body Revival in Breast Cancer Patients

8. **Primary Objective(s):**
   To assess the effect of selected dose of Body Revival on breast cancer patients in combination with / or without regular therapeutic regimen to improve quality of life (QoL) and progression free survival (PFS) and counteract the affirmed side effects

9. **Secondary Objective(s):**
   - To assess the effect of Body Revival on subject reported on Quality of Life (QoL)
   - To assess the effect of Body Revival on Karnofsky Performance
   - To assess the effect of Body Revival on CA-15.3 defined PFS and serologic response, based on Krebs et al (1987) criteria
   - To assess the effect of Body Revival on complete blood haemogram
   - To assess the safety and tolerability of Body Revival
   - To assess the effect of Body Revival on adverse events, based on CTCAE v.5 criteria

10. **Exploratory Objective(s)**
    Examinations of serological, biochemical and radiological markers as a surrogate for interventive therapeutic response

11. Study Design:

This is a single centre, open label, randomized, case-control, longitudinal, cross sectional cohort study with single dose of Body Revival (6 ml, oral, in every six alternative day) on breast cancer post surgery recovery patients in combination with / or without regular therapeutic regime to assess the effectiveness of Body Revival supplement to prolong PFS and improvement of QoL. Randomization will be stratified by 1:1 treatment vs. case control of selected four arms. The groups or arms will be as follows:

- Arm I: Radiotherapy (RT) + Body Revival
- Arm II: RT + Control
- Arm III: Chemotherapy (CT) + Body Revival
- Arm IV: CT + Control

All selected subjects will be randomized within 6 months after surgery and will receive standard therapy after their surgery. Additionally, Arm I and Arm III will receive interventive test medicine for 12 weeks, while Arm II and Arm IV without interventive medicine. All subjects will be examined and monitored for consecutive 12 weeks. Follow-up schedule visit period will be:

- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

12. Study Population:

Approximately 48 subjects at single site with radiotherapy and chemotherapy treated post-operative breast cancer of greater than 1 and no more than 6 months from their surgery and chemotherapy/radiotherapy will be randomized.

13. Test Drug, Dose and Mode of Administration:

Body Revival suspension, per oral, 6 ml (one teaspoon) in every 6th alternative day before going to bed (preferably in night)

14. Duration of Treatment:

12 Weeks

15. Trial Duration:

12 months

16. Efficacy & Safety Assessments:

- Physical examinations (including vital signs)
- Subject reported on Quality of Life (QoL)
- Karnofsky Performances
- Progression free survival (PFS) based on serologic CA-15.3 response
- Complete blood haemogram
- Clinical laboratory tests (serum chemistry)
- Radiological assessments (CT-Scan)
- Adverse events (AEs)

17. Statistical Methods:

For the primary efficacy analyses, multiplicity for the comparison of Body Revival vs. control group will adjusted so that the study level type I error rate controlled to be lower than 0.05 significance level. Specific testing procedures which maintain the study level type I error rate at a lower level for this purpose are specified in statistical analysis plan.

- Intent-to-Treat Population (ITT), defined as all randomized subjects. This is the primary analysis population for all efficacy endpoints.
- Safety Analysis Set (SAS), defined as all randomized subjects who will received at least one dose of study drug and who has at least one safety assessment following the first follow up, analyzed by the treatment received.
- Evaluable population defined as all randomized subjects who has baseline and at least one on-treatment assessment performed.

18. Primary Efficacy Endpoint Evaluation:

- PFS is defined as the time from the randomization to the date of the first observation of progression based on the independent radiologic (X-ray/CT-Scan) or serologic CA-15.3 assessments. PFS will be analysed between treatment groups vs. case control groups.
- Subject reported QoL and Karnofsky Performances are the other efficacy endpoints. Pair-wise comparisons between treatment groups vs. case control groups will be conducted.
- Blood corpuscles (RBC & WBC) are the important parameters of bone marrow suppression during Chemotherapeutic/Radiotherapeutic treatments in cancer patients. In this study, comparisons between treatment groups vs. case control groups will be conducted.
- Significant reduction of Chemotherapeutic/Radiotherapeutic treatments related systemic adverse events (AEs) by supplementary interventive medicine will be also be considered.

19. Secondary Endpoint Evaluation:

- Hypersensitivity (drug hypersensitivity) and Tolerability of interventive medicine will be considered as secondary endpoints.

20. Sample Size Calculation:

Sample size considerations are base on epidemiological information. The overall incidence rate is 12.5%. There is no recent reliable report of the incidence of breast cancer in Kolkata. Hence it is assumed with an overall type I error rate of 0.05 will has at least 70% power of 12.5% population proportion. The sample size is considered to 48. This means 48 (12 in each arm) or more measurements are needed to have a confidence level of 70% that the real value is within ±5% of the measured value.

Confidence interval	Margin of error	Population proportion	Sample size
95%	5%	12.5%	169
90%	5%	12.5%	120
85%	5%	12.5%	91
80%	5%	12.5%	72
70%	**5%**	**12.5%**	**48**

Undertaking by the Investigators:

We agree to conduct the study in accordance with the current protocol.

We will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favourable opinion from the ethics committee of the amendment, except where necessary to eliminate an immediate hazard to the trial subject or when the changes involved are only logistical or administrative in nature.

We will maintain confidentiality of the identification of all participating subjects and assure security and confidentiality of study data.

Signature of the Investigators:

1. Dr. Srikanta Pandit:

2. Prof. (Dr.) Tuhin Kanti Biswas:

3. Prof. (Dr.) Utpalendu Jana:

Signature of Head of the Institution

Glossary of Terms

Stages of breast cancer: After diagnosed breast cancer, the stage of the cancer has to be established. The stage helps determine the prognosis and the best treatment options. Stage 0, which is non-invasive ductal carcinoma *in situ* (DCIS), and stages I through IV, which are used for invasive breast cancer. Stage IV breast cancer (metastatic breast cancer) indicates that it has spread to other parts of the body. The stage of the cancer may be determined after surgery. Breast cancer stages also takes into account the cancer's grade; the presence of tumor markers, such as receptors, for estrogen, progesterone and HER2; and proliferation factors.

Tests and procedures used to stage breast cancer: (i) Blood tests, such as a complete blood count; (ii) Mammogram of the other breast to look for signs of cancer; (iii) Breast CT scan/MRI

Treatment Procedures:

(i) Surgeries-

(a) Lumpectomy: During a lumpectomy, which is also referred to as breast-conserving surgery or wide local excision, the surgeon removes the tumor and a small margin of surrounding healthy tissue. A lumpectomy may be recommended for removing smaller tumors. For larger tumors, patients may have to undergo chemotherapy to shrink the tumor to make it possible to remove it by a lumpectomy procedure.

(b) Mastectomy: A mastectomy is an operation to remove breast tissue completely. Most mastectomy procedures remove the lobules, ducts, fatty tissue and some skin, nipple and areola (total or simple mastectomy). Newer surgical techniques such as skin-sparing mastectomy and nipple-sparing mastectomy are increasingly becoming common.

(c) Sentinel node biopsy: The surgeon will remove the lymph nodes that are the first to receive the lymph drainage from the tumor, to determine whether cancer has spread to the lymph nodes. If the tests are negative, no other nodes will need to be removed as there is very little chance of finding cancer in any of the remaining nodes.

(d) Axillary lymph node dissection: In case, cancer is found in the sentinel lymph nodes, the surgeon will remove additional lymph nodes in the armpit.

(e) Contralateral prophylactic mastectomy: Some women with cancer in one breast may choose to have their other healthy breast removed, because of a genetic predisposition or strong family history of cancer.

(ii) Therapy-

(a) Radiation therapy: Radiation therapy uses high-energy, such as X-rays and protons, to destroy undetectable cancer cells and reduce the risk of cancer recurring. Breast cancer radiation can last from three days to six weeks, depending on the treatment. The kinds of radiation therapy that may be considered are –

- External beam breast cancer radiation is most commonly used. A machine outside the body aims a beam of radiation on the area affected.
- Internal breast cancer radiation is newer treatments that inject radioactive cancer-killing treatments only in the affected area.
- Brachytherapy (internal radiation) delivered through an implantable device, which is placed inside the breast during surgery or shortly thereafter which carries targeted radiation to the tumor bed.

Side effects of radiation therapy include fatigue and a red, sunburn-like rash where the radiation is aimed. Breast tissue may also appear swollen or more firm. Rarely, more-serious problems may occur, such as damage to the heart or lungs or, very rarely, second cancers in the treated area.

(b) Chemotherapy:

- **Adjuvant therapy -** Chemotherapy uses drugs to destroy the fast-growing cancer cells. If the cancer has a high risk of returning or spreading to another part of the body, doctors may recommend chemotherapy after surgery to decrease the chance of the cancer recurring.
- **Neo-adjuvant therapy -** Chemotherapy is sometimes given before surgery for women with larger breast tumors to shrink the tumor to a size to make it easier to remove with surgery.

Chemotherapy has some side effects depending on the drugs given. Hair loss, nausea, vomiting, fatigue and an increased risk of developing an infection are the common side effects. Rare side effects can include premature menopause, infertility (if premenopausal), damage to the heart and kidneys and nerve damage.

(c) Hormone therapy:

Hormone therapy is used to treat breast cancers that are sensitive to hormones. These cancers are referred to as estrogen receptor positive (ER positive) and progesterone receptor positive (PR positive) cancers. It can be used before or after surgery or other treatments to decrease the chance of the cancer recurring. If the cancer has already spread, hormone therapy may shrink and control it. Treatments that can be used in hormone therapy include:

- Medications that block hormones from attaching to cancer cells: selective estrogen receptor modulators
- Medications that stop the body from making estrogen after menopause: aromatase inhibitors
- Surgery or medications to stop hormone production in the ovaries

Hormone therapy side effects depend on your specific treatment, but may include hot flashes, night sweats and vaginal dryness. More serious side effects include a risk of bone thinning and blood clots.

(d) Targeted therapy:

Targeted drug treatments attack specific abnormalities within cancer cells without harming normal cells. This therapy may block the action of an abnormal protein (such as HER2) that stimulates the growth of breast cancer cells.

(e) Immunotherapy:

Immunotherapy employs the patient's immune system to combat the disease when the body's immune system which normally battles illness may not attack the cancer cells because they generate proteins that render the immune system cells blind. Immunotherapy might be an option for triple-negative breast cancer, which means that the cancer cells do not have receptors for estrogen, progesterone or HER2. Immunotherapy is combined with chemotherapy to treat advanced cancer that has spread to other parts of the body.

(f) Palliative care:

Palliative care is specialised medical care that provides relief from pain and other symptoms of serious illness through surgery, chemotherapy, or radiation. When it is used along with other treatments, people with cancer may feel better and live longer. The aim is to improve the quality of life for people with cancer. This form of care is offered along with curative or other treatments the patient may be receiving.

(g) Alternative medicine:

Till date no alternative medicine treatments have been found to cure breast cancer. But complementary and alternative medicine therapies may help to cope with the side effects of treatment when combined with the doctor's care. Many breast cancer survivors experience fatigue that can continue for many years. Complementary and alternative medicine therapies may help relieve fatigue, pain, anxiety and other serious side effects of conventional therapy of breast cancers.

Table of Contents

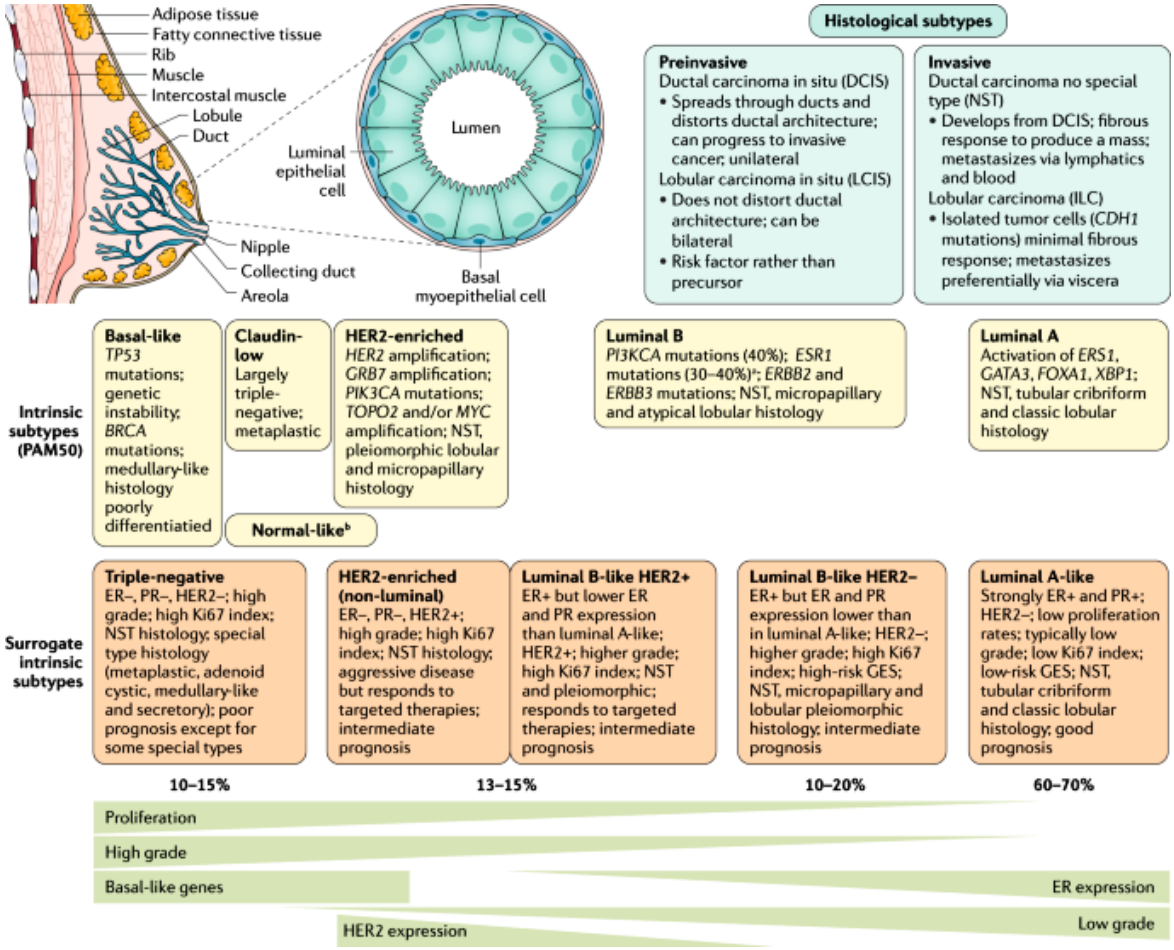
[1] Introduction

Cancer is a term implicated for an uncontrolled cell division that may invade nearby tissues and spread to other body parts via blood and lymph systems. The major risk factors for this disease include age, family history, hormones, tobacco use, irradiations, chronic inflammation, diet, and sedentary lifestyle. The leading risk factors contributing to global cancer burden in 2019 were behavioural, whereas metabolic risk factors found the largest increases between 2010 and 2019 (GBD 2019 Cancer Risk Factors Collaborators, 2022). The Cancer registry specifies 18.1 million new cases and 10 million global deaths due to cancer in 2020. The most common cancers are breast, lung, colorectal and prostate, contributing 12.5%, 12.2%, 10.7% and 7.8% respectively to the total number of new cases diagnosed in 2020 (Sung H et al., 2021).

Breast cancer is the most common cancer diagnosed worldwide, with an estimated 2.3 million new cases in 2020 alone (American Cancer Society; 2021). Incidence rates have historically been elevated in higher human development index (HDI) countries in North America and Western Europe, reflecting a longstanding prevalence of reproductive, hormonal, and lifestyle risk factors in these regions. However, breast cancer incidence has been rising in Asian countries like Japan, China and India where rates have historically been low (Cardoso F et al., 2018). Recent data suggest, 1 in 9 Indians has a lifelong risk of developing cancer. The most common malignancies among men and women, respectively, were lung and breast cancers (Kumar SK et al., 2022).

It is well established that cancer cells display significant difference in their metabolic pathways than the normal cells. Furthermore, the tumor microenvironment and the amount of oxygen and nutrients available for uptake have a major impact on tumor cell metabolism. The major hallmarks of cancer cells are 'self-sufficiency in growth signals', 'insensitivity to anti-growth signals', 'evasion of apoptosis', 'limitless replicative potential', 'sustained angiogenesis', 'tissue invasion and metastasis', 'deregulating cellular energetics and metabolism' and 'avoiding immune destruction' (Hanahan D, Weinberg RA, 2011). The microenvironment at the invasive front of tumors is significantly different than that of the tumor core (Quail DF, Joyce JA, 2013). Excessive fatty acid metabolism is one of the key hallmarks for several breast cancer types exhibiting fat metabolism-based therapeutic opportunities (Ruidas B et al., 2022).

Breast cancer is a genetically and clinically heterogeneous disease. Unlike colon cancers, defining the progression of breast cancer has not been possible due to lack of markers that define hyperplasia (typical and atypical), carcinoma *in situ* and invasive cancer (Malhotra GK et al., 2010). There has been much progress in our understanding of the pathology and molecular biology of breast cancer in the last few years. In 2012, WHO updating and classified breast cancers based on traditional tumor classification, precursor lesions, lesions of low malignant potential, benign epithelial proliferations, fibroepithelial, myoepithelial and mesenchymal neoplasms, among others (IARC, 2012). In contrast to Ductal carcinoma *in situ* (DCIS), where the use of molecular markers is still debated, the utility of ER, PR and HER2/neu is well accepted for infiltrating ductal carcinoma (IDC) and it is recommended that their status be determined on all invasive carcinomas (Harris L et al., 2007). Now-a-days five main molecular classes of breast cancer are recognized: Luminal A, Luminal B, HER2, Basal and Unclassified (Shawarby MA et al., 2016).



Breast cancer is treated in 5 ways, depends on the kind of breast cancer and how far it has spread. These are surgery (removal of cancer tissue), chemotherapy (special medicines to kill the cancer cells), hormonal therapy (blocks cancer cells), radiation therapy (high-energy rays to kill the cancer cells) and biological therapy (improve immune system to fight cancer cells or to control side effects from other cancer treatments)(WHO, 2006). But the disadvantages associated with these treatments exceed their desired therapeutic outcomes. For instance, an increased wound complication with damage to surrounding tissues during radiation therapy, site-specific complications with more risks of infections after surgery, and systemic toxicities following systemic therapy are few of the uncontrolled circumstances reported after treatment. Single or more than one type of treatments is frequently given to patients with breast cancer. All the chemotherapeutic medicines and radiation therapy have serious side effects including anorexia, vomiting, abdominal pain, diarrhea, hot flashes, headache, dyspnea, skin rash, fever, back pain, muscle cramps, fatigue, dizziness, edema (periorbital & peripheral) etc. (NIH, 2023; CDC, 2023; ACS, 2023). To overcome these barriers, numerous herbal medicines are being used in combination with chemotherapy or radiotherapy to improve the efficacy of cancer therapy and reduce side effects and complications (Yin SY, et al., 2013; Abdullah ASM, et al., 2003; Dash MK, 2021). Clinical trials for herbs and herbal products are also increasing where studies are performed to evaluate the effectiveness and therapeutic safety (Ahmad R, et al., 2020).

The word "cancer" was coined by a Greek physician, Hippocrates (460–370 BC). He used the terms "carcino" and "carcinoma" to describe non-ulcer forming and ulcer-forming tumours (ACS, 2018). Prior to that, two well-known Ayurvedic classics from India, *Charaka*

Samhita and *Sushruta Samhita*, refer to cancer as either an inflammatory or non-inflammatory swelling and refer to it as either *Granthi* (a little neoplasm) or *Arbuda* (a big neoplasm). The tissues are affected by aggravated *Vata* and *Kapha doshas*, which leads to the development of a round, hard, big, deeply rooted, slowly expanding fleshy growth accompanied by slight pain. Based on the aggravating *dosha* and the tissue implicated, Ayurveda has identified six different types of tumours: *Vataj, Pittaj, Kaphaj, Medoj, Mamsaj,* and *Raktarbuda* (CCRAS, 2023). Various Ayurvedic scriptures provide detailed descriptions of numerous remedies for both internal and exterior neoplasms (Balachandran P, Govindarajan R, 2005). Ayurvedic remedies work to strengthen the body's natural defences and immunity, revitalise important body systems, and encourage long-term recovery from illness (Arnold, 2022).

Numerous research investigations have been carried out based on data from folk and traditional medicines across the globe, using modern approaches for finding anticancer medications from natural resources. Several anticancer drugs extracted from plant sources after purification are tested in both *in vitro* and *in vivo* models and then sent to clinical trials (Sinha K, et al., 2021). Newman and Cragg reported that of 98 new small-molecule anticancer drugs that had been approved by the US Food and Drug Administration (FDA) between 1981 and 2010, only 20 were synthetic. The remaining 78 drugs either were natural products (11) or were derived from natural products (67) based on a series of classifications (Newman DJ, Cragg GM, 2010). The substances of natural origin that exhibit antitumor or anticancer properties belong to various groups of compounds, such as alkaloids, diterpenes, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, etc. (Subramaniam et al. 2019). The amount of data regarding the use of herbal products in cancer clinical trials at times creates a great challenge for oncologists to prescribe or counsel patients. It urges critical evaluation of the quality of clinical trials. On the basis of three commonly used scales, namely the Jadad, Delphi, and Cochrane scales, Ahmad and his colleagues (2020) have critically analysed clinical trials for herbs used in cancer, and they found that only 16.4% of the studies had excellent quality, mostly because suitable research design was lacking.

The cancer patients experience a variety of symptoms. Inadequate management of symptoms might hamper the performance of the daily activities of an individual. The quality of life (QoL) is one of the most concerning health issues for oncology patients. WHO defines QoL as "an individual's perception of their position in life in relation to their goals, expectations, standards, and concerns in the context of the culture and value systems in which they live". QoL is a specific and multidimensional type of patient-reported outcomes (PROs) which is perceived by patients as something that encompasses the patients' social, financial, psychosocial, and physical activities (Nayak MG et al., 2017). To evaluate the QoL of cancer patients in an Indian context, the majority of researchers employed the QoL questionnaire version II, which was created and validated by Latha et al. (2011) and has a reliability of 0.90 Cronbach's alpha and 0.80 split-half reliability. Despite chemotherapy having a therapeutic effect, it is associated with the development of severe unfavorable drug reactions which can have adverse effects on the QoL of an individual. Moreover, anticancer therapy requires an extended duration of administration to obtain the required effect. Frequent hospitalizations put an undue burden on cancer patients. Thus, anticancer therapy engenders a colossal personal, mental, and emotional anguish among cancer individuals, affecting their overall QoL (Ramasubbu et al., 2021). Herbal medicines in general are applied to hopefully increase the therapeutic benefit and QoL. The treatment of symptoms will help relieve the suffering and improve the QoL (Alam MM et al., 2020).

Progression-free survival (PFS) is defined as the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical

benefit for drug approvals. Living longer is the priority for patients with breast cancer and the time when disease is not progressing is meaningful when coupled with improvements in QoL and no added treatment toxicity (Mertz S et al., 2022).

Serum tumor marker CA15.3 antigen (a protein derived from transcription of the MUC1 gene) is commonly used in conjunction with imaging provides a cost-effective way of supporting the diagnosis of breast cancer and also monitoring the response of the disease to therapy. CA15.3 has been reported to be raised in up to 80% of patients of breast cancer (Duffy et al., 2000; Gaughran et al., 2020).

The Karnofsky Performance Status (KPS) is a widely used method to assess the functional status of a patient. It was introduced by David A. Karnofsky and Joseph H. Burchenal in 1949 (Karnofsky DA, Burchenal JH., 1949). The KPS describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death). In the last three decades years various studies have demonstrated the prognostic value of the KPS, primarily for various cancers (Schag CC, et al., 1984). Furthermore, independent of the role it plays in treatment modality decisions, the KPS has also established itself as a salient prognostic factor in a variety of tumor entities, including breast cancers (Marechal R, et al., 2007). The importance of the KPS as a tool for assessing QoL is a regularly discussed topic in the relevant literatures (Peus D, et al., 2013).

An Ayurvedic medicine, Body Revival® has been developed to treat cancers. The nine natural ingredients of Body Revival® are selected from the Indian traditional medicine as mentioned in the Ayurvedic Pharmacopoeia of India (API, 2008). It contained (5 ml) pure water extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Rubia cordifolia* root (200 mg), *Cucumis melo* seed (200 mg), *Symplocos racemosa* stem bark (95 mg) and honey (Q.s). It is used to improve the body's immune mechanism, repair damaged tissues, rejuvenate healthy cells and helpful to improve QoL and enhance longevity in cancer patients in the last 25 years. The Ayurvedic texts, modern researches, laboratory based information, *in silico* computational analysis, animal trials and case reports on cancer patients supported its claims (Appendix: VII). Currently, the impact of Body Revival® on chemotherapy or radiotherapy regimens in patients with breast cancer will be explored for its synergistic role to improve quality of life (QoL) and progression free survival (PFS) as also to counteract the side effects affirmed by regular therapeutic regimen following longitudinal cross sectional Cohort study.

Rationale of the Study/Key Questions

- Does Body Revival® adjunct therapy enhance the Quality of Life (QoL) of breast cancer patients?
- Does Body Revival®'s adjuvant therapy improve breast cancer patients' progression-free survival (PFS)?
- Does Body Revival®'s adjunct therapy helps breast cancer patients who have side effects from their standard treatment plan?
- Do patients with breast cancer benefit in any way from Body Revival®'s adjunct therapy?

[2] Study Objectives

Primary Objective(s):

To assess the effect of selected dose of Body Revival® on breast cancer patients in combination with / or without regular therapeutic regimen (such as chemotherapy, radiotherapy or surgery) to improve quality of life (QoL) and progression free survival (PFS) and counteract the affirmed side effects.

Secondary Objective(s):

- To assess the effect of Body Revival® on subject reported on Quality of Life (QoL)
- To assess the effect of Body Revival® on Karnofsky Performance
- To assess the effect of Body Revival® on CA-15.3 defined PFS and serologic response, based on Krebs et al (1987) criteria
- To assess the effect of Body Revival® on complete blood haemogram
- To assess the safety and tolerability of Body Revival®
- To assess the effect of Body Revival® on adverse events, based on CTCAE v.5 criteria

Exploratory Objective(s)

Examinations of serological, biochemical and radiological markers as a surrogate for interventive therapeutic response

Study Utility

- Development of an ideal safe therapeutic intervention for breast cancer patients.

[3] Investigational Plan

This is a single centre, open label, randomized, case-control, longitudinal, cross sectional cohort study.

The study will be conducted from the Research Unit, Department of Kayachikitsa, J.B. Roy State Ayurvedic Medical College and Hospital under Department of Health & Family Welfare (AYUSH), Govt. of West Bengal, Kolkata, India.

The Study Team will be as follows:

Principal Investigator:	Dr. Srikanta Pandit, MD (Ay.), Ph.D
Associate Investigators:	Prof. (Dr.) Tuhin Kanti Biswas, MD (Ay.), Ph.D
	Prof. (Dr.) Utpalendu Jana, MD (Ay.)
Consultant Oncologist:	Prof. (Dr.) Himangsu Roy, M.D., M.S.
Associate Members:	Trial Personnel (by Contractual Appointment)
Contact Personnel:	Prof. (Dr.) Supriyo Chaudhuri, MD (Ay.), Ph.D
Trial Coordinator:	Dr. Tapas Kumar Sur, MSc, Ph.D

The study plan will be reviewed and be approved by the Institutional Ethics Committee. The enrollment of the study participants will be started after staff recruitments. The approved protocol will be registered in *Clinical Trials Registry of India* (www.ctri.nic.in).

The study will be performed in compliance with "Good Clinical Practice for Clinical Trials", ICMR, Govt. of India (2017) and relevant SOPs of Institutional Ethics Committee of

J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata for research involving human subjects. Institutional Ethics Committee will be reviewed the project work in due time.

The confidentiality of the identification of all participants will be maintained. Security and confidentiality of study data will be assured and not disclose to any unauthorized parties.

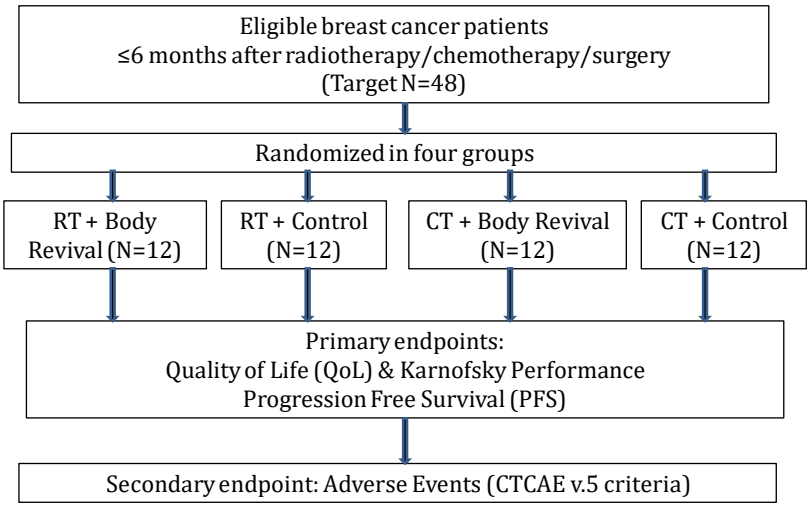
The eligible patients will be randomized into four following arms/groups:

- Arm I: Radiotherapy (RT) + Body Revival®
- Arm II: RT + Control
- Arm III: Chemotherapy (CT) + Body Revival®
- Arm IV: CT + Control

Randomization will be stratified by 1:1 treatment vs. case control of selected four arms.

All selected subjects will be randomized within 1-6 months after surgery/radiotherapy. They will receive standard treatment protocol. Additionally, Arm I and Arm III will receive interventive test medicine for 12 weeks, while Arm II and Arm IV without interventive medicine.

The interventive medicine Body Revival® will be given with a single dose level, *i.e.*, 6 ml or one teaspoon, oral, in every sixth alternative day up to 12 weeks. Hence, 14±1 doses of Body Revival® will be administered to the chosen patients during this time (12 weeks/84 days). Control groups will not receive Body Revival® but will be allowed their regular conventional therapy, if any. Control groups will also be eligible to attend scheduled follow-ups.



Study Design Overview

All subjects will be examined and monitored for consecutive 12 weeks. Follow-up schedule visit period will be:

- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

[4] Study Population Selection

The site will randomise 48 adult female patients with breast cancer (stage II–IV) who have experienced a remission (treatment free interval) of not more than six months following their initial course of chemotherapy, radiation, or surgery.

Subjects will be

- 18 years of age or older
- With a histologically or cytologically confirmed diagnosis of breast cancer (stage II–IV)
- Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months
- Not relapsed during recruitment
- Subjects may not have received Body Revival® or any herbal medicine

Sample size considerations are based on epidemiological information. The overall incidence rate is 12.5%. There is no recent reliable report of the incidence of breast cancer in Kolkata. Hence it is assumed with an overall type I error rate of 0.05 will has at least 70% power of 12.5% population proportion. The sample size is considered to 48. This means 48 (12 in each arm) or more measurements are needed to have a confidence level of 70% that the real value is within ±5% of the measured value.

Confidence interval	Margin of error	Population proportion	Sample size
95%	5%	12.5%	169
90%	5%	12.5%	120
85%	5%	12.5%	91
80%	5%	12.5%	72
70%	**5%**	**12.5%**	**48**

Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study

- Female subjects ≥ 18 years
- A histologically or cytologically confirmed diagnosis of breast cancer (stage II–IV)
- Or must have history of measurable disease by CT or MRI scan
- Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months
- Must have no report of relapsed
- Life expectancy of ≥12 months as estimated by the Investigators
- Other significant medical conditions must be well-controlled and stable in the opinion of the Investigators for at least 30 days prior to Study Day 1
- Subjects must provide written informed consent and be able to comply with the protocol procedures

Exclusion Criteria

Each subject must meet the following criteria to be enrolled in this study

- Clinically significant CNS, hepatic, cardio-respiratory or immunogenic problems
- Pregnant woman and lactating mother
- Subjects have received Body Revival® or any herbal medicine

[5] Study Treatments

The test article is a polyherbal Ayurvedic proprietary medicine in suspension named Body Revival®. This medicine will be used as adjunct/supplements in breast cancer survivors.

Treatment groups: 6 ml or one teaspoon of Body Revival® will be given in every sixth alternative day up to 12 weeks. Hence, 14±1 doses of Body Revival® will be administered to the chosen patients during this time (12 weeks/84 days). Regular treatments (if any) will not be hampered and will be recorded in the CRF (Case Record Form). A single dose will be applied. No dose alteration or acceleration of interventive medicine will be permitted.

Control groups: No interventive medicine will be given. Regular treatments (if any) will not be hampered and will be recorded in the CRF (Case Record Form; Appendix: II).

All recruited participants (n=48, including dropouts) will be blindly randomized into any of the four arms of the treatment and control groups. Each arm will comprise at least 12 participants (including dropouts). Randomization will be stratified by 1:1 treatment vs. case control of selected four arms, as first come first service (sequential manner) and maintained by one of the investigators in the team (preferably one of the Associate Investigators). He will be solely responsible for blinding/masking part of the trial and to keep this information confidential from other members of the study team.

[6] Study Procedures

Informed Consent

Prior to any study-specific Screening evaluation each subject will be informed in detail about the study agent to be administered and the nature of clinical investigation with its risks and discomforts to be expected. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the clinical trial at any time without prejudice.

Written informed consent will be obtained from each subject to be involved in the clinical trial by using the Institutional Ethics Committee (IEC)-approved ICF (Appendix: I). The investigator will verify that the subject has granted consent. Each subject will be given a copy of the signed ICF. Translated (Bengali-Hindi) ICF will be provided. Subjects, who will agree to sign in ICF will only be included in the study.

Medical History

A complete medical history will be obtained at Screening within 30 days prior to the first dose of test article, Body Revival®. The subject's medical history will be recorded in the Medical History section of the CRF.

Physical Examination

A complete physical examination will be performed at Screening within 30 days prior to the first dose of the test article, Body Revival®, and Follow-up visits (4 week interval), including the end of treatment (12 weeks).

Vital Signs, Body Weight and Height

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) and body weight will be collected at the time points listed below:

- At the Screening Visit
- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Height will be measured on all subjects only on Screening Visit.

Quality of Life (QoL) Status

Quality of Life status will be measured at the following time points (Appendix: V):

- At the Screening Visit
- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Karnofsky Performance Status (KPS)

KPS will be measured at the following time points (Appendix: III):

- At the Screening Visit
- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Progression Free Survival Status (PFS)

Progression Free Survival Status (PFS) will be measured by CA-15.3 in blood at the following time points (Appendix: IV):

- At the Screening Visit
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Radiological Assessments

CT scan will be measured at the following time points:

- At the Screening Visit
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Complete Blood Haemogram (CBC):

CBC will be measured in blood at the following time points:

- At the Screening Visit
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Clinical Laboratory Tests

Liver function and renal function tests will be measured at the following time points:

- At the Screening Visit
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

List of Clinical Laboratory Tests

Haematology	
• Hematocrit (Hct)	Automated Cell Counter (HORIBA-PENTRA ES 60)
• Hemoglobin	Automated Cell Counter (HORIBA-PENTRA ES 60)
• Platelet count	Automated Cell Counter (HORIBA-PENTRA ES 60)
• Red blood cell count	Automated Cell Counter (HORIBA-PENTRA ES 60)
• White blood cell count	Automated Cell Counter (HORIBA-PENTRA ES 60)
• Neutrophil	Microscopic, Olympus
• Lymphocyte	Microscopic, Olympus
• Monocytes	Microscopic, Olympus
• Eosinophil	Microscopic, Olympus
• Basophil	Microscopic, Olympus
Serum Chemistry	
• CA-15.3	ELISA (BIOBASE-EL10A)
• Total protein	Automated Analyser (ADVIA, Siemens)
• Albumin	Automated Analyser (ADVIA, Siemens)
• Alkaline phosphatase	Automated Analyser (ADVIA, Siemens)
• Alanine aminotransferase	Automated Analyser (ADVIA, Siemens)
• Aspartate aminotransferase	Automated Analyser (ADVIA, Siemens)
• Blood urea nitrogen	Automated Analyser (ADVIA, Siemens)
• Creatinine	Automated Analyser (ADVIA, Siemens)

Adverse Events (AEs)

Regular conventional cancer treatment related Adverse Events (AEs) and any untoward hypersensitivity will be measured by CTCAE v.5 criteria (Appendix: VI) at the following time points:

- At the Screening Visit
- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Assessing Severity of AEs	
Mild or Grade I	Transient or mild discomfort, no limitation in activity; no medical intervention/therapy required
Moderate of Grade II	Mild to moderate limitation in activity, some assistance may be needed; no or minimum medical intervention/therapy required
Severe or Grade III	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible
Life threatening or Grade IV	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care possible
Death or Grade V	Death

[7] Study Activities

Visit time points are intended as targets, variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Schedule visits are as follows:

- At the Screening Visit
- 1st Follow-up: 4 wks after randomization (± 5days)
- 2nd Follow-up: 4 wks after 1st Follow-up (± 5days)
- 3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

The schedule of events is mentioned as follows:

Screening Visit

Prior to any screening evaluations, written informed consent must be obtained. All screening procedures are to be completed within 30 days prior to the first dose of test article, Body Revival®. The following procedures are to be performed:

- Review and signed ICF
- Review inclusion/exclusion criteria
- Medical history taken
- Physical examination
- QoL assessments
- KPS score
- Radiological assessments
- Blood sampling for CA-15.3 and other haematological and clinical laboratory tests
- Record any adverse events that occur after informed consent is signed

Blood Sample: Maximum 10 ml of blood will be withdrawn by vein puncture in fasting condition, kept into different vials (EDTA/Clot) and preserved until use. For CA-15.3 test, serum will be preserved at -80^{0}C in the site laboratory until estimate.

Treatment Visit

After screening, the subjects will be randomized and dispensed 1 bottle of 100 ml Body Revival® at baseline (Visit 1) by the Principal Investigator. The subjects will return the bottle at the 4-week and investigator team find the residual content. They will return this bottle at the 8-week follow up visit and investigator team find the residual content. Finally they will return the bottle at the 12-week follow up. Adherence will be determined by measuring the amount and by response to the question "On how many days, approximately, did you miss your study medication?"

Visit 1 (Base line): Randomization

The following procedures are to be performed:

- Study medicine dispensing

Follow-up 1: 4 wks after randomization (± 5days)

The following procedures are to be performed:

- Physical examination
- Vital Signs and Body Weight
- QoL assessments
- KPS score
- Record any adverse events
- Concomitant medications record

Follow-up 2: 4 wks after 1st Follow-up (± 5days)
The following procedures are to be performed:

- Physical examination
- Vital Signs and Body Weight
- QoL assessments
- KPS score
- Record any adverse events
- Concomitant medications record

Follow-up 3: 4 wks after 2nd Follow-up (± 5days)
The following procedures are to be performed:

- Physical examination
- QoL assessments
- KPS score
- Radiological assessments
- Blood sampling for CA-15.3 and other haematological and clinical laboratory tests
- Record any adverse events
- Concomitant medications record

[8] Data Collection

The following events/measures are to be followed during data collection:

- Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigators.
- The investigators will be responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.
- All the data will be captured and/or transcribed into paper CRF - including clinical data (including AEs, concomitant medications) and laboratory data.
- Data reported in the CRF derived from source documents should be consistent with the source documents.
- All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. BLACK INK IS REQUIRED TO ENSURE CLARITY OF REPRODUCED COPIES.
- Adverse events must be graded, assessed for severity and causality, and reviewed by the site Investigators or designee.
- Clinical efficacy will be assessed by examining the improvement score at treatment endpoint.
- Security and confidentiality of study data will be assured and not to disclose to any unauthorized parties.
- A completer analysis of clinical efficacy will also be performed, and a sensitivity analysis on participants who are at least 90% adherent during the course of the study.
- All other efficacy and safety outcomes will be assessed in completer analyses because imputation of missing data in these contexts would be scientifically meaningless.

[9] Statistical Evaluation

For the primary efficacy analyses, multiplicity for the comparison of Body Revival vs. control group will adjusted so that the study level type I error rate controlled to be lower than 0.05 significance level. Specific testing procedures which maintain the study level type I error rate at a lower level for this purpose are specified in statistical analysis plan.

- Intent-to-Treat Population (ITT), defined as all randomized subjects. This is the primary analysis population for all efficacy endpoints.
- Safety Analysis Set (SAS), defined as all randomized subjects who will received at least one dose of study drug and who has at least one safety assessment following the first follow up, analyzed by the treatment received.
- Evaluable population defined as all randomized subjects who have baseline and at least one on-treatment assessment performed.
- Categorical data between the baseline and post treatment will be compared with the $\chi 2$ test, and continuous data will be analyzed by ANOVA and post-hoc analysis where applicable.
- Alpha for statistical significance will be set at $p<0.05$.

[10] Activity Grid

The Visit Schedule of Study and Assessment:

	Screening/ Visit-1		Visit-2 4 week	Visit-3 8 week	Visit-4 12week
Review and signed ICF	√				
Review inclusion/exclusion criteria	√				
Medical history	√				
Physical examination	√		√	√	√
QoL assessments	√		√	√	√
KPS score	√		√	√	√
Radiological assessments	√				√
PFS (CA-15.3)	√				√
Haematological examination	√				√
Clinical laboratory tests	√				√
Randomization		√			
Dispensing of study medicine		√			
Adverse events (AEs/SEs)*		√	√	√	√

[11] Administrative Considerations

Institutional Ethics Committee

The study protocol, sample ICF, and any other documents that pertain to subject information, recruitment methods etc. will be reviewed and approved by the Institutional Ethics Committee. The investigators will submit written summaries of the clinical trial status to IEC after end of the study.

Clinical Trial Registration

The approved protocol will be registered in Clinical Trials Registry of India.

State of Compliance

The study will be performed in compliance with "Good Clinical Practice for Clinical Trials", ICMR, Govt. of India (2017)29 and relevant SOPs of Institutional Ethics Committee of J.B. Roy State Ayurvedic Medical College & Hospital, Kolkata for research involving human subjects.

Confidentiality Statement

The confidentiality of the identification of all participants will be maintained. Security and confidentiality of study data will be assured and not disclose to any unauthorized parties.

Insurance Coverage

The study will be INSURED under Health Insurance Policy of Clinical Trial for all participants to compensate any accidental injury or death arising as a result of study-related procedures as per the rules and regulation of clinical research by ICMR, Govt. of India (2017).

Study Monitoring

The sponsor's representative will be allowed, on request, to inspect the various records of the clinical trial (i.e. CRF, source documents and any other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

Role of Sponsor

The study sponsor is Health Reactive, Excellency Bldg, 4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053. The sponsor will approve the study for technical merit. The sponsor will supply the study medications. They will provide financial support for the execution of the study. The sponsor will have no other role in the execution of the study or in the conduct of the analysis of data.

Financial Disclosure

Investigators are required to provide full disclosure of any financial relationship to the sponsor prior to participation in any trial related activities.

Publication Policy

In signing the final protocol, every participating investigator agrees to keep all information and results concerning the clinical trial and investigational product confidential. If applicable, the results of this clinical trial will be published and/or presented at scientific meetings in a timely manner.

Information about Test Drug

The study sponsor is Health Reactive, Mumbai will be provide the information and data report about test drug including chemical standardization, safety data, preclinical study reports, previous clinical trial report (if any) etc. A summary of investigational product is given in the Appendix-VIII.

Clinical Study Report

A final study report will be prepared that is compliant with the ICH guidelines and will be submitted to the study sponsor, Health Reactive, Mumbai.

[12] Reference List

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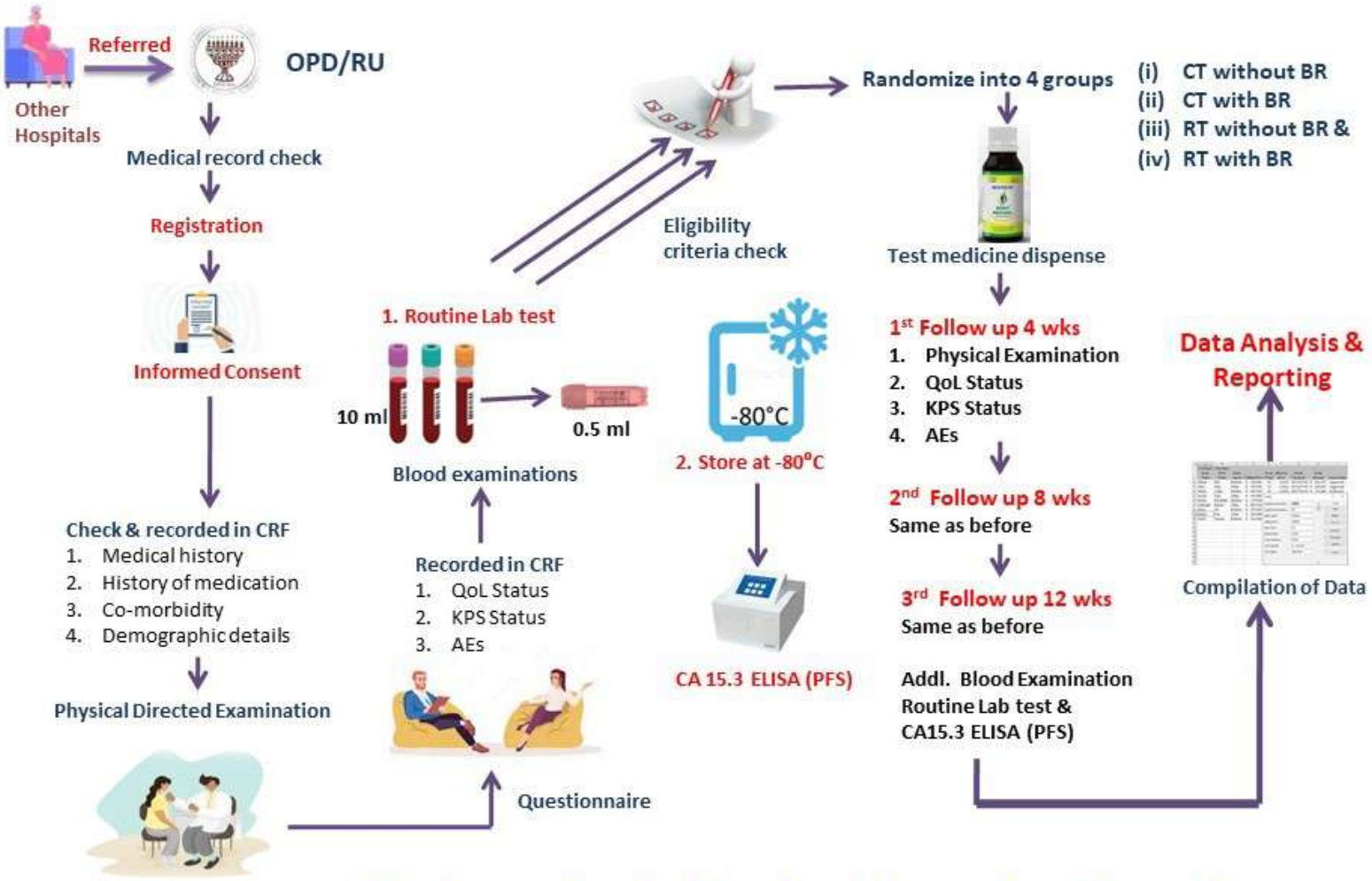


Study protocol: Standard Operating Procedure

Institutional Ethical Committee
J. B. Roy State Ayurvedic Medical College and Hospital
Department of Health and FW, Government of West Bengal
170-172, Raja Dinendra Street, Kolkata 700004

Ref. No. : JBR/IEC/ 06 /2023 Date: July 4, 2023

To
Dr. Srikanta Pandit
Reader, Dept. of Kayachikitsa
J. B. Roy State Ayurvedic Medical College and Hospital
170-172 Raja Dinendra Street, Kolkata 700004

Sub : Ethical permission for clinical research project

Dear Dr. Pandit,

In connection with the research proposal entitled, "**12-week Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy or Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study**" submitted by you, I like to mention that the proposal is ethically permitted for conducting at J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata in accordance with the meeting of the Institutional Ethical Committee held on 04.07.2023.

Thanking you,

Yours faithfully,

Professor Krihnangshu Ray
Chairman 04/07/2023

Ref. No. : JBR/IEC/ 06 /2023 Date: July 4, 2023

Copy to :

1. The Principal-Superintendent, J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata 700004
2. Member Secretary, Institutional Ethics Committee, J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata 700004

Professor Krihnangshu Ray
Chairman 04/07/2023

FULL DETAILS (Read-only) -> Click Here to Create PDF for Current Dataset of Trial

CTRI No	**Pending**
Acknowledgement Number	REF/2023/09/073407
Last Modified On:	26/09/2023
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Ayurveda Process of Care Changes Behavioral Nutraceutical Other (Specify) [Quality of Life]
Study Design	Non-randomized, Placebo Controlled Trial
Public Title of Study	12 Weeks Intervention of Body Revival in Breast Cancer Patients
Scientific Title of Study Clarification(s) with Reply Modification(s)	12-week Intervention of Body Revival (Ayurvedie Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy or Radiotherapy in Post Surgery Breast Cancer Patients: A Randomized Case Control Study
Trial Acronym	BC
Secondary IDs if Any Clarification(s) with Reply Modification(s)	**Secondary ID** / **Identifier** Nil / NIL
Details of Principal Investigator or overall Trial Coordinator (multi-center study) Clarification(s) with Reply Modification(s)	**Name**: Srikanta Pandit **Designation**: Associate Professor **Affliation**: J B Roy State Ayurvedic Medical College and Hospital **Address**: Research Unit, 2nd Floor, Department of Kayachikitsha, J B Roy State Ayurvedic Medical College and Hospital 170 to 172 Raja Dinendra Street Kolkata Kolkata WEST BENGAL 700004 India **Phone**: 9831723650 **Fax**: **Email**: panditsrikanta@gmail.com
Details Contact Person Scientific Query Clarification(s) with Reply Modification(s)	**Name**: Tuhin Kanti Biswas **Designation**: Professor **Affliation**: J B Roy State Ayurvedic Medical College and Hospital Kolkata **Address**: Research Unit, 2nd Floor, Department of Kayachikitsha, J B Roy State Ayurvedic Medical College and Hospital 170 to 172 Raja Dinendra Street Kolkata Kolkata WEST BENGAL 700004 India **Phone**: 9748664647

Fax	
Email	biswastuhin@rediffmail.com

Details Contact Person Public Query
Clarification(s) with Reply
Modification(s)

Name	Utpalendu Jana
Designation	Professor
Affliation	J B Roy State Ayurvedic Medical College and Hospital Kolkata
Address	Research Unit, 2nd Floor, Department of Kayachikitsha, J B Roy State Ayurvedic Medical College and Hospital 170 to 172 Raja Dinendra Street Kolkata Kolkata WEST BENGAL 700004 India
Phone	9433180053
Fax	
Email	janauin@gmail.com

Source of Monetary or Material Support

Health Reactive Excellency Bldg, 1st Floor, Opp. MTNL 4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053

Primary Sponsor

Name	Health Reactive
Address	Excellency Bldg, 1st Floor, Opp. MTNL 4 Bunglow, MHADA Layout, Andheri (W), Mumbai-400053
Type of Sponsor	Pharmaceutical industry-Indian

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

India

Sites of Study
Clarification(s) with Reply
Modification(s)

No of Sites = **1**

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Dr Srikanta Pandit	JB Roy State Ayurvedic Medical College and Hospital, Kolkata	Research Unit, 2nd Floor, Department of Kayachikitsha, 170 to 172 Raja Dinendra Street Kolkata 700004 Kolkata WEST BENGAL	9831723650 srikantapndit@gmail.com

Details of Ethics Committee
Clarification(s) with Reply
Modification(s)

No of Ethics Committees= **1**

Name of Committee	Ethics Committee registered with DHR /CDSCO or not	Ethics Committee Registration No.	Approval Status	Date of Approval	Approval Document	Is IEC?
Institutional Ethics Committe,	No		Approved	04/07/2023	Approval File	No

	J.B.Roy State Ayurvedic Medical College and Hospital, Kolkata						

Regulatory Clearance Status from DCGI

Status	Date	Aproval Document
Not Applicable	No Date Specified	No File Uploaded

Health Condition / Problems Studied

Health Type	Condition
Patients	**(1) ICD-10 Condition:**C509||Malignant neoplasm of breast of unspecified site. **Ayurveda Condition:** GRANTHIH, **(2) ICD-10 Condition:**O||Medical and Surgical. **Ayurveda Condition:** ARBUDAH,

Intervention / Comparator Agent
Clarification(s) with Reply

sno	Intervention/Comparator	Type	Drug-Type	Procedure Name	Details
1	Intervention Arm	Drug	Other than Classical		(1) Medicine Name: Body Revival, Reference: NA, Route: Oral, Dosage Form: Kwatha/Kashaya, Dose: 6(ml), Frequency: hs, Bhaishajya Kal: Pragbhakta, Duration: 12 Weeks, anupAna/sahapAna: No, Additional Information: Body Revival suspension, per oral, 6 ml (one teaspoon) in every 6th alternative day before going to bed (preferably in night)
2	Comparator Arm	Lifestyle	-	-	Dinacarya: Not applicable, Ritucarya: not applicable, Acara Rasayana:not applicable, Other:without intervention, only supportive treatment (if required), Duration 12 weeks, regular follow up (baseline, 4 wk, 8 wk and 12 wk) and check up all parameters similar to intervention arm , Pathya/Apathya:no, Pathya:, Apathya:

Inclusion Criteria

Age From	18.00 Year(s)
Age To	60.00 Year(s)
Gender	Female
Details	18 years of age or older; With a histologically or cytologically confirmed diagnosis of breast cancer (stage II–IV); Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months Not relapsed during recruitment

	Subjects may not have received Body Revival® or any herbal medicine
Exclusion Criteria	**Details**: Clinically significant CNS, hepatic, cardio-respiratory or immunogenic problems;Pregnant woman and lactating mother; Subjects have received Body Revival® or any herbal medicine
Method of Generating Random Sequence	Not Applicable
Method of Concealment	Other
Blinding/Masking	Open Label
Primary Outcome Clarification(s) with Reply Modification(s)	Outcome: (a) Progression free survival by blood CA-15.3, (b) Quality o Life by Questionnaire for cancer patients and (c) Karnofsky Performances (clinical assessments) are the primary outcomes by comparison between Intervention vs. case matched control (without intervention) — TimePoints: 1 year
Secondary Outcome Clarification(s) with Reply Modification(s)	Outcome: (a) Progression free survival by blood CA-15.3, (b) Quality o Life by Questionnaire for cancer patients & (c) Karnofsky Performances (clinical assessments) are the primary outcomes by comparison between Intervention vs. case matched control (without intervention) — TimePoints: 12 weeks
Target Sample Size	**Total Sample Size=**"48" **Sample Size from India=**"48" **Final Enrollment numbers achieved (Total)=** "Applicable only for Completed/Terminated trials" **Final Enrollment numbers achieved (India)=**"Applicable only for Completed/Terminated trials"
Phase of Trial	Phase 2
Date of First Enrollment (India)	30/10/2023
Date of Study Completion (India)	Applicable only for Completed/Terminated trials
Date of First Enrollment (Global)	If country of recruitment is only India, global date would be not applicable.
Date of Study Completion (Global)	Applicable only for Completed/Terminated trials
Estimated Duration of Trial	**Years=**"1" **Months=**"0" **Days=**"0"
Recruitment Status of Trial (Global)	If country of recruitment is only India, global status would be not applicable.

Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	N/A
Individual Participant Data (IPD) Sharing Statement	**Will individual participant data (IPD) be shared publicly (including data dictionaries)?** **Response** - NO
Result Disclosure	**Do you wish to upload results?** **Response** - Summary results have not yet been disclosed
Brief Summary	This is a single centre, open label, case-control, longitudinal, cross sectional cohort study with single dose of Body Revival on breast cancer post surgery recovery patients in combination with / or without regular therapeutic regime to assess the effectiveness of Body Revival supplement to prolong PFS and improvement of QoL. Approximately 48 subjects at single site with radiotherapy and chemotherapy treated post-operative breast cancer of greater than 1 and no more than 6 months from their surgery and chemotherapy/radiotherapy will be randomized. Allocation will be stratified by 1:1 treatment vs. case control of selected four arms.Control groups will not receive Body Revival® but will be allowed their regular conventional therapy, if any. Control groups will also be eligible to attend scheduled follow-ups. **The groups or arms will be as follows:** Arm I Radiotherapy (RT) + Body Revival Arm II RT + Control Arm III Chemotherapy (CT) + Body Revival Arm IV CT + Control Additionally, Arm I and Arm III will receive test medicine for 12 weeks, while Arm II and Arm IV without test medicine. **Selection Criteria** Each subject must meet the following criteria to be enrolled in this study Female subjects ≥ 18 years A histologically or cytologically confirmed diagnosis of breast cancer (stage II–IV) Or must have history of measurable disease by CT or MRI scan Have been treated with surgery / first line chemotherapy / radiotherapy of not more than six months Must have no report of relapsed Life expectancy of ≥12 months as estimated by the Investigators Other significant medical conditions must be well-controlled and stable in the opinion of the Investigators for at least 30 days prior to Study Day 1

Subjects must provide written informed consent and be able to comply with the protocol procedures

All subjects will be examined and monitored for consecutive 12 weeks. Follow-up schedule visit period will be:

1st Follow-up: 4 wks after randomization (± 5days)

2nd Follow-up: 4 wks after 1st Follow-up (± 5days)

3rd Follow-up: 4 wks after 2nd Follow-up (± 5days)

Efficacy & Safety Assessments

Physical examinations (including vital signs)

Subject reported on Quality of Life (QoL)

Karnofsky Performances

Progression free survival (PFS) based on serologic CA-15.3 response

Complete blood haemogram

Clinical laboratory tests (serum chemistry)

Radiological assessments (CT-Scan)

Adverse events (AEs)

Statistical Procedure

For the primary efficacy analyses, multiplicity for the comparison of Body Revival vs. control group will adjusted so that the study level type I error rate controlled to be lower than 0.05 significance level. Specific testing procedures which maintain the study level type I error rate at a lower level for this purpose are specified in statistical analysis plan.Intent-to-Treat Population (ITT), defined as all randomized subjects. This is the primary analysis population for all efficacy endpoints.

Safety Analysis Set (SAS), defined as all randomized subjects who will received at least one dose of study drug and who has at least one safety assessment following the first follow up, analyzed by the treatment received.

Evaluable population defined as all randomized subjects who have baseline and at least one on-treatment assessment performed.

Categorical data between the baseline and post treatment will be compared with the $\chi 2$ test, and continuous data will be analyzed by ANOVA and post-hoc analysis where applicable.

Alpha for statistical significance will be set at $p<0.05$.

Curriculum Vitae

NAME:	**PROF. (DR.) SRIKANTA PANDIT**
PRESENT POSITION:	Professor & Head & Visiting Physician Department of Kayachikitsa J.B. Roy State Ayurvedic Medical College & Hospital Govt. of West Bengal 170-172 Raja Dinendra Street, Kolkata, INDIA
DATE OF BIRTH:	26th day of September, 1967
EDUCATION:	BAMS — University of Calcutta — 1991 MD (Ay) — University of Calcutta — 1997 PhD (Ay) — University of Calcutta — 2017
MEDICAL REGISTRATION NUMBER:	10989 of 1992 under Paschimbanga Ayurved Parishad.
TEACHING EXPERIENCE:	25 years
WORKING EXPERIENCE:	2000-till date at J.B. Roy State Ayurvedic Medical College & Hospital, Govt. of West Bengal, Kolkata
RESEARCH TRAINING:	1995 to till date • Worked on *Louha Bhasma* (Iron) and *Kokilaksha* (*Hygrophila spinosa*) in *Kaphaja Pandu Roga* (Iron Deficiency Anemia) during the course of M.D. (Ayurveda) at the pharmacological, clinical, and chemical levels (1995-1997). • Worked as a Research Fellow and studied Advanced Procedures in the Research Department of Biochemistry and Microbiology BASLER Kinderspital, Basel, University of Basel, Switzerland (April-June, 1998). • Worked as a Research Associate for the CSIR research on the role of plant antioxidants in peptic ulcers at the Indian Institute of Chemical Biology (IICB) in Kolkata (1998-2000). • Associated as Research Investigator in Calcutta-project in collaboration with University of Basel, Switzerland (2000-2001. • Completed Ph.D. (Ayurveda) under the University of Calcutta on the topic entitled, "Chemical and Medicinal Evaluation of *Louha Bhasma*".
RESEARCH INTEREST:	Pharmacological and Clinical Research & Trials in the field of – o Iron deficiency anemia o Peptic ulcers o Diabetes mellitus o Peripheral neuropathy o Hepatoprotective o Prakiti & Ayurgenomics o Aphrodisiac o Hypertension o Stress o Covid-19 o Cancers

RESEARCH PROJECTS & TRIALS:	15 Projects completed • Associate-Investigator in CSIR-TRISUTRA Research Project sponsored by IGIB, CSIR • Associate-Investigator in DST sponsored clinical trial on Anemia • Investigator in Sponsorship Clinical Trials on Diabetes, Neuropathy, Hyperuricemia, Hypertension, Anti-stress, Covid-19 etc.
PUBLICATIONS:	Chapter in Book: 5 Publications: 40 Presentation: 50
	Recent Publication: 10 only 1. Pandit S, Biswas TK, Bera S, Saha S, Jana U, Sur TK. Efficacy of Heart Revival, an Ayurvedic formulation in hypertension and related risks – An exploratory single arm open label trial. Journal of Ayurveda & Integrative Medicine 2024; 15:1-5;100975. 2. Pandit S, Srivastav A, Sur TK, Choudhuri S, Wang Y, Biswas TK. Effects of Withania somnifera extract in chronically stressed adults: A randomized controlled trial. Nutrients 2024: 16: 1293. 3. Hazra A, Chakraborty B, Pandit S, Sur TK. A rapid HPTLC fingerprinting technique for identifying the various geo-floral origins of honeys. Journal of Analytical and Pharmaceutical Research, 2024; 13(1):5-8. 4. Biswas TK, Pandit S, Jana U, Puncha A, Sur TK. Clinical manifestation of polycystic ovarian syndrome and its correlation with thyroid stimulating hormone: A preliminary observational study in eastern India. Journal of Physiological Society of Nepal 2022; 3(2): 18-24. 5. Khan M, Pandit S, Biswas TK, Sur TK. Effect of Indian herbal formulation on hepatomegaly. Advances in Pharmacology & Clinical Trials 2023; 8(4): 1-5. DOI: 10.23880/apct-16000227 6. Khan M, Sur TK, Saha A, Ghosh C, Biswas TK, Chatterjee S, Pandit S. In-vitro and in-silico approach distinguish ER-α and HER-2 antagonistic properties of Indian herbal formulation on breast cancer. Journal of Drug Delivery & Therapeutics 2023; 13(11):6-12. 7. Joshi V, Khan M, Pandit S, Sur TK. Indian medicine can improve quality of life of breast cancer patients: Case studies. Journal of Natural & Ayurvedic Medicine 2023; 7(2):1-4. 8. Khan M, Pandit S, Saha A, Somani R, Joshi V, Singh MG, Bera S, Gupta S, Biswas SK, Biswas TK, Sur TK. Perspective of using Indian polyherbal medicine in the treatment of cancer. Current Research in Complementary & Alternative Medicine 2022; 6(3):165 9. Hazra AK, Ghosh C, Chatterjee S, Biswas TK, Pandit S, Sur TK. In silico studies of essential oil components from Indian herbal formulation against RdRp enzyme in Covid-19 virus. Journal of Analytical and Pharmaceutical Research 2022; 11(3):95-100. 10. Pramanik T, Saha A, Pandit S, Sur TK. The practice of COVID-19 vaccination among the pregnant and lactating women: the present global scenario and decisions taken in India and Nepal. International Journal Dental and Medical Sciences Research 2022; 4(4): 678-682.

Srikanta Pandit

December 30, 2024
Kolkata

(Prof. (Dr.) Srikanta Pandit)

Curriculum Vitae

Name : Dr. Tuhin Kanti Biswas

Date of Birth: 9th Day of April, 1964

Qualification : i) Bachelor of Ayurvedic Medicine and Surgery (University of Calcutta) in 1988.

ii) Post-graduation [M. D. (Ay)] in Ayurvedic Medicine under the University of Calcutta in 1993.

iii) Ph. D. in Kayachikitsa (Medicine) under the University of Calcutta in 2001.

Present Position: Professor cum Visiting Physician, Department of Kayachikitsa (Medicine) at Raghunath Ayurveda Mahavidyalaya and Hospital, Contai, Purba Medinipur, West Bengal.

Medical Registration number : 10842 of 1989 under the Pashchim Banga Ayurveda Parishad

Teaching experience: 23 years.

Research Interest: Pharmacological and Clinical Research in the field of -

a) Clinical and experimental evaluation of Ayurvedic drugs for wound healing drugs

b) Clinical and experimental evaluation of Ayurvedic drugs in diabetes mellitus

c) Evaluation of Prakriti through Ayurgenomics

d) Clinical evaluation of anti-stress and aphrodisiac activity of Aswagandha and Shilajit

e) Clinical evaluation of Ayurvedic drugs in post-COVID-19 patients

Research Project under taken:

a) Principal-Investigator, CSIR-TRISUTRA Research Project sponsored by IGIB, CSIR

b) Principal-Investigator, Wound healing project sponsored by ICMR

c) Principal-Investigator, Clinical Research Project on Diabetes, Hyperuracaemia, Anti-stress and Post Covid patients with herbal drugs sponsored by Natreon Inc. (India)

d) Principal-Investigator, Clinical Research Projects on Aprhrodisiac activity of Aswagandha and Shilajit sponsored by Sakti Naturals Pvt. Ltd., Puducherry, Tamil Nadu

Award:

1992 : 'Dr. K. N. Udupa Memorial Gold Medal' for best paper presentation in International seminar on Traditional Medicine at Kolkata

1998 : Award for best paper presentation at University of Calcutta

2004: Award for advanced research on wound healing by Indian Society of Wound Management at Allahabad

2022: Honoured as 'Doctor in the Indian Health System & Society' by Rotary Club of Aarohee Calcutta

Special credential: Visited Macao, China as Member representative from India in the meeting on "Clinical Research Guideline of Traditional and Complementary Medicine' organized by World Health Organization in 2015.

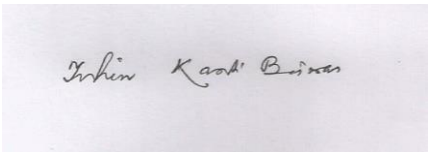
Seminar and Conference attended: More than 100 in home and abroad (Bangladesh, Nepal, China).

Research Guide: Guided two MD (Ayurveda) candidates under the West Bengal University of Health Sciences as Co-Supervisor and three PhD candidates under the West Bengal University of Health Sciences Jadavpur University and West Bengal University of Animal & Fishery Sciences.

Publication: More than 70 publications in reputed journals and books of national and international level. Associate Editors of three books.

Patent : Two Indian patent on Ayurvedic medicinal plants in the field of diabetes mellitus and wound healing.

Date : January 6, 2025



(Dr. Tuhin Kanti Biswas)

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16A Durga Charan Mukherjee Street, Kolkata, INDIA, ZIP Code 700003

Recent Position (2023-2024)	Postdoctoral Fellow (Exchange Visitor) Howard University, Department of Biology EE Just Hall, 415 College Street NW, Washington DC-20059

Research Expertise

- Knowledge of basic and applied research in pharmacology, biochemistry, molecular biology, and genetics.
- Expertise in processing large patient data for epidemiological studies, longitudinal studies, and cross-sectional studies.
- Work experience with overseas regulatory agencies for new drug development from natural resources.

Education

Year	Degree	Institution	Field of Study
1989	BS	University of Calcutta, Kolkata, INDIA	Physiology
1991	MS	University of Calcutta, Kolkata, INDIA	Physiology
2000	PHD	University of Calcutta, Kolkata, INDIA	Neurophysiology, Neuropharmacology

Research Training/Certified

Training Course	Field of Study	Year(s)
Good Clinical Practice	Clinical Trials/Studies GCP-ICH Schedule Y	2013, 2018, 2022, 2023
Good Animal Practice	Laboratory Animal Trials	2013, 2016, 2018, 2023
Good Laboratory Practice	Analytical Techniques	2008, 2014, 2023
Pharmacovigilance	Drug Monitoring & Safety	2022

Research Methodology & Management Skills

(i) Qualified in operating / regulating Clinical Trials with GCP-ICH Schedule Y

(ii) Experienced in protocol preparation, executing, monitoring, data analysing, and presenting Research and Clinical Trials

(iii) Skilled in PC operation, statistical analysis & presentation. Certified in online Clinical Data Entry Administration (DEA)

(iv) Managerial capabilities to executing multidisciplinary research projects and field studies

(v) Experienced in staff recruitments; staff training; supervise laboratory technical personnel; supervise other biologists

Position / Scientific Appointments (1993-2024)	Affiliation
	Postdoctoral Fellow, Howard University, Washington DC, USA
	Scientist C, R.G. Kar Medical College and Hospital, Kolkata, India
	Postdoctoral Fellow, Dept. of Pharmacology, I.P.G.M.E. & R., Kolkata, India
	Research Fellow, Dept. of Pharmacology, University college of Medicine, Kolkata

Research Honours / Awards*	Year(s)	Title	Agency
	2021	Incredible Scientist of India Award-2021**	Record Owner, Delhi
	2020	Innovative Research Award	Society of Pharmaceutical Education & Research, AKS University, Satna, M.P
	2019	Excellent Research in Pharmacology	World Research Council & United Medical Council, Trichy
	2009	PC Dandiya Award	Pharmacological Society of India, India
	2004	BR Sengupta Memorial Award	Asian Network Research, Kolkata, India
	2002	Best Research Award	Indian Science Congress Association, Lucknow, India
	2000	Best Research Award	Physiological Society of India, ICMR, Kolkata

Total Research Award 19, * https://www.youtube.com/watch?app=desktop&v=bEOLwbAkS_c

Contributions to Science	Clinical Research: (some recent work highlighted)
	○ Transcriptomic studies to develop blood-based biomarkers to detect the risk of Alzheimer's disease in African Americans. . ○ Hospital-based observational study on biomarkers in COVID-19 infections. ○ Assessed chronic stress-related biomarkers in a double-blind clinical trial. ○ A phase IV randomized controlled multicentre study to assess the safety & immunogenicity of GSK Biological HPV-16/18 L1 VLP AS04 vaccine in HIV+ female subjects aged 15-25 yrs.
	Pharmacological Research: (some recent work highlighted)
	○ Neuroinflammatory markers in Alzheimer's disease. ○ Metastatic growth inhibition in breast cancer through intracellular energy depletion. ○ Neurochemical profiles of stress in animals and their interaction with antidotes. ○ Mapping of neurotransmitters in brain during hepatic encephalopathy.

Complete List of Published Work	
	PubMed: https://pubmed.ncbi.nlm.nih.gov/?term=Tapas+Sur
	Research gate ID: https://www.researchgate.net/profile/Tapas-Sur
	Google Scholar: https://scholar.google.com/citations?authuser=1&user=KbgrsjUAAAAJ

Research Publications	
	Books (Chapter): 5
	Research Articles: 126
	Research Presentation: 93

Tapas Kumar Sur

Tapas Kumar Sur

Appendix-XIII

Publications

Project Title: 12 Weeks Intervention of Body Revival (Ayurvedic Medicine) to Improve Quality of Life (QoL) and Progression Free Survival (PFS) to Counter Adverse Events of Chemotherapy and Radiotherapy in Post-Surgery Breast Cancer Patients: A Randomized Case Control Study
Study Site: Research Unit, J. B. Roy State Ayurvedic Medical College & Hospital, Kolkata
Study Sponsor: Health Reactive, Mumbai & Rajasthan, India

Abstract for Oral Presentation: 10th World Ayurveda Congress
Section: 13. Kayachikitsa

A Randomized Case Control Study of Body Revival® to Improve Quality of Life and Progression Free Survival in Breast Cancer Patients

Dr. Tapas Kumar Sur and Dr. Srikanta Pandit

Dept. of Kayachikitsha, J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata 700004

drtapaskumarsur@gmail.com; srikantapandit@gmail.com

Background: Body Revival® (BR) is an Ayurvedic proprietary medicine prepared by Health Reactive, Mumbai. Previous research found that it has cytotoxic effects on breast cancer cells (MCF-7). It also demonstrated a robust affinity for ligand binding to ER-α and HER-2 receptors. However, the clinical trial on breast cancer patients necessitates more information.

Objectives: The primary aim of this study was to evaluate the impact of BR on breast cancer patients in order to enhance quality of life (QoL) and progression-free survival (PFS).

Methods: This was a longitudinal, cross-sectional, open-label, randomized, case-control study conducted at a single center (CTRI/2023/11/059465, Nov 2, 2023). The study included 42 adult female patients with breast cancer (stage II-IV) who have had a remission (treatment-free interval) for no more than 6 months after their initial course of chemotherapy (CT), radiotherapy (RT), or surgery. They were randomized into 4 groups: RT with BR, RT without BR, CT with BR and CT without BR. BR was administered at a single dosage of 6 ml, orally every 6 alternate days for 12 weeks. Protocol-compliant physical examinations, vital sign assessments, Karnofsky Performance Status (KPS), Quality of Life (QoL), Progression Free Survival (PFS), and blood analyses were performed. Conventional cancer treatment related Adverse Events (AEs) and any untoward hypersensitivity were thoroughly measured by CTCAE v.5 criteria.

Results: KPS and QoL scores in both groups were statistically ($p<0.001$) improved by BR therapy. In comparison to the control group, PFS (CA 15.3 in serum $\leq$ 25 IU/ml) was recorded in the treatment groups. BR significantly ($p<0.01$) reduced adverse events (AEs) associated with cancer treatment in patients with breast cancer. The results were more promising in the CT groups than in the RT groups. The underlying mechanisms were also explained.

Conclusion: Body Revival® demonstrated effectiveness as an adjuvant treatment for patients with breast cancer.

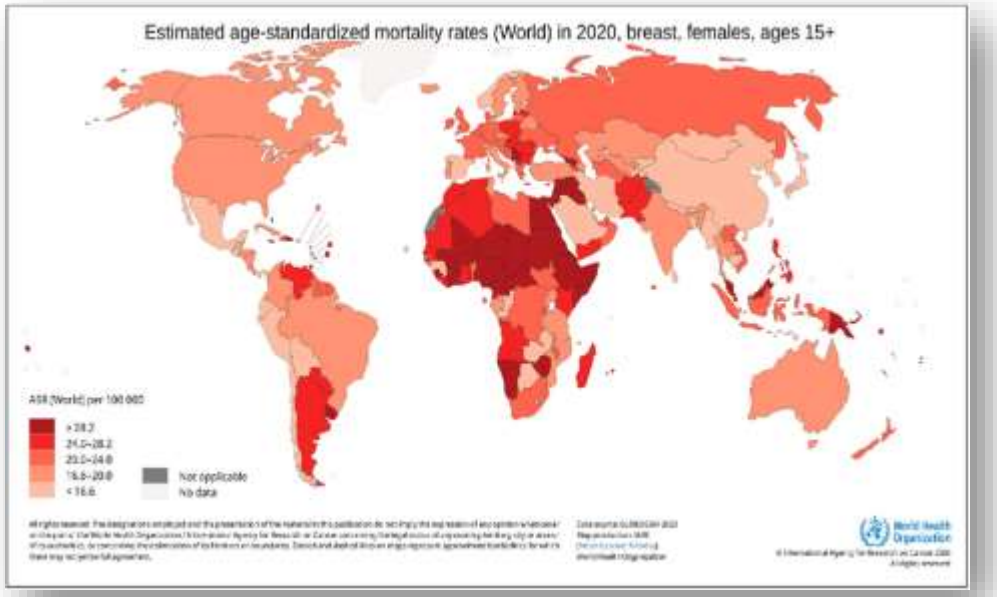
A Randomized Case Control Study of Body Revival® to Improve Quality of Life and Progression Free Survival in Breast Cancer Patients

Tapas Kumar Sur

Dept. of Kayachikitsha

J. B. Roy State Ayurvedic Medical College & Hospital
Kolkata

Breast Cancer: Incidence



- **18.1 million** new cases & **10 million** global deaths due to cancer in 2020.
- **1** in **9** Indians has a lifelong risk of developing cancer.
- **Most common cancer is breast cancer (12.5%).**

- **Lancet 2022; 400: 563–591.**
- ***Indian J Med Res* 2022; 156(4-5):598-607.**
- ***CA Cancer J Clin* 2021; 71:209-249.**

Classification & Treatment Options

Breast cancer is a genetically & clinically heterogeneous disease.

5 molecular classes:
Luminal A, Luminal B, HER2, Basal & Unclassified

Biological therapy:
Improve immune system to fight cancer cells or to control side effects from other cancer treatments

Treated in 5 ways:

Surgery

Chemotherapy

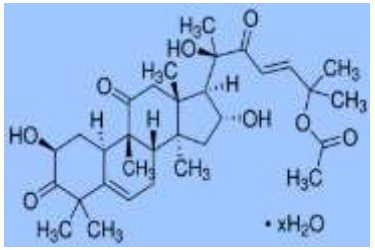
Radiation therapy

Hormonal therapy

Biological therapy

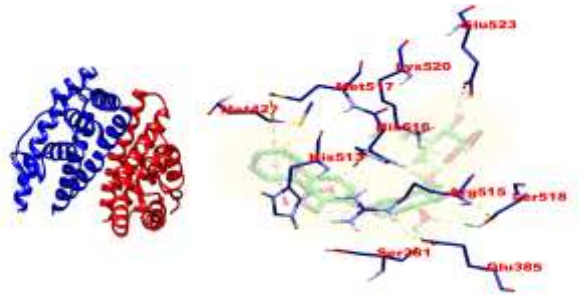
Trial Product: Body Revival®

Body Revival (*HP-177-AY*) is a composite Ayurvedic medicine (*M/s Health Reactive, Mumbai*) with multiple phytoconstituents recognized as having anticancer therapeutic potential.



Cucurbitacin B

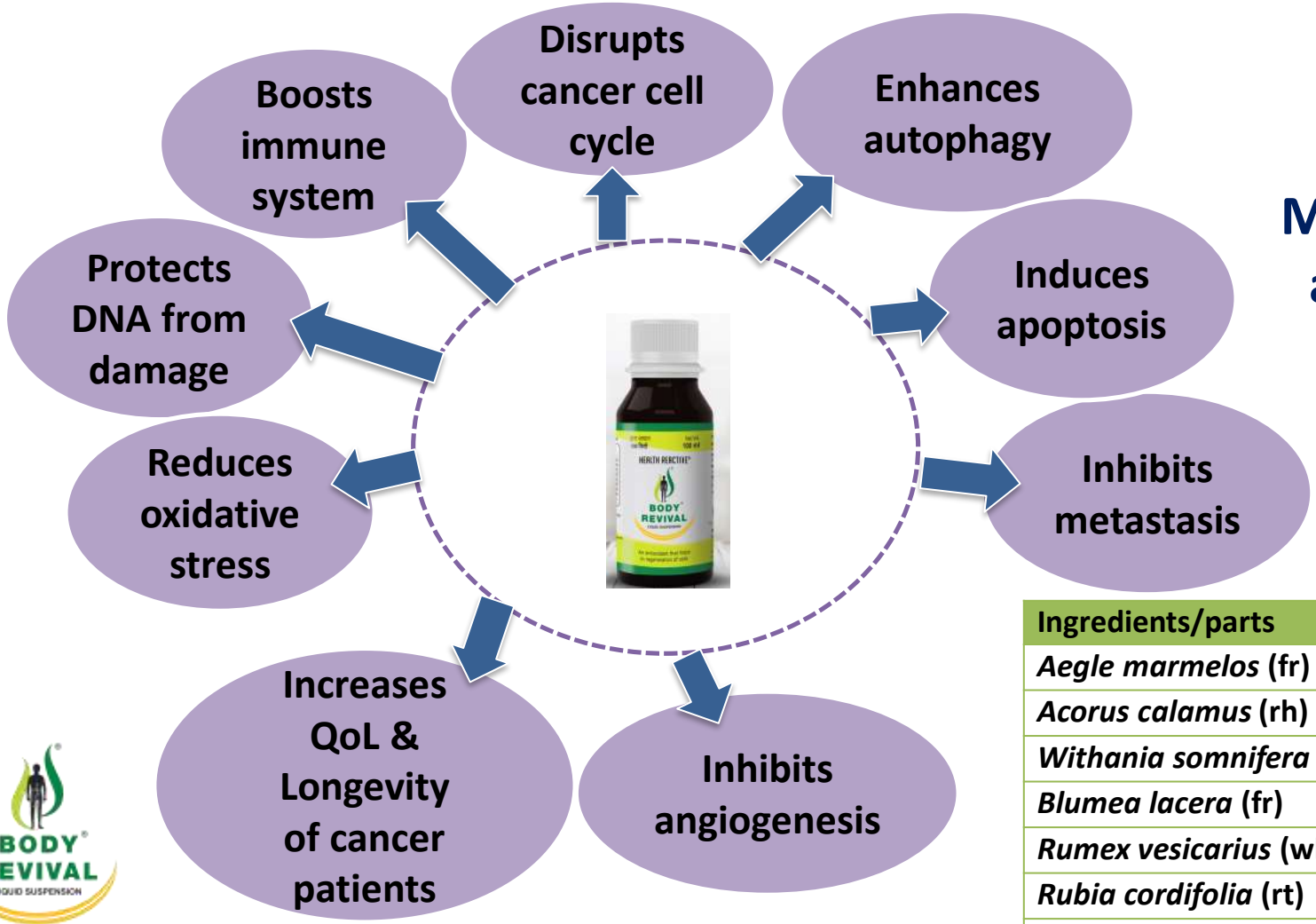
Most active anticancer phytoconstituents: Cucurbitacin, Symconosides, Withaferin & Quercetin.



***In silico* HER-2 receptor binding affinity with Symconoside B similar to Tamoxifen.**

Ayurvedic literature, contemporary research, laboratory data, in silico computational analysis, animal experiments, and cancer patient case reports substantiated its claims.

Body Revival®: Anticancer Activity



Multifaceted anticancer activities

Ingredients/parts	5 ml
Aegle marmelos **(fr)**	150 mg
Acorus calamus **(rh)**	175 mg
Withania somnifera **(rt)**	325 mg
Blumea lacera **(fr)**	115 mg
Rumex vesicarius **(wh pl)**	240 mg
Rubia cordifolia **(rt)**	200 mg
Cucumis melo **(sd)**	200 mg
Symplocos racemosa **(bk)**	95 mg
Honey	qs

BODY® REVIVAL LIQUID SUSPENSION HEALTH REACTIVE®

Body Revival®: Proof based on Research

1. Khan et al. *Adv Pharmacol Clin Trials* **2023**; 8(4): 1-5.
2. Khan et al. *J Drug Delivery Ther* **2023;** 13(11):6-12.
3. Joshi et al. *J Nat Ayurvedic Med* **2023;** 7(2):1-4.
4. Joshi et al. *Adv Pharmacol Clin Trials* **2023**; 8(2):1-6.
5. Khan et al. *Curr Res Comp Alt Med* **2022**; 6(3):165.
6. Khan et al. *Eur J Med Health Sci* **2020**; 2(2):1-6.
7. *Sur et al. J Chinese Int Med* **2011**; 9(7): 746-751.


Current Research in Complementary & Alternative Medicine

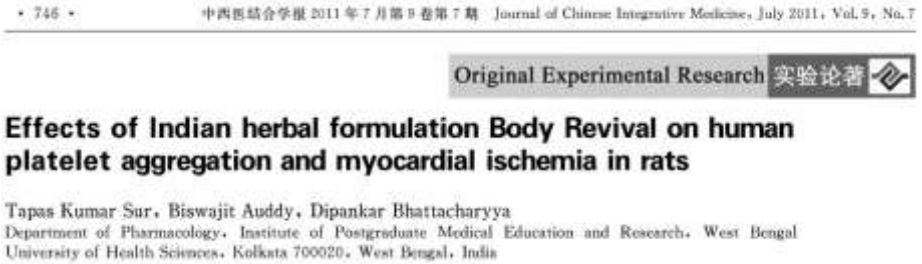
Review Article

Perspective of using Indian Polyherbal Medicine in the Treatment of Cancer

Munir Khan[1], Srikanta Pandit[2], Avijit Saha[2], Rampal Somani[1], Vasudha Joshi[1], Mani G. Singh[1], Sayantan Bera[2], Sweety Gupta[2], Soumya K. Biswas[3], Tuhin K. Biswas[2], Tapas Kumar Sur[2*]


Journal of Natural & Ayurvedic Medicine

Indian Medicine Can Improve Quality of Life in Breast Cancer Patients: Case Studies


· 746 · 中西医结合学报 2011 年 7 月第 9 卷第 7 期 Journal of Chinese Integrative Medicine, July 2011, Vol. 9, No. 7

Original Experimental Research 实验论著

Effects of Indian herbal formulation Body Revival on human platelet aggregation and myocardial ischemia in rats

Tapas Kumar Sur, Biswajit Auddy, Dipankar Bhattacharyya

Department of Pharmacology, Institute of Postgraduate Medical Education and Research, West Bengal University of Health Sciences, Kolkata 700020, West Bengal, India


Journal of Drug Delivery and Therapeutics

Research Article

In-Vitro and *In-Silico* Approach Distinguish ER-α and HER-2 Antagonistic Properties of Indian Herbal Formulation on Breast Cancer

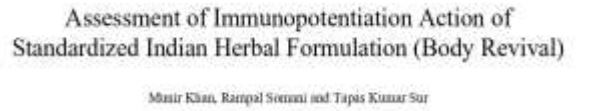
Munir Khan[1], Tapas K. Sur[2], Avijit Saha[2], Chandreyt Ghosh[3], Tuhin K. Biswas[4], Sirshendu Chatterjee[3], Srikanta Pandit[1*]


Advances in Pharmacology and Clinical Trials

Assessment of Quality of Life in Cancer Patients Supplemented with Ayurvedic Medicine (Body Revival): Case Reports


Advances in Pharmacology and Clinical Trials

Effect of Indian Herbal Formulation on Hepatomegaly: An Evidence Based Case Report


Assessment of Immunopotentiation Action of Standardized Indian Herbal Formulation (Body Revival)

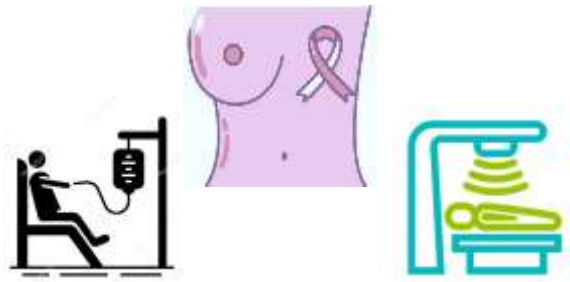
Munir Khan, Rampal Somani and Tapas Kumar Sur

Objectives

Research Questions

Does BR® adjunct therapy -

- **(a) Enhance QoL?**
- **(b) Improve PFS?**
- **(c) Reduce side effects?**



Study Objectives

To evaluate the impact of Body Revival® on breast cancer patients in order to enhance quality of life (QoL) and progression-free survival (PFS).

- ***QoL: Indian J Cancer 2011; 48(4):500-506***
- ***PFS: Br J Cancer 1987; 55(5): 567-569***
- ***KPS: Evaluation of chemotherapeutic agents. NY: CUP; 1949:191–205.***

Methods: Selection of Patients

Study Design

Longitudinal, cross-sectional, open-label, randomized, case-control study conducted at a single center (CTRI/2023/11/059465; 2-11-2023).

Selection Criteria

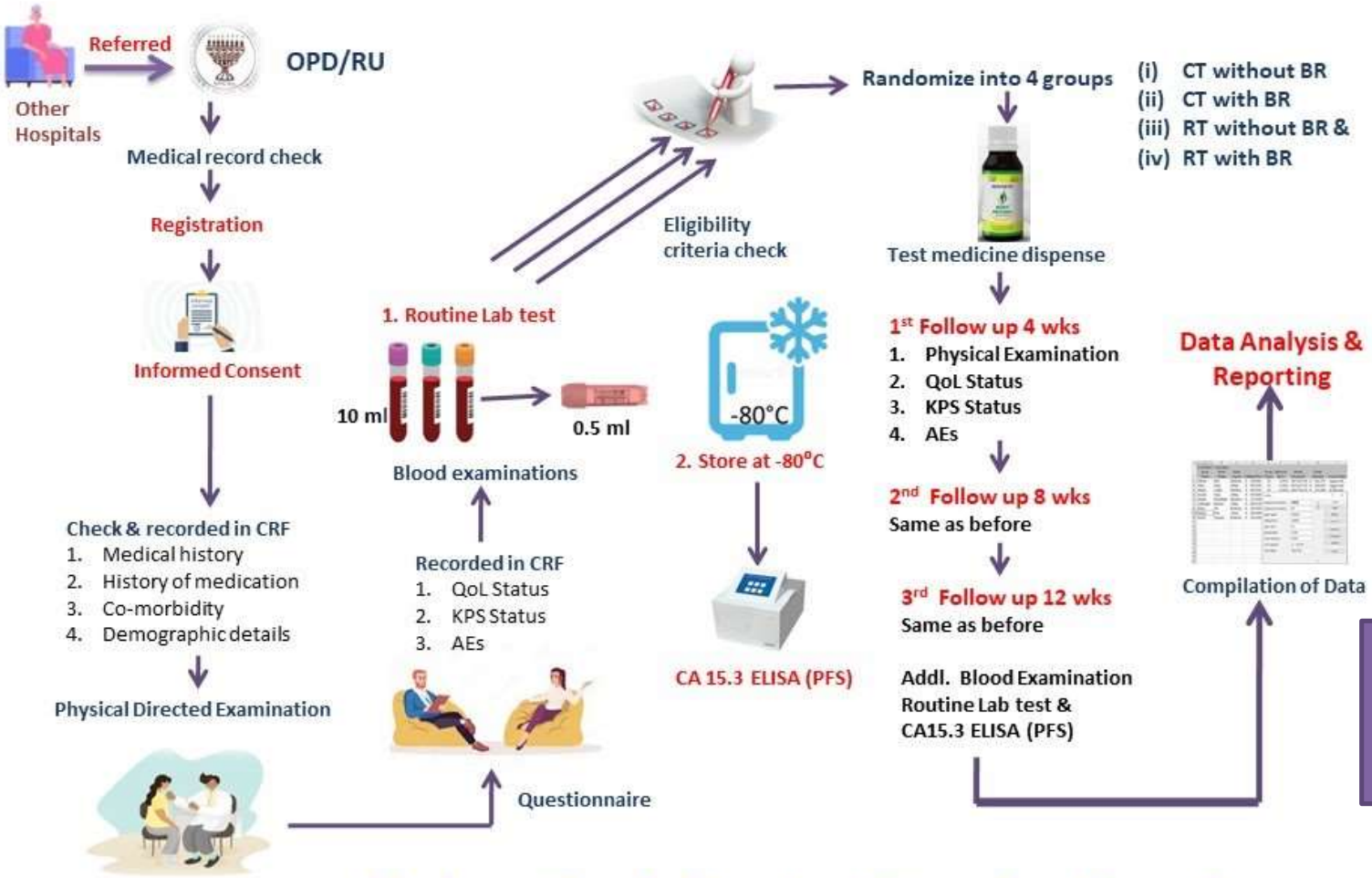
i. **Female subjects ≥ 18 years**
ii. **Diagnosed of breast cancer (stage II–IV)**
iii. **Treated with surgery/chemotherapy / radiotherapy**
iv. **Treatment-free interval ≤6 months after surgery / CT/ RAD**

Randomization

Stratified by 1:1 treatment vs. case control

4 groups: (i) CT without BR (ii) CT with BR (iii) RAD without BR & (iv) RAD with BR

CT: Standard Operating Procedure



Study done: Nov 2023 to Nov 2024

Study protocol: Standard Operating Procedure

Evaluation Measures

Screening Visit & Final Visit:
(Day 0 & 12 wks)

1. Physical examinations & vital signs
2. Karnofsky Performance Status (KPS)
3. Quality of Life (QoL)
4. Progression Free Survival (PFS): CA 15.3
5. Blood analyses: CBC, Glucose, LFT, BUN, Cr
6. Adverse Events: CTCAE v.5 criteria

Follow-Up Visits:
(4 wks & 8 wks)

1. PE & vital signs
2. KPS
3. QoL
4. AEs

Treatment: Interventive Medicine

Body Revival® suspension, per oral, 6 ml in every 6th alternative day before going to bed (preferably in night) for 12 weeks

Results: Demographic Details

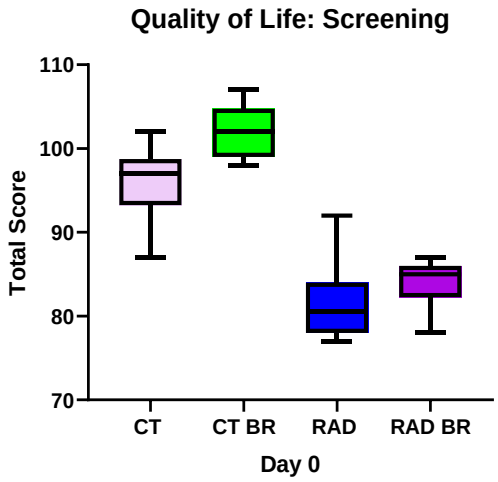
	ALL	CT-CONTROL	CT-BR	RAD-CONTROL	RAD-BR
Number of Subjects	44	12	12	10	10
Age	53.73±7.69	51.75±7.32	58±5.93	53±8.41	51.7±8.26
Marital status					
Unmarried	0	0	0	0	0
Married	39	11	11	10	7
Widow	5	1	1	0	3
Total family income (INR)					
<25000	7	1	2	2	2
25000-50000	31	10	8	6	7
Above 50000	6	1	2	2	1
Tobacco chewing habit					
Never use	29	7	9	6	7
Presently use/ex- use	15	5	3	4	3

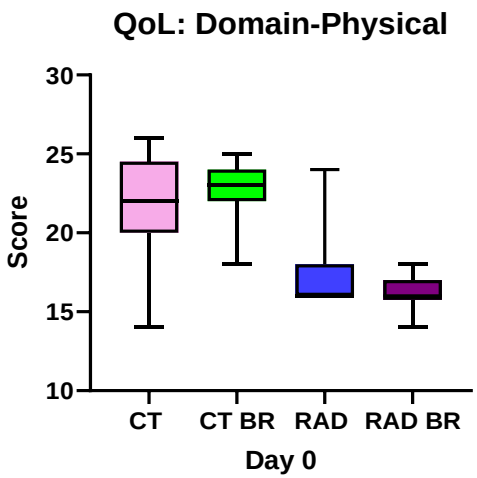
Physical Directed Examination

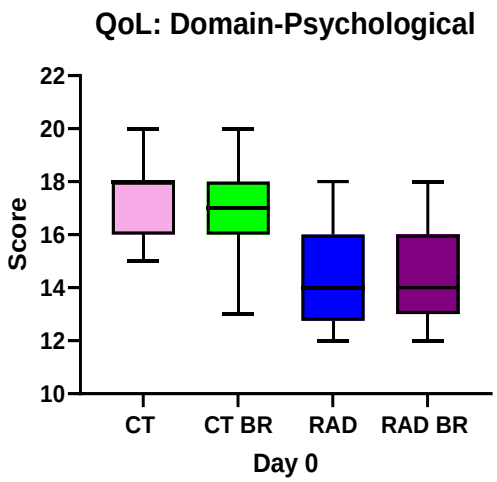
	CT		CT-BR		RAD		RAD-BR	
	Day 0	12 wk	Day 0	12 wk	Day 0	12 wk	Day 0	12 wk
BMI	21.92 ± 1.98	23.68 ± 10.15*	22.24 ± 1.70	22 ± 1.47	22.2 ± 1.99	20.93 ± 1.84*	22.19 ± 2.43	21.67 ± 2.20*
Pulse rate (bpm)	82.50 ± 3.72	82.75 ± 2.73	82.08 ± 4.35	82.42 ± 4.93	80.6 ± 5.16	80.6 ± 3.89	81.6 ± 4.59	82.3 ± 4.05
Blood pressure (Systole)	131.92 ± 19.2	133 ± 16.41	127.75 ± 13.05	126.75 ± 9.81	128.3 ± 12.61	128.8 ± 12.18	137.9 ± 15.57	90.3 ± 19.30
Blood pressure (Diastole)	86.25 ± 6.74	83.5 ± 5.68	83.91 ± 5.14	82.66 ± 3.55	84.6 ± 3.50	83.9 ± 4.06	90.3 ± 4.13	88 ± 4.80

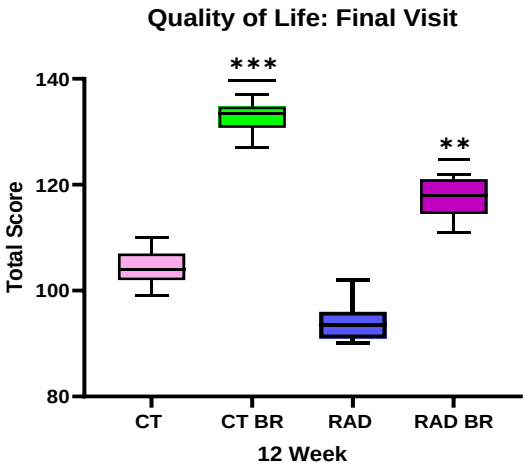
Paired sample t test; * $p<0.05$ when compared to Day 0

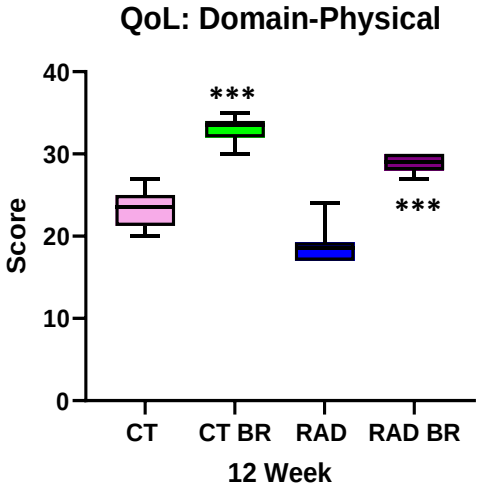
Quality of Life

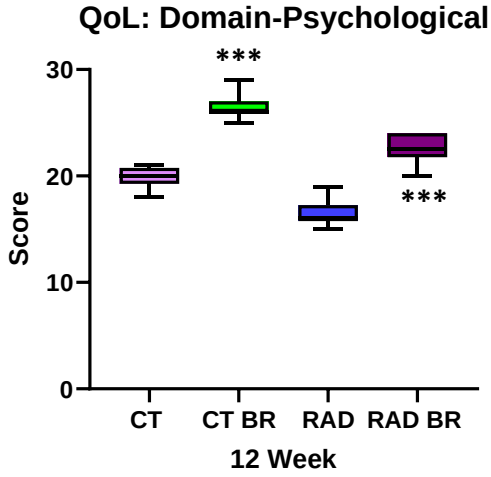






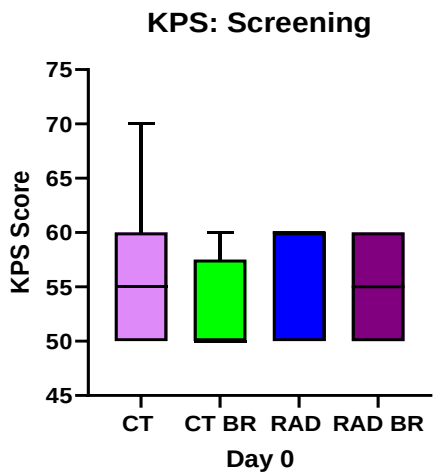


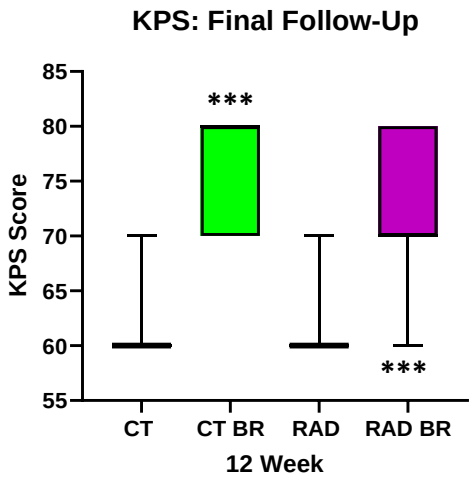


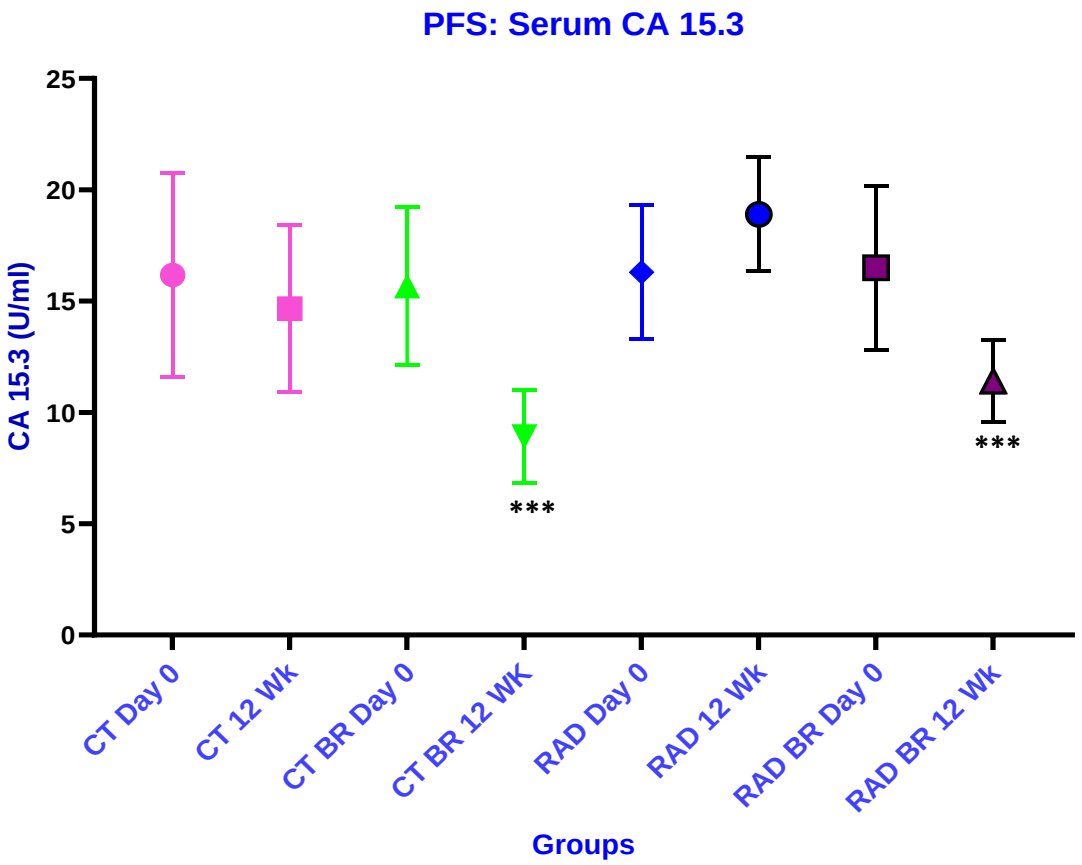


Chi –Square test; **p<0.01 and ***p<0.001 when compared to Control

Karnofsky Performance Status & Progression Free Survival

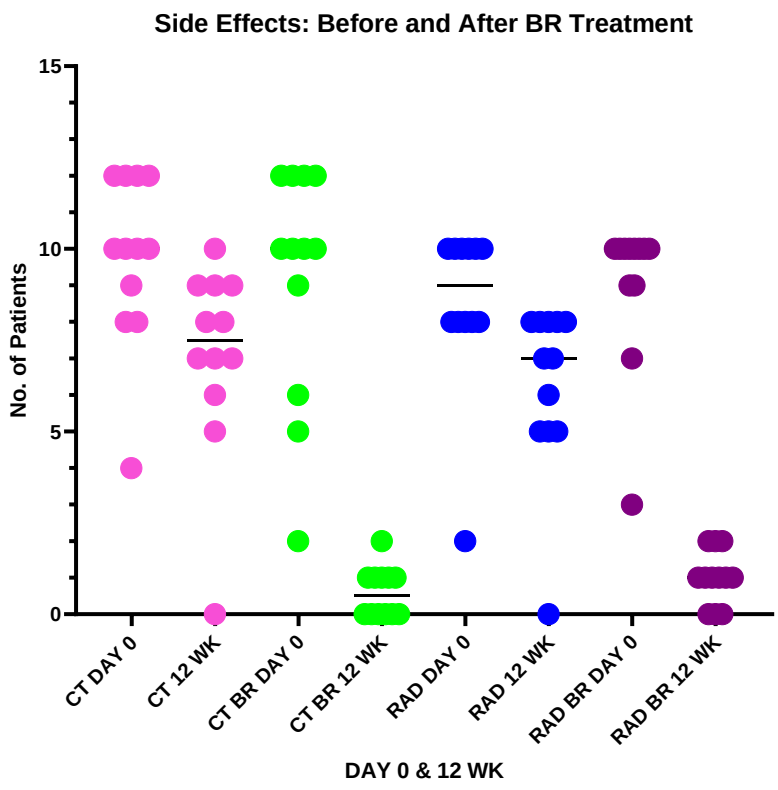






Chi –Square test; ***p<0.001 when compared to Day 0

Body Revival® on Adverse Events



	CT DAY 0	CT 12 WK	CT BR DAY 0	CT BR 12 WK	RAD DAY 0	RAD 12 WK	RAD BR DAY 0	RAD BR 12 WK
1. Anorexia	10	8	12	1	10	8	10	2
2. Constipation	8	8	10	1	8	7	7	2
3. Diarrhoea	4	0	2	0	2	0	3	0
4. Dizziness	12	10	12	1	10	8	10	1
5. Dry skin	10	7	10	2	10	8	10	1
6. Fatigue	12	9	12	1	10	7	10	2
7. Hot flashes/flushes	12	9	12	0	10	8	10	1
8. Muscle weakness	10	7	10	1	10	8	10	1
9. Nausea	12	9	10	0	8	5	10	0
10. Pruritus/itching	8	6	9	0	8	5	9	0
11. Rash	9	5	6	0	8	5	9	1
12. Vomiting	10	7	5	0	8	6	10	1

Common Terminology Criteria for Adverse Events v5.0

Grade 1 Mild; Grade 2 Moderate; Grade 3 Severe; Grade 4 Life-threatening; Grade 5 Death

Conclusion

- **Body Revival® treatment significantly enhanced QoL for patients with breast cancer in terms of physical well-being and psychological well-being.**
- **It improved Performance Status in daily life.**
- **It lowered the tumor biomarker CA-15.3 (≤ 25IU/ml) in blood.**

Cont'd

- It significantly ($p<0.01$) reduced the side effects of chemotherapy and radiation.
- BR increased appetite, physical stamina and endurance while decreasing nausea, constipation, muscle weakness, dizziness and fatigue.
- BR decreased liver enzymes and enhanced blood proteins & hemoglobin.
- The CT group showed greater outcomes than the RAD group.

Acknowledgements

- Principal, *J. B. Roy State Ayurvedic Medical College & Hospital*
- Director of Ayurveda, *Govt. of West Bengal, Kolkata*

Special Thanks to :

- Sponsor: M/s Health Reactive, Mumbai

Team Members:

- Prof. Srikanta Pandit
  Principal Investigator
- Prof. Tuhin K. Biswas
  Associate Investigator
- Prof. Utpalendu Jana
  Associate Investigator
- Prof. Himangsu Roy
  Consultant Oncologist
- Dr. Baidyanath Debnath
  Research Fellow Physician
- Mr. Amartya Dalui
  Assistant

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Uttarakhand

10th WORLD AYURVEDA CONGRESS & AROGYA EXPO

Organiser

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AN INITIATIVE OF VIJNANA BHARATI

Focal Theme

DIGITAL HEALTH - AN AYURVEDA PERSPECTIVE

12 - 15 December, 2024 | Parade Ground, Dehradun, Uttarakhand

Certificate of Participation

WE WOULD LIKE TO THANK

DR. TAPAS KUMAR SUR

for participating in the 10th World Ayurveda Congress & Arogya Expo 2024
held at Parade Ground, Dehradun, Uttarakhand from Dec 12 to15, 2024

Prof Anup Thakar
Secretary General
10th WAC & AROGYA

World Ayurveda Foundation ★ Bangalore ★

Dr Jayaprakash Narayan
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Current Research in Complementary & Alternative Medicine

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Review Article

Perspective of using Indian Polyherbal Medicine in the Treatment of Cancer

Munir Khan[1], Srikanta Pandit[2], Avijit Saha[3], Rampal Somani[1], Vasudha Joshi[1], Mani G. Singh[4], Sayantan Bera[2], Sweety Gupta[5], Soumya K. Biswas[6], Tuhin K. Biswas[2], Tapas Kumar Sur[3*]

[1]Health Reactive, Jaipur, India

[2]J.B. Roy Ayurvedic State Medical College & Hospital, Kolkata, India

[3]R.G. Kar Medical College & Hospital, Kolkata, India

[4]Eska Safety Solutions, Jaipur, India

[5]State General Hospital, Howrah, India

[6]Bengal Institute of Pharmaceutical Sciences, Kalyani, India

***Corresponding Author:** Tapas Kumar Sur, Research Scientist II, Multidisciplinary Research Unit (ICMR), R.G. Kar Medical College & Hospital, 1 Khudiram Bose Sarani, Kolkata – 700004, West Bengal, India

Citation: Khan M, Pandit S, Saha A, Somani R, Joshi V, et al. (2022) Perspective of using Indian Polyherbal Medicine in the Treatment of Cancer. Curr Res Cmpl Alt Med 6: 165. DOI: 10.29011/2577-2201.100065

Received Date: 29 November 2022; **Accepted Date:** 6 December 2022; **Published Date:** 12 December 2022

Abstract

Body Revival is a composite traditional herbal medicine with multiple phytoconstituents recognized as anticancer therapeutic potentials. These bioactive anticancer phytoconstituents are β-asarone, cucurbitacin B, 1-hydroxytectoquinone, marmelin, methylglyoxal, mollugin, quercetin, withanone, withanolid, withaferin A etc. This review is based on mechanistic analysis of individual phytoconstituents as chemotherapeutics and their synergistic impacts on the management of cancer. The possible modes of anticancer actions of Body Revival are multifactorial. It stimulates the immune system, protects DNA from injury, restores damaged DNA, lowers oxidative impairment, antiproliferation, cancer cell cycle arrest, initiation of apoptosis, suppression of angiogenesis and metastasis, chemo preventive or restore/protects normal cells from harmful effects of radiation. Furthermore, it is devoid of any toxic effect. The goal-oriented programmed clinical approaches are desirable to strengthen its anticancer efficacies as a safe chemotherapeutic agent.

Keywords: Cancer; Chemotherapeutics; Apoptosis; Phytochemicals; Herbs

Abbreviations: Bcl-xL=B-cell lymphoma extra large; Erα=Estrogen receptor-α; HCC=*hepatocellular carcinoma*; MAP kinase=mitogen-activated protein kinase; MMP=matrix metalloproteinase; NF-KB=Nuclear factor kappa B; ROS=reactive oxygen species; STAT3=signal transducer and activator of transcription 3; TGF-β=transforming growth factor β; TRIM16=Tripartite motif-containing protein 16; VEGF=vascular endothelial growth factor; Wnt=wingless-type.

Cancer cell lines: breast: MCF-7, MDA-MB-231, MDA-MB-435S; cervical: HeLa, WRL68; colon: LoVo, HCT116, HCT-15, CoLo-05; colorectal: HT29; fibroblast: HSKMC; gastric: AGS; hepatic: Hep3, HepG2; laryngeal: HEp-2; leukaemia: K562, P338,

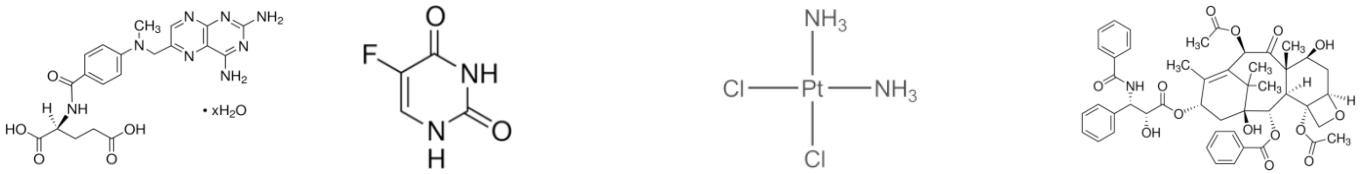
THP-1, U937, Jurkat; lung: A-375, A-549; lymphoma: BC-1/KMC; melanoma: B16F10; neuroblastoma: IMR-32; pancreatic: BxPC-3 and prostrate: DU-145, PC3, LNCaP.

Introduction

Cancer is a global health problem because of its high prevalence and poor prognosis. It can affect any part of the body and spread one part to other organs. Widespread metastases are the most imperative reason of death in cancer [1]. The Cancer registry specifies 18.1 million new cases and 10 million global deaths due to cancer in 2020. Although the most common cancers are breast, lung, colorectal and prostate, contributing 12.5%, 12.2%,10.7% and 7.8% respectively to the total number of new cases diagnosed in 2020 [2]. Moreover, in India, 1.3 million new cancer cases and 0.85 million deaths were reported [3]. The burden of cancer incidence and mortality is rapidly growing worldwide [4].

Cancer occurs due to over expression of oncogenes or damage in DNA. Conversely, oxidative stress or reactive oxygen species (ROS) play a considerable role in key cellular pathways of DNA damage, mutagenesis and apoptosis. Besides genetic injury, habitual use of tobacco, alcohol dependence, inadequate diet, physical apathy, radiation, chemical and environmental pollutants are the major threats considered for any type of cancer [5]. The International Agency for Research on Cancer (IARC) has already identified more than 150 chemicals, drugs, foods, airborne particles, ionizing radiation and other consumer products as potential carcinogens [6].

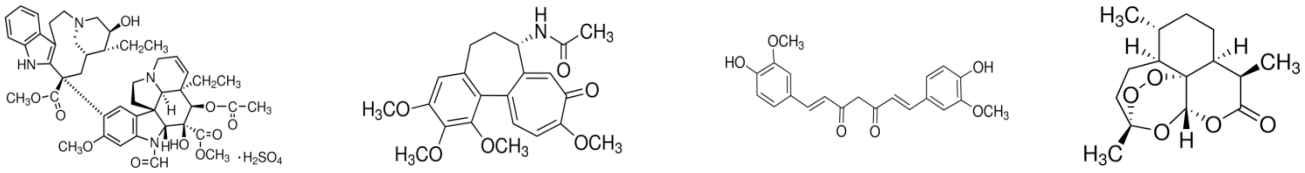
There are four types of therapeutic modalities in cancer depending upon the nature, progression of disease conditions and possibilities of recovery, viz. surgery, chemotherapy, radiation therapy and palliative care. In the early 1900s, the term "chemotherapy" was first introduced by German chemist Paul Ehrlich to treat specific infective conditions like cancer with chemicals. After several attempts, methotrexate (1948), chlorambucil (1957), cyclophosphamide (1959), 5-fluorouracil (1970), Doxorubicin (1974) and Cisplatin (1978) were developed for the treatment of cancers [7]. Cytotoxic chemotherapeutics target directly to DNA; while the target chemotherapeutics aim at the abnormal protein expression inside the malignant cells [8]. At this time, although chemotherapy is the most powerful weapon to treat deadly cancers, causes widespread cytotoxicity of healthy cells and causes severe side effects, such as nausea, emesis, anorexia, diarrhoea, skin damage and hair loss. To overcome these unwanted side effects, searching for novel and safe chemotherapeutics for cancer is crucial. Consequently, alternative medicine may provide a safe chemotherapeutic to treat cancer without undesirable side effects.



Methotrexate **5-Fluorouracil** **Cisplatin** **Paclitaxel**

Figure 1: Anticancer medicines

The anticancer properties of plants have been recognized from ancient times. The innovation of the application of the plant alkaloids (Vincristine and Vinblastine from *Vinca rosea)* for both leukaemia and Hodgkin's disease has been considered a major breakthrough in the research of chemotherapeutics (1963). From that time to till now, numerous chemotherapeutics have been isolated, identified or developed from natural resources. Paclitaxel (Texol) was obtained from the bark of *Taxus baccata* (2002), while colchicine alkaloid was first isolated from the corn of *Colchicum autumnale* (2009) and has exhibited clinical significance against different cancers such as ovarian, breast, prostate and lung cancer [9,10]. There are reports that several natural supplements, including single or mixed herbal extracts and pure compounds are able to reduce the harmful side effects of chemotherapy and can improve the quality of life (QoL) of cancer patients [11-13].



Vincristine **Colchicine** **Curcumin** **Artemisinin**

Figure 2: Anticancer phytoconstituents

Furthermore, phytochemicals derived from secondary metabolites of medicinal herbs, such as alkaloids, terpenes, quinones, steroids, polyphenolics etc. have shown promising clinical efficacy in cancers [14]. Artesunate derived from *Artemisia annua,* β-Asarone from *Acorus calamus*, Crocetin from *Crocus sativus,* Cucurbitacin B from *Cucumis melo*, Curcumin from *Curcuma longa*, Mollugin from *Rubia cordifolia*, Resveratrol from *Vitis vinifera,* Roscovitine from *Raphanus sativus,* Silibinin from *Silybum marianum,* Withanolids and Withaferin from *Withania somnifera,* etc. have been reported for their potential therapeutic role in cancer and metastasis [15,16].

Materials and Methods

A bibliographic search of PUBMED, MEDLINE, Academic Google, and other relevant websites (2010-2022) was performed for the present study. Indian medicinal plants employed in the Indian herbal formulation (Body Revival) have been the top search terms. Following the rigorous reading of the titles and abstracts used in the original search, only fully published papers were selected to take part in this review.

Results and Discussion

Herbal extracts consisting of multiple herbs for the management of cancer have been used in Ayurveda, Indian System of Medicine, since immortal time. These formulations are reported to work on multiple biochemical pathways simultaneously [17]. It is observed that mixed herbal formulations are more effective than any single herb due to their similar cumulative actions. On this concept Body Revival (Health Reactive, Rajasthan, India), a formulated herbal liquid suspension has been developed based on immunotherapy to treat cancers as mentioned in ancient Ayurvedic texts. The nine natural ingredients of Body Revival are selected from the traditional medicines as mentioned in Ayurvedic Pharmacopoeia of India [18]. The composition of Body Revival suspension (5 ml) contained pure extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Rubia cordifolia* root (200 mg), *Cucumis melo* seed (200 mg), *Symplocos racemosa* stem bark (95 mg) and honey (Q.s). Earlier preclinical studies reported, it has potent antiinflammatory, immunomodulatory, chemo preventive and antithrombotic actions. Body Revival contained polyphenolic compounds and exhibited beneficial action on myelosuppression and cardiac ischemia [19-21]. It has been reported that Body Revival therapy unquestionably better the health condition in general and mental disabilities and illness due to weak immune circumstances by modulating signalling pathways or/and cellular functions. In due course, it is helpful to fight infections from environmental pathogens or chemicals that suppress physical immunity [21].

Body Revival is used to improve the body's defence mechanism, repair damaged tissues, flush out harmful metabolites through excretion and rejuvenate healthy cells and helpful to improve quality of life and enhance longevity during palliative care in cancer patients in the last 25 years. In this juncture, we are trying to focus on the importance and the perspective of the use of Body Revival in cancers with comprehensive evidence and justification. The main part of this review is based on underlying plausible mechanistic analysis of its individual phytoconstituents as chemotherapeutics/or adjuncts and their synergistic impacts on the management of cancer.

Table 1: Bioactive anticancer components present in the ingredients of Body Revival

Natural Ingredients	Part	Extract/Active component	Anticancer action	Reference
Aegle marmelos	fruit	extract marmelin	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7, MDA-MB-231, HEp-2, PC3, A549, CoLo-05, THP-1	22,25-28
Acorus calamus	rhizome	extract β-asarone	• apoptosis • antiproliferative activity • cytotoxicity: MDA-MB-435S , Hep 3B, HeLa, HCT116, AGs, HSKMC, LoVo, HT29, LNCaP • down-regulate mitochondrial membrane potential • down regulate VEGF mRNA expression • down regulate Bcl-2/Bax ratio • up regulate caspase-9 and caspase-3 cascades	29-35
Withania somnifera	root	extract withaferin withanolide withanone	• apoptosis • antiproliferative activity • cytotoxicity: DU-145, HCT-15, A-549, IMR-32, A375, • inhibit cancer cell G2/M cycle • inhibit angiogenesis • inhibit proteosomal enzymes • inhibit tumor growth • activate TRIM16 expression • inhibits JAK1, MAP kinase P38, Bcl-xL	37-44
Blumea lacera	fruit	extract glycoalkaloids	• apoptosis • antiproliferative activity • cytotoxicity: MDA-MB-435S, BBC-1/KMC, B16F10 • anti-leukemic activity • anti-HSV activity	45-49
Rumex vesicarius	whole plant	extract	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7 and WRL68 • inhibits angiogenesis • inhibit tumors	50-52
Rubia cordifolia	root	extract mollugin furomollugin dehydro-a lapchone 1-OH tectoquinone	• apoptosis • antiproliferative activity • cytotoxicity: HEp-2, MDA-MB-231, HepG2, HeLa, MCF-7, P338, A-375, BxPC-3, U937 • protect radiation	53-59
Cucumis melo	seed	extract cucurbitacin B	• apoptosis • antiproliferative activity • cytotoxicity: K562, PC3, HCT116, HeLa, Jurkat • inhibits STAT3 activation • inhibit Raf/MEK/ERK pathway • effective in hepatocelluar cancer	60-64

Symplocos racemosa	bark	extract glycosides	• apoptosis • antiproliferative activity • cytotoxicity: Hep3B	65-68
Honey		polyphenols methylglyoxal	• apoptosis • antiproliferative activity • cytotoxicity: MCF-7, MDA-MB-231, HepG2 • suppress angiogenesis • arrest cell cycle • inhibit tumor growth • down regulate ATP production in cancer cells • protect against mutagen-induced DNA damage • protect from harmful effect of radiation	69-74

Anticancer activities of phytochemicals present in the ingredients of Body Revival

The anticancer properties of the ingredients present in Body Revival are pure aqueous extracts of *Aegle marmelos* fruit pulp, *Acorus calamus* rhizome, *Withania somnifera* root, *Blumea lacera* fruit, *Rumex vesicarius* whole plant, *Rubia cordifolia* root, *Cucumis melo* seed, *Symplocos racemosa* stem bark and honey.

Aegle marmelos

Aegle marmelos known as "bael" or "wood apple" is associated with in the family of Rutaceae. It contains marmelin, lupeol, marmelosin, furocoumarins and scopoletin [22]. It has antioxidant, antiproliferative, cytoprotective, anticancer, radio-protective, immunomodulatory, hepatoprotective and cardioprotective properties [23]. Marmelin stimulates tumor necrosis factor-α (TNF-α) and caspases to triggers apoptosis in the malignant cells [24]. Fruit pulp extract of *Aegle marmelos* exhibited anti-proliferative activity through suppressing the breast tumor growth rate [25]. It did not increase ERα mRNA levels in MCF7 and MDA-MB-231and thereby reduced the viability of cancer cells [26]. It can protect blood lymphocytes from γ-radiation [27]. It can protect buccal epithelial DNA from oxidative stress [28].

Acorus calamus

Acorus calamus well-known as "bach" or "sweet flag" is associated in Acoraceae family. The rhizome contains two main bioactive principles, (α)-asarone and (β)-asarone [29]. It has antioxidant, anti-inflammatory, anti-cancer, radioprotective, gastoprotective, neuroprotective and cardioprotective effects [30]. (β)-Asarone showed chemo preventive and anticancer effect on all kinds of cancer cell lines, such as Hep3 (hepatic carcinoma), MDA-MB-435S (breast cancer), AGS (gastric cancer), HSKMC (fibroblast), LoVo (Colon cancer), HT29 (colorectal cancer) and HeLa (cervical cancer) cells. Recently, it has been reported that β-asarone by activating the innate immune system can successfully inhibit liver metastasis and proliferative action in HCT116 colon cancer cells [31]. The underlying mechanism of β-asarone involves suppression/inhibition of cell proliferation and angiogenesis, while exaggerating apoptosis [32-35].

Withania somnifera

Withania somnifera familiar as "ashwagandha" or "winter cherry" or "Indian ginseng" is belongs to the family of Solanaceae. It exhibits antioxidant, anti-inflammatory, anti-stress, immunomodulatory, adaptogenic, chemo preventive effects, anti-cancer activity. The rhizome/root contains two main bioactive anticancer components, Withanolide and Withaferin A [36]. *W. somnifera* is a promising therapeutic agent for a broad range of cancers. It showed cytotoxicity against four human cancer cell lines such as prostrate DU-145, colon HCT-15, lung A-549 and neuroblastoma IMR-32 [37]. Several studies demonstrated that Withaferin A (WA) has the potential to restrict the genesis and proliferation of cancer cells via controlling the non-genetic influences on gene expression [38,39]. It also reduced the side effects of some cancer chemotherapeutic agents, viz. cyclophosphamide and paclitaxel without interfering with the cancer-reducing actions of the drugs [40]. Recently, it has been reported WA inhibited cell cycle, angiogenesis, proteasomes and tumor growth in the prostate [41]. Nagy and his co-workers (2020) reported that WA activates TRIM16 (tripartile motif 16) expression, which acts as tumor suppression in melanoma [42]. In molecular docking studies, Withanolide, WA and Withanone showed the best binding affinity against Protein kinase C and (ii) NF-KB. Furthermore, enzyme ligand binding affinity have also been noted against Tyrosine-protein kinase JAK1, Mitogen-activated protein kinase P38, Glutathione Reductase and Glutathione S-Transferases [43,44]. Molecular docking study also provides evidence that Withanolide, Withaferin A and Withanone robustly attach to the macromolecules to restrain escalation of cancer cells, as a promising anticancer medicine.

Blumea lacera

Blumea lacera frequently known as "kakronda" or "lettuce"

is associated in the family of Asteraceae. It possesses antioxidant, anti-ulcer, anti-diarrheal, hepatoprotective, antiviral activities [45]. It contains phenolics, glycoalkaloids and essential oils [47,48]. *B. lacera* leaves have shown non-selective cytotoxic activity against MDA-MB-435S, BBC-1/KMC, B16F10 cells [45, 48]. It exhibited a broad spectrum of anti-leukemic activity and strong anti-HSV activity [49].

Rumex vesicarius

Rumex vesicarius also known as "amlabet" or "bladder dock" is belongs to the family of Polygonaceae. It is used in the treatment of tumors, liver diseases, cardiovascular disease, asthma, bronchitis and nausea [50]. It possessed a promising anticancer potential against MCF-7 and WRL68 cell lines and HCC induced hepatic carcinoma model. It showed potent antiangiogenic and antiproliferative activities [51,52].

Rubia cordifolia

Rubia cordifolia commonly known as "manjishtha" or "Indian maddar" is belongs to the family of Rubiaceae. It contains anthraquinones, glycosides, terpenes and carboxylic acid groups of compounds such as mollugin, furomollugin, dehydro-α lactone, 1-hydroxytectoquinone, alizarin, rubuadin, lucidine, manjisthin and bicyclic hexapeptides [53,54]. The active constituent, Mollugin, exhibited considerable activity against P338 lymphoid leukemia [53,55]. Tripathy and Singh (2007) reported the herb has radioprotective action. Aqueous root extract of *R. cordifolia* exhibited cytotoxcity on HeLa cells [56]. Moreover, 1-hydroxytectoquinone isolated from *R. cordifolia* cytotoxic has an effect against A375 human malignant melanoma [57]. The methanolic extract of *Rubia cordifolia* demonstrated antiproliferative and apoptotic properties on HEp-2 (human laryngeal carcinoma) cell line in a dose-dependent manner [58]. Furthermore, it showed cytotoxic action on MDA-MB-231, HepG2, BxPC-3 and MCF-7 cancer cells [59].

Cucumis melo

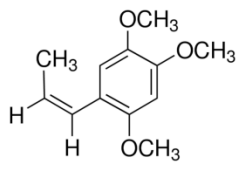
Cucumis melo or "madhuphala" or "muskmelon" is belongs to the family of Cucurbitaceae. Cucurbitacin B (CuB) is a tetracyclic-triterpenes present in *Cucumis melo* [60]. The anticancer activity of CuB in human leukemia cells has been observed. It restrains STAT3 activation and the Raf/MEK/ERK pathway in K562 leukemic cells [61]. It is also used as a liver protection medicine in curing hepatic lesions and liver cancer [60,62]. CuB also inhibited multiple myeloma cells in the G2/M phase [63]. *Cucumis melo* exhibited cytotoxicity against PC3, HCT116, HeLa, and Jurkat cell lines [64].

Symplocos racemosa

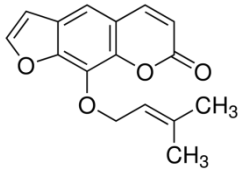
Symplocos racemosa or "Lodhra" is associated with the family of Symlocaceae. It has been extensively applied in traditional medicine for gastro-intestinal and liver problems, uterine complaints, menstrual disorders and solid tumors. It has several bioactive glycosides such as symplocomoside, symponoside, benzoyl salireposide, salireposide etc. [65,66]. *Symplocos racemosa* bark showed cytotoxic action on Hep3B hepatocellular carcinoma cells [67]. Raval and his coworkers (2009) evaluated the chloroform, butanol and methyl acetate bark extracts for their cytotoxicity assay against leukemia and cervical cancer cell lines. They reported that the butanol extract had the highest cytotoxicity activity against HeLa cell line [68].

Honey

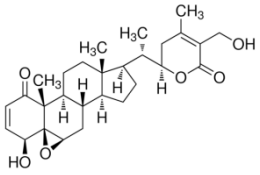
Honey is composed of sugars, amino acids, proteins, enzymes, vitamins, flavonoids, phenolic acids and other compounds. Bioactive polyphenolic compounds such as kaempferol, quercetin, chrysin, luteolin, apigenin, naringenin etc are present in honey [69]. Honey has potential apoptotic, antiproliferative and immunomodulatory activities [70]. It antagonizes estrogenic activity, restricts cell proliferation, exaggerates apoptosis and reduces mitochondrial membrane potential in the two most widely used breast cancer cell lines, MCF-7 and MDA-MB-231[71,72]. It inhibits cell proliferation, suppresses angiogenesis, induces apoptosis, protects against mutagen-induced DNA damage in HepG2 liver cancer cells and HT 29 colorectal cancer [73]. Honey contains other anticancer molecules such as methylglyoxal, which inactivates glyceraldehyde-3-phosphate dehydrogenase (GA3PD) and down regulates ATP production in cancer cells and thereby accelerating the death of cancer cells [74]. Hence, honey is potentially helpful to resist cancer via controlling three key steps of carcinogenesis: initiation, proliferation and progression.



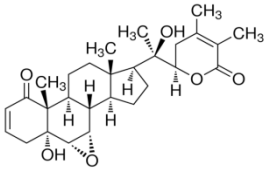
β-Asarone



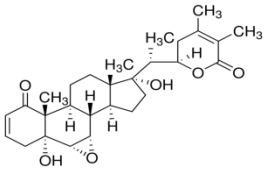
Marmelin



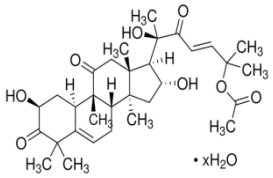
Withaferin A



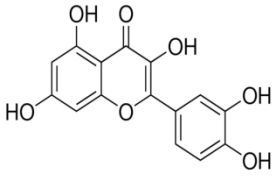
Withanolide



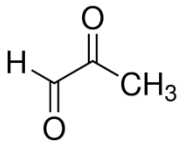
Withanone



Cucurbitacin B



Quercetin



Methylglyoxal

Figure 3: Anticancer phytoconstituents present in Body Revival

Body Revival: Possible modes of anticancer actions

Body Revival is a composite of herbal medicines and honey with multiple phytoconstituents recognized as anticancer therapeutic potentials. It is assumed that herbal formulations with multiple phytochemicals may have better therapeutic effects than the same phytochemicals taken alone. Based on this thought, a combination of the anticancer phytochemicals is blended in suspension to get a more potent therapeutic anticancer agent. Some of the known bioactive anticancer phytoconstituents present in Body Revival are β-asarone, cucurbitacin B, furomollugin, 1-hydroxytectoquinone, luteolin, marmelin, methylglyoxal, mollugin, naringenin, quercetin, symplocomoside, withanone, withanolid, withaferin A etc. Most of them target in the plasma membrane, transmembrane receptors, tyrosine kinases and G-protein coupled receptors. Therefore, possible modes of anticancer actions of Body Revival are (i) stimulate the immune system; (ii) prevent DNA damage and repair damaged DNA; (iii) reduce oxidative damage; (iv) antiproliferation; (v) cancer/tumor cell cycle arrest; (vi) induction of apoptosis and (vii) inhibition of angiogenesis; (viii) inhibition of metastasis; (ix) restore normal cell from toxic chemicals (chemoprevention); and (x) restore/protect normal cell from harmful effect of radiation. It is presumed that natural resource derived components in amalgamation with anticancer agents have immense potential to fight with tumour/cancer cells without affecting normal cells like lymphocytes or fibroblasts. But still, it is not fully understood whether Body Revival suspension is cytotoxic anticancer medicine or targeted anticancer medicine.

Therapeutic Application of Herbal Formulations in Cancer

Herbal formulations frequently composed with some primary herbs which are responsible for the target therapeutic actions and accessory herbs which have either synergetic actions to improve the therapeutic properties of primary herbs or nullifying the other effects related to disease. There are multiple scientific evidences and clinical trial reports of using herbal formulations on cancers. In this juncture, some marketed anticancer drugs are tabulated in the Table 2. Most of these formulations are now applied as a combination therapy with the conventional chemotherapy, radiotherapy or palliative care treatment to enhance the therapeutic advantages by reducing the side effects or complications.

Herbal Formulation	No. of Ingredients	Country Origin	Anticancer Actions	Reference Number
PC-SPES	8	China	Prostate cancer	75
Sho saiko-to (TJ-9)	7	Japan	Hepatic cancer	76
Compound 861	10	China	Hepatic cancer	77
Bu-Zhong-Yi-Qi	8	China/Japan	Lung, ovarian and colorectal cancer	78
Goshajinkigan	10	Japan	Colorectal cancer	79
Rikkunshito	8	Japan	Chemotherapy induced nausea and vomiting	80
HUMA	8	India	Oral cancer, chemotherapy	81
Carctol	8	India	Chemotherapy induced nausea and vomiting	82
MaZiRenWan	6	China	Palliative care	83
HC-9	9	India	Breast cancer	84
BASANT	7	India	Cervical cancer	85
Varunadi Ghritha	18	India	Head-neck cancer	86

Table 2: Herbal formulations used in cancer therapy.

Anorexia, vomiting, constipation, diarrhoea, anaemia, headache, fatigue, pain, infection and hair loss are the common sign and symptoms of conventional therapy in cancers. A substantial number of meta-analysis and review of randomized control trials specifically informed that herbal medicines and formulations could improve the quality of life of cancer patients during conventional therapy and palliative care [87-90]. Other than that life style modifications including food habits, exercise, meditation and Yoga can improve the quality of life of cancer patients, particularly during palliative care [91,92].

Conclusions

The burden of cancer in society can be lowered by early detection and to starting effective and specific treatment management of cancer. Most cancers have high possibility of curing if diagnosed early and preventing the spread of disease. Body Revival is a polyherbal medicine intended to use broad spectrum cancer patients. From literatures based on ancient knowledge and modern research, strongly admits that Body Revival is able to stimulate the immune system, protect DNA from injury, restores damaged DNA, lower oxidative impairment, anti-proliferation, cancer cell cycle arrest, initiation of apoptosis, suppression of angiogenesis and metastasis, chemo preventive or restore/protects normal cells from harmful effects of radiation. The goal-oriented programmed clinical approaches are highly desirable in future to conclude the effectiveness and nature of the anticancer drug of natural origin.

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Research Article

In-Vitro and *In-Silico* Approach Distinguish ER-α and HER-2 Antagonistic Properties of Indian Herbal Formulation on Breast Cancer

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Abstract

Objectives: The anticancer effect of an Indian herbal preparation was studied under a cancer cell line, as well as the in silico computational methods that explain the probability of protein ligands binding to ER- α and HER-2 receptors.

Method: The *in vitro* anticancer activity of Body Revival® suspension (BR) was determined using cytotoxicity tests, cell invasion and migration assays, and metastatic protein expression assays using MCF-7 breast cancer cells. The computational predictive biological method was applied to find out the pharmacodynamic and pharmacokinetic interactions between the active molecules present in the BR and ER- α/and HER-2 of breast cancer.

Results: BR showed significant and dose dependent cytotoxic effects on MCF-7 cells. The 50% effective cytotoxic dose of BR was 34.27µl/ml. It restricted invasion (26%) and migration (28%) of cancer cells than BSA control. MMP-9 and IL-6 concentration were reduced significantly ($p<0.001$) after treatment. Cucurbitacin B had maximum *in silico* binding energy score (-7.8) with ER-α, while symconoside B had with HER-2 (-8.4); but, among the other interactions between the two ligands and receptors, withaferin A had the highest affinity (-15.3). Additionally, withaferin A, symconoside A, and symconoside B curcurbitacin A demonstrated bioavailability and fulfilled safety standards.

Conclusion: Body Revival® showed as a powerful multi-target inhibitor of ER- α and HER-2 that has prospective anticancer action without side effects, and may be useful in the therapy management following a successful trial in breast cancer patients.

Keywords: Breast cancer, Cytotoxicity, MCF-7, ER- α, HER-2, Herbs, *In Silico*

INTRODUCTION

Breast cancer is the most common cancer diagnosed worldwide, with an estimated 2.3 million new cases in 2020 alone. Due to the long-standing predominance of risk factors related to reproduction, hormones, and lifestyle in North America, Canada, and Western Europe, incidence rates in these countries have been higher[1-2]. However, Asian nations like China, Japan, and India have also seen an increase in the prevalence of breast cancer[3]. Recent data suggest, 1 in 9 Indian female has a lifelong risk of developing breast cancer[4].

Breast cancer is a genetically and clinically heterogeneous disease. Due to a lack of diagnostic markers, it has been difficult to measure the progression of this disease[5]. Breast cancers were categorized using conventional tumor classification such as fibroepithelial, myoepithelial, and mesenchymal neoplasms[6-7]. Human epidermal growth factor receptor-2 (HER-2) and hormone receptors (ER and PR) are the most relevant clinical markers that are now frequently employed in stratifying the disease[8]. HER-2 is positive in 1 in 5 individuals with breast cancer, while ER-α is positive in 1 in 3 cases[9]. On that molecular classes, this disease has now recognized as estrogen receptor positive (ER^+), HER-2-positive ($HER2^+$), triple-negative (TN), and unclassified[10]. Chemotherapeutics are used for its treatment, which either acts on one or more of these up- or down-regulating receptor signaling pathways to confront the deadly disease, but they are accompanied by serious side effects, including emesis, anorexia, diarrhea, skin rashes, hot flashes, headaches, fever, exhaustion, and hair loss[11-13]. Numerous herbal medications are used in conjunction with chemotherapy/or radiation therapy to overcome these challenges and increase the effectiveness of cancer treatment while minimizing side effects and consequences[14-16].

Body Revival® (BR), a polyherbal suspension has been developed (M/s Health Reactive, Mumbai) to treat cancers. Each 5 ml BR contained dry water extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Rubia cordifolia* root (200 mg), *Symplocos racemosa* stem bark (95

mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Cucumis melo* seed (200 mg), and honey (qs). These substances, together with their active constituents, have anticancer characteristics, including β-asarone, cucurbitacin B, methylglyoxal, quercetin, symconoside A, symconoside B and withaferin[17]. In addition, it has a substantial quantity of polyphenols such gallic acid, p-coumaric acid, quercetin, and apigenin[18]. BR was reported to prevent myocardial infarction and decrease vascular platelet aggregation in animal models[19]. Furthermore, it enhanced cellularity in bone marrow and leukocyte, granulocyte, and lymphocyte counts in peripheral blood of immunosuppressive animals[18]. Recent study suggested BR improved quality of life, especially in the psychological and physical spheres of daily living of breast cancer patients[20]. However, at this time, its mode of action in cancer environments is a matter of debate. Hence, extensive research was carried out using *in vitro* and *in silico* computational methodologies to ascertain the potential effect of BR on breast cancer cells and the underlying protein-ligands binding interaction probabilities with ER- and HER-2 receptors.

MATERIAL AND METHODS

In vitro anticancer activities

The following verified standard procedures for screening cancer drugs were employed.

Cytotoxicity Test

MCF-7 cells were maintained in Dulbecco's modified eagle medium (DMEM) containing 10% FBS and incubated at 37°C in CO_2 incubator (Thermo Fisher, USA). Streptomycin and penicillin (100µg/ml) was used to avoid any contamination. Approximately, 1×10^4 cells were grown separately in 96 well plates and treated with varying concentrations of BR (*i.e.*, 0, 6.25, 12.5, 25, 50, 100 µl/ml) at 37°C for 24h. In the following day, post-treated cells were washed with PBS, and incubated with MTT (1 mg/ml stock) at 37°C for 4h. The absorbance was measured at 570 nm using a micro-plate reader (Sinothinker, China). All tests were done in triplicate. The 50% cytotoxic concentration of the test compound was identified for treated cell line[21].

Cell Invasion and Migration Assay

1×10^4 MCF-7 cells were cultured in 24 well plates at 37°C in CO_2 incubator for 24h. The post-treated cells were then further incubated for another 24h after constructing scratches on the monolayer cells, and the migration was observed using an inverted microscope (Zeiss, Germany). In invasion assay, 1×10^4 MCF-7 cells were seeded in Transwell chamber (ECM 555, Sigma, USA) for overnight at 37°C in a CO_2 incubator. Non-invaded cells were stained with Trypan blue dye (Sigma, USA) and washed sequentially to remove death cells. The invasive cells in the matrix were observed under an inverted microscope and the corresponding intensities were measured using a micro-plate reader at 450 nm[22].

Metastatic Protein Expression Assay

Briefly, 1×10^3 MCF-7 cells were incubated with BSA vehicle or BR for 24 h at 37°C. Thereafter, relative protein expression analysis was carried out using matrix metalloproteinase-9 (MMP-9) and inflammatory cytokine, interleukin-6 (IL-6) specific ELISA kits (RayBio, USA) following the supplier's protocol. The micro-plate was read at 450 nm.

In Silico Molecular Docking

The computational predictive biological method was applied to find out the pharmacodynamic and pharmacokinetic interactions between the molecules present in BR and breast cancer receptors.

(i) Receptors preparation: The crystal structures of ER-α and HER-2 were downloaded from the Protein data bank (https://www.rcsb.org/). The structure of the protein was validated using SAVES 6.0 server. Energy minimization was done using SPDBV software. The structural quality of the target protein was determined using PROCHECK server.

ii) Determination of active sites: The presence of amino acids in the active site was determined by the CASTp web server[23].

(iii) Ligand preparation: The structure data format of the selected 10 bioactive compounds of BR (apigenin, cucurbitacin B, gallic acid, methylglyoxal, p-coumaric acid, quercetin, symconoside A, symconoside B, withaferin and β-asarone) was retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov). Gasteiger charges (polar hydrogen charges) were drafted and non-polar hydrogen molecules were combined with carbons. The protein and ligand were converted to PDBQT format using Autodock 4.2 tools.

(iv) Molecular docking: The docking of all 10 compounds was done into a 3D X-ray structure by Autodock 4.2 and AutodockVina. This is a fruitful automated method to investigate the binding of macromolecule and ligands. With the help of Autodock tools, Gasteiger charges and hydrogen atoms were added to the protein and for simulation AutodockVina was used. The algorithm that AutodockVina uses is the Broyden-Fletcher-Goldfarb-Shanno algorithm that improves the accuracy of docking and prediction of the binding mode. Finally, the binding complexes were visualized by Bovia Discovery Studio Visualizer[24].

Pharmacokinetic, toxicity and safety studies:

Absorption, Distribution, Metabolism, and Excretion (ADME)

ADME were measured at the SwissADME website (https://www.swissadme.ch). The following parameters such as aqueous solubility (LogS), skin permeation (Log kp), bioavailability Score, human intestinal absorption, blood-brain barrier and CYP2C9 inhibitors were measured and compared.

Toxicity and Safety Prediction

The tolerance capacity of animal models as well as human before application and ingestion are important. To predict the toxicity level, an online server named pkCSM (http://biosig.unimelb.edu.au/pkcsm/) was used where the structure can be drawn otherwise input the SMILES which were downloaded from Drugbank, Pubchem or Zinc15 database. The pkCSM allows the study of toxicological effects by analyzing AMES toxicity, oral rat chronic and acute toxicity and maximum tolerated dose for human.

Statistical Analysis

The research results were input in the electronic data-sheet for statistical analysis using SPSS version 20 (IBM, Chicago, USA). Categorical variables were presented as percentages. All data were presented as mean and standard deviation (SD) and statistically analyzed by t-test. P-value ≤0.05 was considered significant.

RESULTS

The results of cytotoxic effects of different doses of BR in MCF-7 cells were presented in Fig. 1A. The 50% cytotoxic dose of BR was noted 34.27µl/ml ($y=-0.964x+83.04$; $r^2=0.825$). In transwell cell membrane, BR exhibited 34% invasion (34±8.2)

by low dose (10µl/ml) and 26% by high dose (10µl/ml) than BSA control (Fig. 1B). Moreover, BR showed 42% (42±9.44) migration at low dose and 28% (28±10.23) at high dose, compared to 70% (70±8.25) migration in the BSA control (Fig. 1C).

MMP-9 or metastatic matrix protein expression of MCF-7 cells showed dose dependent inhibition after BR treatment (Fig. 1D). BR at the dose of10 µl/ml inhibited 36% (56±5.28 pg/ml) and 52% (42±9.14) of MMP-9 respectively than BSA control (88±3.24). BR demonstrated dose dependent down regulation of IL-6 concentrations in the MCF-7 cells (Fig. 1E). At the dose of 10 µl/ml BR reduced 32.9% (63±8.3) IL-6 and at the dose of 20 µl/ml (48±7.6) diminished 48.9% compared to BSA control (94±5.8).

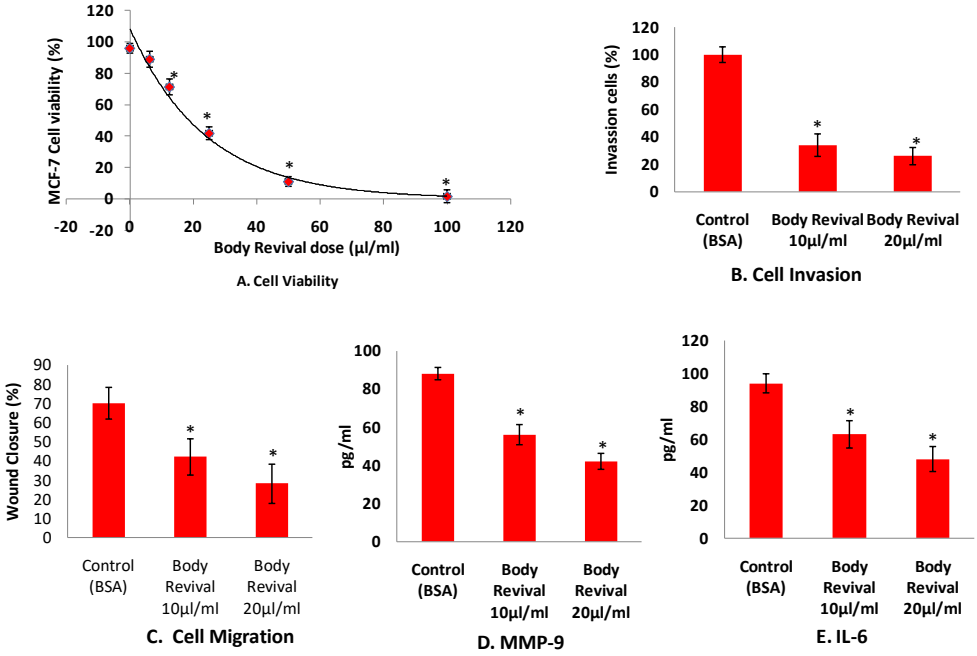

Figure 1: *In vitro* anti-cancer effect of BR on MCF-7 cells

The result of *in silico* molecular docking analysis of protein-ligands binding was described in Table 1. The binding energy score of cucurbitacin B (-7.8) was the maximum, followed by withaferin (-7.7), symconoside A (-7.2), symconoside B (-6.8) and quercetin (-6.3) with ER-α indicating their strong therapeutic inhibitory properties with the protein ligands binding. Furthermore, the binding energy score of symconoside B (-8.4) was the highest, followed by symconoside A (-7.9), withaferin A (-7.6), quercetin (-7.5), cucurbitacin B (-6.9), apigenin (-6.9) and gallic acid (-6.4) with HER-2 also. With regard to interactions between ligands and receptors (ER-α and HER-2), withaferin A had the highest affinity (-15.3).

Table 1: *In silico* protein–ligands binding energy of active components of BR

Active Components	Protein – Ligands binding energy (kcal/mol)		
	ER-α (5JIH)	HER2 (5T92)	Total
Apigenin	-5.5	-6.9	-12.4
Cucurbitacin B	**-7.8**	-6.9	-14.7
Gallic acid	-5.2	-6.4	-11.6
methylglyoxal	-2.8	-3.3	-6.1
p-Coumaric acid	-5.2	-6.1	-11.3
Quercetin	-6.3	-7.5	-13.8
Symconoside A	-7.2	-7.9	-15.1
Symconoside B	-6.8	**-8.4**	-15.2
withaferin	-7.7	-7.6	**-15.3**
β-asarone	-4.5	-4.9	-9.4

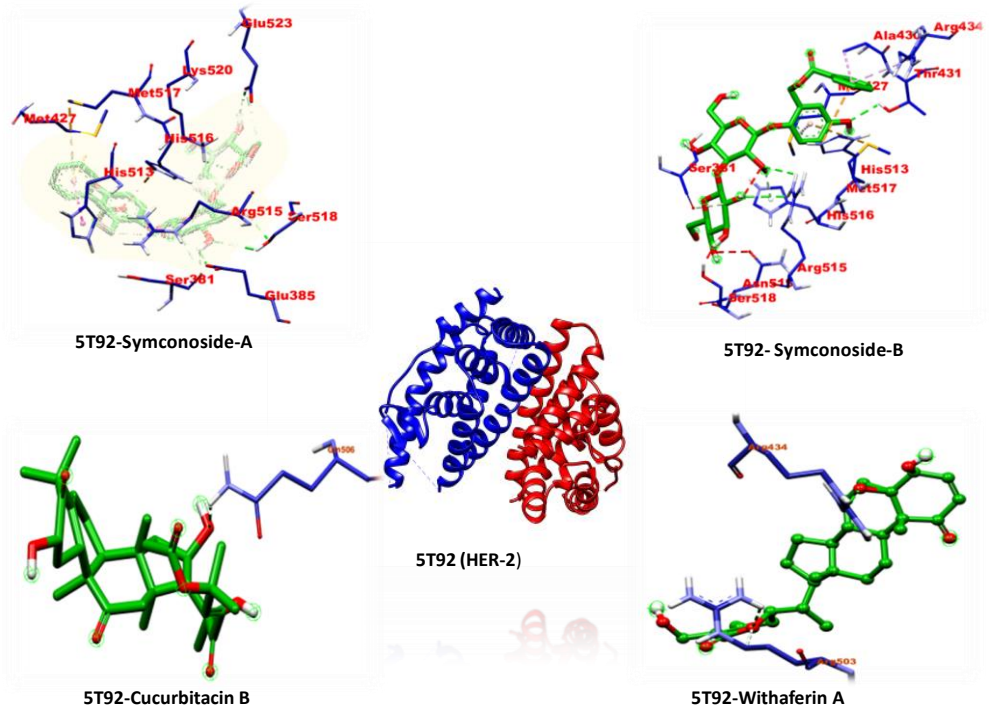

Figure 2: *In silico* HER-2 receptor binding sites of 4 most active components of BR

The four most active ingredients present in BR, symconoside A, symconoside B, curcurbitacin, and withaferin A with HER-2, were shown in Fig. 2 as protein-ligand binding sites with amino acid consequences. Figures showed symconoside A binds with 10 amino acids: Ser_381, Glu_385, Met_427, His_513, Arg_515, His_516, Met_517, Ser_518, Lys_520 and Glu_525 of HER-2; symconoside B binds with 11 amino acids: Ser_381, Met_427, Ala_430, Thr_431, Ala_434, His_513, Arg_515, His_516, Met_517, Ser_518 and Arg_519 of HER-2; cucurbitacin B binds with 1 amino acid: Gln_506 of HER-2; and withaferin A binds with 2 amino acids: Arg_434 and Arg_503.

Table 2. *In silico* pharmacokinetic, ADME and toxicological properties of active components of BR

Properties	Symconoside A	Symconoside B	Curcurbitacin B	Withaferin A
Molecular formula	$C_{26}H_{32}O_{14}$	$C_{26}H_{32}O_{14}$	$C_{32}H_{46}O_8$	$C_{28}H_{38}O_6$
Molecular weight (g/mol)	568.52	568.52	558.7	470.6
H-bond donor	14	8	3	6
H-bond acceptor	8	14	8	2
Lipinski violation	3	3	1	0
Skin permeation (LogKp)	-2.73	-2.73	-3.50	-3.02
Aqueous solubility (LogS)	-2.606	-2.79	-4.28	-4.46
Bioavailability score	0.17	0.17	0.55	0.55
Human intestinal absorption	32.58 (Low)	30.24 (Low)	79.86 (High)	86.31 (High)
Caco-2 permeability	-0.651	-0.261	0.582	-0.651
Blood Brain Barrier	-1.45	-1.52	-1.17	-0.03
CYP2C9 inhibitor	No	No	No	No
AMES Toxicity	No	No	No	No
Rat Oral Chronic Toxicity (log mg/kg bw/day)	5.42	5.53	1.66	0.95
Rat Oral Acute Toxicity (LD_{50}) log mg/kg bw	2.50	2.71	3.82	2.78
Maximum tolerable dose (human) log mg/kg/day	-0.008	-0.194	-0.77	-0.41

Table 2 shown the *in silico* anticipated ADME and toxicity evaluations of the four major interacting molecules found in BR, including symconoside A, symconoside B curcurbitacin B, and withaferin A. The strongest H-bond donor was symconoside A, although symconoside B also has the ability to act as an H-bond acceptor. The Lipinski rule was only not broken by withaferin A. Withaferin A and cucurbitacin B both had a 0.55 bioavailability score. Withaferin A showed the highest permeability in Caco-2 cells (0.885 cm/sec). Withaferin A had an intestine absorption rate of 86.32, followed by cucurbitacin B at 79 and symconosides at 30 to 32. The blood-brain barrier (BBB) can be more easily crossed by withaferin A than by the other three substances. No active ingredients have been found to be harmful to AMES or to inhibit CYP2C9. Symconoside B, cucurbitacin B, and withaferin A all had human tolerated doses (log mg/kg/day) of -0.194, -0.77, and -0.412, respectively, demonstrating their non-toxic nature.

DISCUSSION

Alkaloids, flavonoids, terpenoids and polyphenols compounds are a few examples of natural compounds that have been extensively used in preclinical research of breast cancer over the past 20 years due to their abundance in the natural world, low toxicity, and high efficacy. Recently published studies revealed active components of BR possess anticancer effects. These components might improve the immune system's capacity to defend DNA against damage, reduce oxidative damage, or initiate the apoptotic process[17-18]. However, its role in cancer has not been explored as a composite. Cancer immunotherapy has gained increasing attention over the past few decades and has grown into an excellent option for cancer treatment[25]. Clinical adjunct therapies for the treatment of cancer have a long history in traditional Indian medicine.

MTT cell proliferation assay is one of the most widely used for evaluating anticancer activity of both synthetic derivatives and natural products. The viable cells contain NAD(P)H-dependent oxido-reductase enzymes, which reduce the MTT to formazan. In the present study, BR dose dependently and significantly enhanced the cytotoxicity and cell viability was seen to drop in MCF-7 breast cancer cells. This single study unequivocally demonstrated BR has anticancer effect. In a previous study, withaferin A, one of the active ingredients in BR, demonstrated cytotoxicity against four human cancer cell lines: DU-145 for the prostate, HCT-15 for the colon, A-549 for the lung, and IMR-32 for the neuroblastoma[26]. Similarly, cucurbitacin B has been found to have anticancer properties in human leukemia cells[27].Moreover, symconosides showed cytotoxic action on Hep3B hepatocellular carcinoma cells[28].

In the transwell cell migration assay, the ability of cells to chemotactically move in the direction of a chemo-attractant is quantified. Cell migration studies tally the quantity of cells that pass through a porous membrane, whereas cell invasion procedures quantify cell movement across extracellular matrix, a critical step in angiogenesis. The topology of the extracellular environment, adhesion, confinement, and stiffness are the main physical factors affecting cell movement[29-30]. Additionally, it might evaluate distinct migratory capacities brought on by the over-expression of a receptor[21]. Present study demonstrated BR has the ability to prevent cancer cells from spreading over normal cells into the surrounding tissues. Fruit pulp extract of *Aegle marmelos,* one of the important components of BR exhibited anti-proliferative activity through suppressing the breast tumor growth rate[31].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases. MMP-9 plays vital roles in cancer cell invasion and tumor metastasis. It supports angiogenesis by weakening matrix barriers and has the ability to reduce tumor neovascularization. It also plays a part in the breakdown of the basement membrane[32]. Breast cancer tissues have high levels of MMP-9, which is directly linked to lymph node metastases and tumor stage[33]. Triple-negative and HER-2-positive breast tumors clearly exhibit over expression of MMP-9[34]. It can serve as a guide for determining the prognosis and course of treatment for breast cancer. Hence, development of MMP-9 inhibitors is an important area for breast cancer research[35]. In the present study, metastatic matrix protein expression, particularly MMP-9 showed dose dependent inhibition after BR treatment in MCF-7. Withaferin A showed a significant correlation with a decrease of MMP-9 mRNA expression levels in metastatic Caski cell line[36].

Furthermore, many cancers, including breast cancer, have been shown to over express the cytokine interleukin-6 (IL-6), which is found in the tumor microenvironment. In the tumor microenvironment, fibroblasts associated with the tumor and tumor cells are the main producers of IL-6[37-38]. The immunopathogenic role of IL-6 and its signaling in breast cancer tumor development, metastasis, and treatment resistance has been shown in numerous investigations[39]. It is clear that the presence of high levels of IL-6 in breast cancer tissues encouraged the production of Jagged-1, which in turn helped the cancer cells proliferate and maintain their aggressive nature[40]. Therefore, it would seem that IL-6 targeting and/or its receptor in combination with other effective anticancer medicines could be a potent therapeutic approach for breast cancer therapy[41]. In this study, BR treatment showed significant inhibition of IL-6 concentrations in the MCF-7 metabolites. Other studies confirmed that withaferin A blocked IL-6 and TNF-α-induced cancer cell invasion and thereby eliminated the interactions between STAT3, STAT1, and NF-kB and suppressed STAT3 phosphorylation[42].

Breast stem cell proliferation, differentiation, and cell death are regulated by ER-α and HER-2 signaling pathways, and breast cancer is mostly caused by the over expression of these signaling pathways. Hence, ER-α and HER-2 antagonists have received a lot of interest as possible anti-cancer drugs[43]. The target of the present grid based *in silico* docking study was to screen out the potential antagonists of ER-α and HER-2 from the most effective compounds or ligands present in BR, like apigenin, cucurbitacin B, gallic acid, methylglyoxal, p-coumaric acid, quercetin, symconoside A, symconoside B, withaferin A and β-asarone[17]. The present study revealed cucurbitacin B has the highest binding score with ER-α, followed by withaferin A, symconoside A, and B, indicating their strong antagonistic properties in breast cancer. In addition, symconoside B has the greatest binding score to HER-2, followed by symconoside A, withaferin A, quercetin, cucurbitacin B, and apigenin. Withaferin A also displayed the most encouraging potentiating qualities when taking into account the overall protein-ligands binding affinity for ER-α and HER-2. Withaferin A has previously been shown to treat down-regulation of ER-α protein expression, which correlates with a decline in nuclear level, suppression of mRNA level, and inhibition of E2-dependent activation of ERE2e1b-luciferase reporter gene[44]. Thus, four of the ten active molecules—symconosides A and B, cucurbitacin B, and withaferin A of BR—exhibited synergistic therapeutic potentials for breast cancer. In order to predict preclinical toxicological endpoints, clinical side effects, and ADME characteristics of these substances, *in silico* approaches were further explored. This study offers a powerful systems pharmacology approach for identification of promising and safe molecules from BR for development of breast cancer therapy.

Withaferin A interacts with the positively charged residual amino acids of HER-2 at Arg_434 and Arg_503 and possesses 6

hydrogen donor bonds and 2 hydrogen acceptor bonds; whereas symconoside A interacts with 10 residual amino acids, symconoside B with 11, and cucurbitacin B with a single (Gln_506). Since withaferin A adheres to all five of Lipinski's principles, it may be termed orally bioavailable than other three components. Withaferin A has the greatest aqueous solubility, whereas symconoside is poorly soluble. The Caco-2 human colon cancer cell line is an example of an experimental screen used in drug discovery to measure membrane permeability and estimate human oral absorption. The most rapid rate of oral absorption and Caco-2 permeability was found in withaferin A. The blood-brain barrier (BBB) has been described as a dynamic interface that regulates the passage of substances between the blood and the brain to maintain the best possible circumstances for neuronal and glial activity[45]. BBB prevents the entry of harmful substances into the brain. All four substances were expected to pass the BBB.

The Ames test is typically used in predicted toxicity models to assess potential carcinogenic/mutagenic effects of substances. In the current investigation, the Ames test revealed that none of the bioactive components were carcinogenic. Moreover, Cytochrome P450 2C9 (CYP2C9) enzyme in liver is involved in drug metabolism and excretion. CYP2C9 inhibition may lead to toxic drug accumulation and hazardous drug-drug interactions in the body. Present *in silico* study highlighted that the components present in BR did not have any role in CYP2C9 inhibition. Additionally, they failed to exhibit oral acute and chronic toxicity in animal models, and they were categorized as class V according to the poisonous class of the Globally Harmonized System of classification of chemical labels.

Therefore, taking into account *in vitro* and *in silico* studies, it may be concluded that the bioactive ingredients present in Body Revival®, exhibit as potent multi-target inhibitors of ER-α and HER-2 with potential anticancer activity without side effects and may be helpful in the treatment management after successful trial in breast cancer patients.

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Conflict of Interest

There is no conflict of interest.

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Assessment of Immunopotentiation Action of Standardized Indian Herbal Formulation (Body Revival)

Munir Khan, Rampal Somani and Tapas Kumar Sur

***Abstract*—Immunity is a prime indicator of the balance between health and disease. Malnutrition, aging, chronic stress, chronic infections, antibiotics and chemotherapeutic agents can suppress the immune function. Body Revival (BR) an herbal preparation was standardized by physicochemical parameters and HPLC. Body Revival pretreatment significantly and dose dependently (200-400 mg/kg) improved the leukocytes, granulocytes and lymphocytes counts in peripheral blood and cellularity in bone marrow in Cyclophosphamide induced immune suppressive mice. Therefore, Body Revival has immunopotentiating action and can be therapeutically useful for acute and chronic infections or other immune suppressive diseases.**

***Index Terms*—Chemotherapeutics; Cyclophosphamide; HPLC; Immunopotentiation.**

I. Introduction

Immune systems protect our body against any kind of infections from deadly virus, bacteria and other harmful microorganisms. The immune system develops appropriate tolerance to avoid unwanted response to healthy tissues. This system is more and more found to be involved in the development of several chronic illness including Alzheimer's disease, type 1 diabetes and hepatocellular carcinoma [1]. Innate and adaptive immunity mainly depends on the activity of white blood cells. Innate immunity largely depends upon granulocytes, macrophages and dendritic cells; while adaptive immune response depends upon lymphocytes for providing long term immunity [2]. The innate immune system also consists of interferons (IFNs) and pro-inflammatory cytokines or interleukins. During the viral threat IFNs acts to prevent the spreads of virus in the host [3]. It is general believes that older and younger people are susceptible to infectious diseases, particularly viral and bacterial infections due to their poor/weak immune system in their body.

Immunomodulators could act (stimulate or suppress) on both the innate- and adaptive immune systems to exert positive effects on the host defence mechanisms or enhance the host's ability to tolerate damages caused by toxic compounds (such as chemotherapeutics) [4]. Consequently, research efforts largely focus on identifying and investigating specific groups of herb-related compounds (such as flavonoids, polysaccharides, lactones, alkaloids, diterpenoids, and glycosides) and their potential implication in immunomodulation [5],[6]. Drugs of natural origin have also demonstrated their usefulness against a wide variety of viral infections and diseases [7]. These groups of herbal medicines are gaining popularity as a means to control viral infections due to their safety and low incidence of side effects [8],[9]. Some of the important herbs having immunomodulation, antibacterial, antiviral, antioxidant and anti-inflammatory properties are *Panax ginseng*, *Withania somnifera, Ocimum sanctum, Rubia cardifolia*, *Phyllanthus emblica, Aegle marmelos, Glycyrrhiza glabra, Blumea lacera*, *Symplocos racemosa Acorus calamus, Cucumis melo.* Mehrotra et al., (2003) have been reported the anticellular and immunosuppressive properties of *A. calamus* [10]. Badam (1995) reported *A. calamus* has antiviral activity against *Herpes simplex* virus HSV-1 and HSV-2 [11]. Marmelide, a coumarin derivative isolated from *Aegle marmelos* proved to be highly potent compound against human coxsackieviruses B1-B6 compared to ribavirin [12]. *Blumea lacera* reported for its antimicrobial and anti cancer activities [13]. Antimicrobial and antiviral actions of *Cucumis melo* and *Rubia cordifolia* have been established [14],[15]. *Symplocos racemosa* has also antiviral and anticancer activity [16]. *Withania somnifera* is known as Indian adaptogen and its role on immunity and cancer research is well documented [17],[18]. Perhaps, it is assumed that these herbal and natural medicines drugs are devoid from drug resistance and drug dependence.

It is assumed that mixed herbal formulations are more therapeutically potent than any single herb, because of their synergistic actions. In this context Body Revival (BR), a new formulation, prepared with the active parts of herbs reported for antimicrobial, antiviral, anticancer and detoxification activities was screened for its immune potentiating action, although it has already been reported for effective in cardio protective function [19]. Therefore, the present study was aimed to validate the herbal formulation in the view point of pharmaceutical approaches and also establish its immunotherapeutic role against chemotherapeutic immunosuppressive experimental model.

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II. MATERIALS AND METHODS

A. Animals

Swiss mice, body weight between 20-30g of either sex were housed 4-6 in groups on polypropylene cages with steel nozzle water bottle. The sterile cutting straw was used as matting substances and was changed every day. The room temperature was maintained at 25°±2°C, humidity between 40 and 60% and 12 h light cycle (7 a.m. to 7 p.m. illumination) [20]. Mice were fed balanced diet for animal and water *ad libitum*. The permission from Institutional Animal Ethic Committee was also obtained prior to experiments.

B. Chemicals

Fine chemicals like cyclophosphamide (CPx), quercetin, gallic acid, catechin, coumarin, rutin, p-coumaric acid, myrecetin, chlorogenic acid, caffeic acid, apigenin, naringenin, kaempferol etc. were purchased from Sigma Aldrich (USA). All other common chemicals and reagents were AR/GR grade.

C. Test Drug

BR was prepared and supplied by M/s Health Reactive, Kota, India. Each 5 ml of BR contained active dry extracts of *Aegle marmelos* (150 mg), *Acorus calamus* (175 mg), *Withania somnifera* (325 mg), *Blumea lacera* (115 mg), *Rumex vesicarius* (240 mg), *Rubia cardifolia* (200 mg), *Cucumis melo* (200 mg), *Symplocos racemosa* (95 mg) and honey. The test drug was store in a brown bottle and kept in refrigerator at 4ºC before use.

D. Physiochemical Analysis

Specific gravity.

5 ml of BR was poured carefully into pre-weighed pycnometer. The weight of the samples was taken and specific gravity was calculated by comparing the weight of equal volume of water [21].

Ash Content.

5 g of BR was placed in silica crucible and heated in muffle furnace for 5h at 500°C. It was cooled in desiccators and weighed [21].

Crude Lipid.

10 g of BR was extracted with petroleum ether (60-80°C) in a soxhlet apparatus for about 6h. The residual petroleum ether extract was filtered and the filtrate was evaporated in a pre-weighed beaker. Increase in weight of beaker gave crude lipid [22].

Crude Fibre.

10 g of BR was treated with 200 ml of 1.25% H_2SO_4 and the residual part was neutralized with 1.25% NaOH. Then it was the filtered, washed with hot water and mixed with 1%HNO_3. The washed residue was dried in oven at 130°C to constant weight. The residue was scraped into a pre-weighed porcelain crucible, weighed, ashed at 550°C for two hours, cooled in a dessicator and reweighed. Crude fibre content was expressed as percentage loss in weight on ignition [22].

Crude Protein.

The crude protein was determined using micro Kjeldahl method [22]. 10 g of BR was decomposed by digestion with concentrated sulphuric acid in the presence ammonium sulphate. An excess of sodium hydroxide solution was added to dilute the reaction mixture. The liberated ammonia was distilled in steam and absorbed in standard sulphuric acid. Titration of the residual mineral acid with standard sodium hydroxide gives the equivalent of ammonia obtained from the weight of the sample taken. From this the percentage of nitrogen in the compound was calculated. The average nitrogen (N) content of proteins was found to be about 16%, which led to use of the calculation [N×6.25(1/0.16=6.25)] to convert nitrogen content into protein content.

Carbohydrate.

The presence of carbohydrate was determined by the following formula [22]:

100 – (ash% + fat% + protein% + crude fibre%).

Nutritive Value (Energy Content).

1 g carbohydrate and protein yield 4 kcal energy; whereas 1 g lipid yields 9 kcal energy. The energy content of BR was determined by multiplying the values obtained for protein, fat and available carbohydrate by 4, 9 and 4 respectively and adding up the values [22].

Mineral Contents.

5 g BR was taken in a silica crucible and heated in a muffle furnace at 400°C till there was no evolution of smoke. The carbon-free ash was moistened with concentrated sulphuric acid and heated on a heating mantle till fumes of sulphuric acid ceased to evolve. The crucible with sulphated ash was then heated in a muffle furnace at 600°C. 1 g of sulphated ash obtained above was dissolved in 100 ml of 5% HCl to obtain the solution ready for determination of mineral elements (sodium, potassium and calcium) through atomic absorption spectrophotometer (Agilant, USA) [23].

I: PHYSICOCHEMICAL ANALYSIS OF BODY REVIVAL

Parameters	Mean ± SD
Specific gravity (%)	1.31±0.002
Ash content (%)	8.35±0.02
Crude fibre (%)	9.16±0.01
Crude lipid (%)	0.0004±0.00006
Crude protein (%)	0.18±0.01
Carbohydrate (%)	82.26±0.08
Nutritive value (Kcal/100g)	330.79±0.65
Sodium (mg/100 g)	4.18±0.005
Potassium (mg/100 g)	1.15±0.01
Calcium (mg/100 g)	3.76±0.03

N=6 in each experiment

HPLC Analysis.

HPLC fingerprint of BR was performed with Dionex Ultimate 3000 liquid chromatograph (Germany) with solvent delivery system (LPG 3400 SD) including a diode array detector (DAD 3000) and Chromeleon 6.8 system manager as data processor. The separation was achieved by

a reversed-phase AcclaimTM120 C18 column (5 µm particle size, i.d. 4.6 x 250 mm). The test sample and standards were prepared and filtered through micro filtration unit. The mobile phase contains 1% aqueous acetic acid solution (Solvent A) and acetonitrile (Solvent B), the flow rate was adjusted to 0.7 ml/min, the column was thermostatically controlled at 28°C and the injection volume was kept at 20 µl. Total analysis time per sample was 115 min. HPLC Chromatograms were detected using a photo diode array UV detector at 280 nm according to absorption maxima of analysed compounds. Each compound was identified by its retention time and by spiking with standards under the same conditions. The quantification of the sample was done by the measurement of the integrated peak area and the content was calculated using the calibration curve by plotting peak area against concentration of the respective standard sample [24].

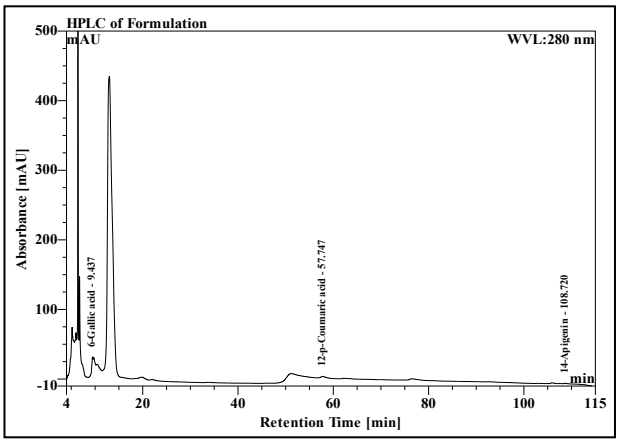

Fig. I: HPLC chromatogram of Body Revival.

E. Pharmacological Studies

Acute Toxicity Studies.

BR was examined for its safety measure following the OECD guidelines No. 423 [25]. BR was given to 18 h fasted female Swiss mice (20-30g body weight) as arithmetically progressive manner by oral route at 0.5 ml/100 g, 1 ml/100 g, 1.5 ml/100 g and 2.0 ml/100 g, in a single dose and observed for 3 days. The rate of mortality up to 3 day was recorded for the selection of 50% lethal dose of BR.

Immunopotentiation Studies

Swiss male mice (20-30 g) were divided into four groups of six animals each: Group I and Group II animals were pre-treated orally with normal saline (5 ml/kg), while, Group III with BR (200 g/kg) and Group IV with BR (400 g/kg) orally for 7 consecutive days. On day 7, CPx (Sigma, St Louis, MO) at the dose of 300 mg/kg was given subcutaneously to all mice, except Group I. The treatments were continuing in all groups for another 10 days [26]. Total count of leukocytes was determined on the day of CPx injection (day 0), day 5 and day 10 using hemocytometer after the red blood cell lysis. Deferential counts were determined on Leishman's stained blood smears made from whole blood. Absolute granulocyte and lymphocyte counts were calculated from the total leukocytes and the differential count. Bone marrow cellularity was determined by the method of Mehra and Vaidya (1993) [27]. Briefly, on day 10, all mice were sacrificed under deep anaesthesia (sodium hexabarbitone 40 mg/kg, i.p) and the bone marrow cells were collected carefully from both femurs and suspended in RPMI media in cold condition. The suspended cells were washed with the medium and centrifuged. The suspended cells were reconstituted with the medium and their numbers was counted microscopically using hemocytometer and expressed as total number of cells/femur.

F. Statistical Analysis

The data were expressed as mean ± standard deviation (SD). The differences between the groups were analyzed statistically (t-test) using software (spss v20, IBM, USA). The level of significance was considered at less than 0.05.

III. RESULTS

Physiochemical Analysis.

Body Revival was a thick dark brown suspension of eight different medicinal plants and honey. The basic physicochemical characteristics are given in Table I. It contained nearly 9.16% fibre and practically lipid free. It is also a moderate calorie product.

HPLC Chromatographic Analysis.

HPLC analysis revealed out of twenty four known standard polyphenolics, only three important biomarkers gallic acid, p-coumaric acid and apigenin were matched and quantified in Body Revival [Fig. I, Table II].

II: POLYPHENOLIC COMPOUNDS BY HPLC

Parameters	Mean ± SD
Gallic acid (µg/g)	18.40±0.015
p-Coumaric acid (µg/g)	2.41±0.02
Apigenin (µg/g)	0.29±0.0004

N=6 in each experiment

Pharmacological Studies.

No mortality was observed in BR treated mice up to the maximum dose limit *i.e.,* 2ml/100g body weight for 3 days and considered safe for oral use.

CPx treatment gradually decline the number of peripheral leukocytes compared to non-immune suppressive mice (Table III). Pretreatment with test drug, BR at the dose of 400 mg/kg body weight restore the number up to 65% within 10 days.

III: LEUKOCYTES IN PERIPHERAL BLOOD ON CPx INDUCED IMMUNOSUPPRESSIVE MICE

	Leukocytes (per mm^3) in blood		
	Day 0	Day 5	Day 10
Normal	6540±30.2	6480±36.8	6530±32.5
CPx	6450±32.7(a)	2860±28.3(a)* [-59%]	3190±31.4(a)* [-51%]
CPx+BR 200 mg/kg	6560±35.6(b)	4090±36.7(b)* [43%]	4930±38.1(b)* [54%]
CPx+BR 400 mg/kg	6570±35.6(b)	4350±33.2(b)* [52%]	5280±43.6(b)* [65%]

N=6; Mean±SEM; student t-test; (a) Normal vs. CPx; (b) CPx vs. BR;
* indicate <0.05; % change in parentheses

Furthermore, CPx injection gradually diminished the granulocytes and lymphocytes numbers 54% and 44% respectively within 10 days [Table IV-V]. On the other hand, pretreatment with BR at the dose of 400 mg/kg

significantly restored the numbers of granulocytes and lymphocytes up to 77% and 49% than immune suppressive mice.

Moreover, 10 days after injection of CPx, bone marrow cells were declined to 61% in femur. But, pretreatment with BR dose dependently (45% and 72%) and significantly improved the cellularity of bone marrow in femur than CPx immune suppressive mice [Fig. II].

IV: GRANULOCYTES IN PERIPHERAL BLOOD ON CPx INDUCED IMMUNOSUPPRESSIVE MICE

	Granulocytes (per mm^3) in blood		
	Day 0	Day 5	Day 10
Normal	830±10.8	836±9.9	842±11.6
CPx	840±11.3(a)	310±14.9(a)* [-63%]	390±17.2(a)* [-54%]
CPx+BR 200 mg/kg	836±10.8(b)	420±15.1(b)* [35%]	570±13.8(b)* [46%]
CPx+BR 400 mg/kg	852±10.6(b)	490±12.7(b)* [58%]	690±14.9(b)* [77%]

N=6; Mean±SEM; student t-test; (a) Normal vs. CPx; (b) CPx vs. BR;
* indicate <0.05; % change in parentheses

V: LYMPHOCYTES IN PERIPHERAL BLOOD ON CPx INDUCED ON IMMUNOSUPPRESSIVE MICE

	Lymphocytes (per mm^3) in blood		
	Day 0	Day 5	Day 10
Normal	5250±30.5	5130±29.8	5280±27.4
CPx	5130±31.9(a)	2440±28.3(a)* [-52%]	2930±33.7(a)* [-44%]
CPx+BR 200 mg/kg	5060±28.6(b)	2740±30.5(b)* [12%]	3510±34.2(b)* [19%]
CPx+BR 400 mg/kg	5080±29.8(b)	3020±26.9(b)* [23%]	4360±32.7(b)* [49%]

N=6; Mean±SEM; student t-test; (a) Normal vs. CPx; (b) CPx vs. BR;
* indicate <0.05; % change in parentheses

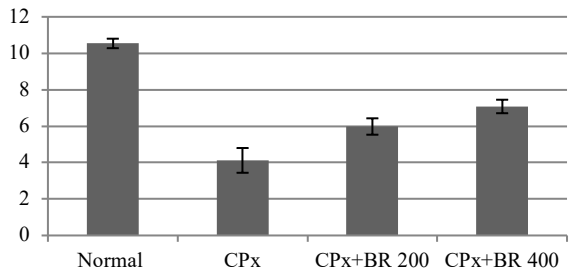

Fig. II: Bone marrow cells (10^5/femur) on CPx induced immunosuppressive mice

IV. DISCUSSION

The body's immunity has been shown to be suppressed in conditions such as malnutrition, under nutrition, aging, chronic stress, chronic infection, side effect of antibiotics and chemotherapeutic agents etc. Any imbalance occurring between regulatory and effectors cells of immune system can also lead to immunological breakdown and pathogenesis. Cyclophosphamide (CPx) is well-documented antineoplastic agent and enlisted on World Health Organization's (WHO) list of essential medicines [28]. It is a potent immunosuppressive agent and in high-dose CPx is increasingly used to treat both autoimmune and alloimmune conditions. It is also the most commonly used drug in blood and marrow transplantation [29]. It is basically nitrogen mustard and can transfer alkyl radicals, that react with the nucleic acid bases and inhibit DNA synthesis and also bring about cross-linkage of DNA strands in resulting as well as in dividing cells and thus interfere with cell replication [30]. At over dosage, CPx produces acute myelosuppression and thereby suppressing both cellular and humoral immunity [31]. For this, CPx is used as a pharmacological tool for searching new Immunomodulators.

The concept of immunomodulation relates to nonspecific activation of the function and efficiency of macrophages, granulocytes, complement, natural killer cells and lymphocytes and also to the production of various effectors molecules generated by activated cells. The test drug, Body Revival (BR) is consisted with the active parts of eight medicinal plants and honey. These individual component like, *Aegle marmelos*, *Acorus calamus*, *Withania somnifera*, *Blumea lacera*, *Rumex vesicarius*, *Rubia cardifolia*, *Cucumis melo*, *Symplocos racemosa* and honey have been used in traditional and complementary medicine for their anti-inflammatory, antimutagenic, immunostimulant, antimicrobial, antiviral, adaptogenic and rejuvenation properties, particularly detoxifying actions during pathophysiological situations or disease conditions. But their role in a combination could not be work out. Thus, we investigated whether the herbal formulation Body Revival could improve down-size leukocyte populations in CPx treated hosts.

In the present study, initial dose of CPx injection quickly reduced the number of leukocytes within five to ten days. More specifically, it significantly diminished the numbers of granulocytes and lymphocytes in the peripheral blood and suppressed the macrophage proliferative action significantly in bone marrow. Earlier it was reported by Jang and his colleagues (2013) that CPx treated mice exhibited significant reduction in natural killer cell (NK cell) in splenocytes [32]. It can influence the immune function that include Th2/Th1 shifts or repressed in cytokine production, like TNF-α, IFN- γ, IL-1α, IL-2, IL-6, IL-12 in serum suggesting that CPx is a potent immunosuppressive agent [33]. It was noted that, CPx infected animals exhibited signs of sickness and lethargies and that was reversed in BR pretreated animals.

Physicochemical analysis revealed that BR is rich in calcium, fibre and polyphenolics, mainly gallic acid, p-coumaric acid and apigenin. It is well established facts that polyphenols have anti-inflammatory and immunomodulatory effects and their antioxidant properties are mainly mediated through down-regulate the nuclear factor NF-kB, modulating important cell signalling pathways involved in inflammation even in cancer [34],[35]. The antioxidants properties of gallic acid are p-coumaric acid facilitated in the modulation of immune function either prevent the expression of inflammatory mediators including cytokines and histamines [36],[37]. Immunostimulatory potential of gallic acid against CPx immunosuppressant mice has also been reported [38]. In the present study, BR at the dose of 400 mg/kg drastically recovered the peripheral

leukocytes to 52% within five days and to 65% within ten day after CPx injection. Moreover, BR has also capability to restore the granulocytes and lymphocytes after CPx, indicating its role on both inner and adaptive immune function. Bone marrow cells, however, are also an integral part of innate immunity, and lack of these cells, regardless of a normal level predisposes hosts to infections. In the present study, pretreatment with BR exhibited enhancement of cell population in bone marrow compared to CPx mice. Safety studies in animals also confirmed its non hazardous action. Considering these observations it may be inferred that pretreatment with BR has effectively improved the immune suppression induced by CPx. The major ingredients of BR especially *W. somnifera, A. marmelos*, *A. calamus*, *R. cardifolia* and honey have already been reported for their protections in deadly infectious diseases. The test product, BR has the ability to overcome the untoward situation due to viral/microbial infections or chemotherapeutic regimens in tumour/cancer treatment.

V. CONCLUSION

Body Revival pretreatment undoubtedly improves the health condition during weak/suppressive immune state, either by regulating the signalling pathways of inflammations or modifying the cellular mechanisms to regenerate/restore the cell functions. Eventually, it may be effective to combat acute and chronic infections from environmental pathogens or drug/chemically induced immune suppressive conditions.

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Original Experimental Research 实验论著

Effects of Indian herbal formulation Body Revival on human platelet aggregation and myocardial ischemia in rats

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Objective: To study the effect of Body Revival (BR), a compound traditional Indian herbal medicine, on human platelet aggregation and isoproterenol (IS)-induced myocardial ischemia (MI) damage in male Wistar rats.
Methods: BR suspension 10, 20 and 30 μg was mixed with platelet-rich plasma and incubated at 37 ℃ for 30 min, respectively. Then, adenosine diphosphate (ADP, 20 mmol/L) or collagen (2 μg) was added in the mixture and the aggregation was observed against platelet-poor plasma mixed with equal volume of suspension of the same test samples. Wistar rats divided into 4 groups were used to investigate BR's effects on IS-induced MI. Levels of serum creatinine kinase (CK), aspartate transaminase (AST) and alanine transaminase (ALT) were estimated by standard commercial biological kits. Serum nitric oxide (NOx) was also measured. The lipid peroxides (LPO) and protein concentrations in heart tissues were measured.
Results: BR could inhibit ADP- or collagen-induced human platelet aggregation dose-dependently. Moreover, it could protect MI caused by IS in rats. BR reduced the levels of serum CK, AST, ALT and NOx dose-dependently and also lowered LPO in heart tissues in comparison with the MI control ($P<0.01$).
Conclusion: BR can inhibit human platelet aggregation and protect MI caused by IS in rats.

Keywords: platelet aggregation inhibitors; myocardial ischemia; lipid peroxidation; nitric oxide; plant extracts; rats

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morbidity worldwide[1]. It has been projected by the World Bank Health Sectoral Priority Review that in India, CVDs alone will account for 33.5% of deaths at all ages by 2015[2]. In modern medicine, the treatment for CVDs involves expensive drug therapy or equally expensive interventional procedures, such as thrombolytic therapy and surgical recanalization[3]. Many herbal secondary metabolites, chemical compounds and herbal formulations have been studied for their biological actions related to preventing human diseases by using models such as adenosine diphosphate (ADP) or collagen induced-platelet aggregation and isoproterenol (IS)-induced myocardial infarctions[4, 5]. Body Revival (BR) is a compound medicinal herbal formulation prepared based on traditional Indian medicine, containing cardioprotective, lipid-lowering, antihypertensive, anti-inflammatory, antioxidant and immunomodulatory properties. The rationale behind such formulations is provided by modern research, which documents that cholesterol, hypertension and vascular injury play a predominant role in the arteriosclerosis or infarction that predominantly leads to progression of the disease and its secondary complications[6]. BR is a suspension of *Aegle marmelos* (fruit pulp), *Acorus calamus* (rhizome), *Saussurea lappa* (roots), *Blumea lacera* (whole plant), *Rumex vesicarius* (leaves), *Rubia cordifolia* (root), *Cucumis melo* (seed), *Symplocos racemosa* (bark) and honey. The medicinal properties of these herbs have been reviewed[7-15]. In the present context, BR was studied to find out its role in human platelet aggregation and IS-induced myocardial ischemia (MI) in rats.

1 Materials and methods

1.1 Animals Wistar strain male albino rats (body weight (150±10) g) were used in the study. In the present experiment, recommended guidelines for the care and use of the animals were strictly followed[16] and permission from the Institutional Animal Care and Use Committee (IACUC) was also obtained. Rats were housed 4 in groups in polypropylene cages with steel nozzle water bottle. The cutting straw was used as matting substances and was changed every day. The room temperature was maintained at (25±2) ℃ and humidity between 40% and 60%. The light cycle was also maintained (a 12 h light/dark cycle). The rats were fed with supplementary balanced diet feed for animal and water *ad libitum*.

1.2 Test drugs and reagents ADP, collagen, IS, sodium nitrite and malondialdehyde were procured from the Sigma Chemical Company (St. Louis, MO, USA) and commercial kits of creatinine kinase (CK), aspartate transaminase (AST) and alanine transaminase (ALT) from the Coral Clinical Systems (Goa, India). All the other chemicals used were of analytical grade. BR suspension (5 mL) consists of *Aegle marmelos* (150 mg), *Acorus calamus* (175 mg), *Saussurea lappa* (325 mg), *Blumea lacera* (115 mg), *Rumex vesicarius* (240 mg), *Rubia cordifolia* (200 mg), *Cucumis melo* (200 mg), *Symplocos racemosa* (95 mg) and honey. All the components (except honey) were extracted with hydro-ethanol (volume ratio 1∶1), dried out to powder and mixed proportionately to make the suspension. The atomic absorption study exhibited that BR was free from arsenic, lead, cadmium and mercury. Moreover, the microbiological study showed absences of harmful bacterial contaminations (*Escherichia coli*, *Staphylococcus aureus* and *Pseudomonus aeruginosa*) or mould contents. BR suspension was suspended in required amount of distilled water prior to use.

1.3 Safety evaluation BR was weighed and dissolved in distilled water and was given orally to rats in single dose in a graded manner (0.5, 1 and 2 g/kg body weight) and the lethality was observed up to 72 h. Further, increment of doses could not be possible due to insolubility of BR on required volume given. No lethality was noted within 72 h up to 2 g/kg orally fed rats.

1.4 Platelet aggregation The test has been developed originally by Born[17] and standardized by Sur *et al*[18] and is used to evaluate quantitatively the effect of compounds on induced platelet aggregation *in vitro*. In this study, 6 volunteers of either sex were selected from the medical out patients' department of the Institute of Postgraduate Medical Education & Research, Kolkata, India after the written consents were obtained. The study was approved by the institutional human ethical committee. A careful drug history was taken from the subjects. Patients not receiving drugs like aspirin, sulfinpyrazone, chlorpromazine, amitriptyline, furosemide or penicillin and its derivatives for last two weeks, which will interfere with the platelet aggregation activity, were selected for the present research program. Specimens of blood samples were collected using 3.2% sodium citrate at the ratio 1∶9 with the blood in plastic container with minimum trauma or stasis at the venipuncture site. Testing was performed 30 min after venipuncture at room temperature. The platelet-rich plasma (PRP) was prepared by centrifuging the blood at 100 × *g* under 4 ℃ for 15 min. The platelet-poor plasma (PPP) was prepared by centrifuging the blood at approximately 2 400 × *g* for 20 min. The platelet count was adjusted to 2×10^5 to $3\times10^5/mm^3$ by diluting PRP with normal saline. Samples were maintained at 37 ℃ before testing. The test substance, BR suspension 10, 20 and 30 μg was mixed with PRP and incubated at 37 ℃ for 30 min, respectively. Then, ADP (20 mmol/L) or collagen (2 μg) were added in the incubation mixture and the aggregation was observed against PPP mixed with equal volume of suspension of the same test samples. The

optical density due to platelet aggregation was recorded in a Chrono-Log optical platelet aggregometer (Model 490, USA). The light transmission was set at 0% with PRP and at 100% with PPP.

1.5 IS-induced MI Wistar strain male albino rats (body weight (150±10) g) were used in this study. The rats were divided into 4 groups each containing 6 rats. Group Ⅰ served as normal control, group Ⅱ as ischemic model control and group Ⅲ and group Ⅳ as test drug-treated groups. Test compound BR was orally administered for 7 d to rats of group Ⅲ (200 mg/kg) and group Ⅳ (400 mg/kg), while group Ⅰ and Ⅱ received an equivalent amount of distilled water. At day 5, ischemia was induced by an intraperitoneal injection of IS (85 mg/kg) for 2 d[19]. BR treatment was continued on days 6 and 7 along with IS injection. After 48 h from the first injection of IS, all rats were sacrificed and blood and heart were taken for analysis of biochemical studies. Levels of serum CK[20], AST and ALT were estimated by standard commercial biological kits[21]. Serum nitric oxide (NOx) was measured by using Gress's method[22]. The lipid peroxides (LPO)[23] and protein[24] concentrations were measured in heart tissues.

1.6 Statistical analysis Data were expressed as $\bar{x}\pm s_{\bar{x}}$. The statistical significance was determined by one-way analysis of variance followed by Newman-Keuls multiple comparison tests. $P<0.05$ was considered statistically significant.

2 Results

2.1 Platelet aggregation There was 23.8% inhibition in human platelet aggregation against ADP with a dose of 10 μg BR, which gradually increased the inhibition as 40.3% for 20 μg BR and 46% inhibition for 30 μg BR in comparison with the ADP-induced aggregation control (Table 1). Also, 10 μg BR inhibited 17.2% platelet aggregation against collagen, 20 μg BR inhibited 32.9% and 30 μg BR inhibited 38.3% in comparison with the collagen-induced aggregation control (Table 2).

Table 1 Effects of BR on ADP-induced platelet aggregation ($\bar{x}\pm s_{\bar{x}}$, %)

Group	n	ADP-induced platelet aggregation (%)
ADP control (ADP 20 mmol/L)	6	86.23±0.51
BR 10 μg	6	65.66±0.23**
BR 20 μg	6	51.41±0.45**
BR 30 μg	6	46.53±0.48**

** $P<0.01$, *vs* ADP control. BR: Body Revival; ADP: adenosine diphosphate.

Table 2 Effects of BR on collagen-induced platelet aggregation ($\bar{x}\pm s_{\bar{x}}$, %)

Group	n	Collagen-induced platelet aggregation (%)
Collagen control (collagen 2 μg)	6	72.10±0.49
BR 10 μg	6	59.68±0.38△△
BR 20 μg	6	48.37±0.31△△
BR 30 μg	6	44.51±0.28△△

△△ $P<0.01$, *vs* collagen control. BR: Body Revival.

2.2 IS-induced MI IS markedly enhanced the levels of serum CK, AST and ALT compared with the normal control rats, due to infarct-like myocardial lesions in cardiac muscles in rats. However, the test drug BR (200 and 400 mg/kg) showed dose-dependent reduction of CK, AST and ALT production in serum when compared with the ischemic model control rats (Table 3). Moreover, IS enhanced the NOx level within 48 h. BR treatment showed dose-dependent reduction of NOx level in rats (Table 3). Furthermore, in the ischemic model control rats, the increased activities of LPO confirmed the onset of myocardial necrosis when compared with the normal control. Pretreatment with BR significantly reduced the levels of LPO ($P<0.01$).

Table 3 Effects of BR on IS-induced myocardial ischemia in rats

Group	n	Serum level				Heart tissue LPO (nmol/L)
		CK (U/L)	AST (U/L)	ALT (U/L)	NOx (μmol/L)	
Normal control	6	88.10±3.69	38.01±1.23	46.50±1.28	13.83±1.22	0.71±0.02
Ischemic model control (IS 85 mg/kg)	6	268.50±8.28▲▲	90.65±2.57▲▲	106.62±2.38▲▲	40.83±1.01▲▲	2.16±0.09▲▲
IS (85 mg/kg)+BR (200 mg/kg)	6	193.50±4.42□□	62.16±1.47□□	82.15±3.02□□	28.82±0.60□□	1.54±0.03□□
IS (85 mg/kg)+BR (400 mg/kg)	6	159.65±5.76□□	50.51±1.25□□	69.84±1.70□□	24.31±0.88□□	1.29±0.06□□

▲▲ $P<0.01$, *vs* normal control; □□ $P<0.01$, *vs* ischemic model control. BR: Body Revival; IS: isoproterenol; CK: creatinine kinase; AST: aspartate transaminase; ALT: alanine transaminase; NOx: nitric oxide; LPO: lipid peroxides.

3 Discussion

The present investigation is aimed to evaluate and explore the cardioprotective effect of BR, a compound traditional Indian herbal medicine, on human platelet aggregation and IS-induced MI in rats. Infarct-like myocardial lesions in rat induced by IS have been described by many researchers[19]. IS, a non-selective β-adrenergic agonist, has been reported to cause oxidative stress in the myocardium resulting in infarct like necrosis of the cardiac muscles and increase in the levels of lipids in the myocardium. Free radical generation and lipid peroxidation could be involved in IS-induced

cardiac damage[25]. The pathophysiological changes during IS induction are comparable to those taking place in human myocardial infarction, due to alteration of lipid metabolism[5]. Many herbal secondary metabolites, chemical compounds and herbal formulations have been studied for their biological actions related to preventing human diseases by using models such as IS-induced MI[7, 26]. It is well documented that, all the components of BR, like *Aegle marmelos*, *Acorus calamus*, *Saussurea lappa*, *Blumea lacera*, *Rumex vesicarius*, *Rubia cordifolia*, *Cucumis melo*, *Symplocos racemosa* and honey have several medicinal properties, particularly antioxidant, anti-inflammatory, hypolipidemic, hypotensive, anti-thrombolytic and detoxifying actions during pathophysiological situations[7-13]. Pervious reports suggested that *Aegle mermelos*[7] is one of the most important components of BR which has the ability to combat IS-induced MI.

In the present study, IS markedly enhanced the levels of serum CK, AST and ALT due to infarct-like myocardial lesions in cardiac muscles in rats. Wildenthal *et al*[27] showed that in CVDs, phospholipase and acid phosphatase levels were elevated due to lysosomal membrane destruction. BR treatment showed marked reduction in serum CK, AST and ALT in rats with IS-induced MI. This results suggest that BR may prevent the damage to lysosomes induced by IS and hence avoid leakage of these enzymes, which means it may act by stabilizing the structure of biological membranes. The study also reveal that BR, like other natural products namely, gugulip, guggulsterone and coleonol and compound herbals like Abana could be employed as a potential cardioprotective agent[28, 29].

During the last two decades, numerous studies have been done that focused on the roles of NOx in the pathogenesis progress and pharmacological intervention of MI[30]. NOx may cause cytotoxicity through formation of iron-NOx complexes with several enzymes including electron transport chain, oxidation of protein sulfhydryls and DNA nitration and potent activator of lipid peroxidation[31]. In the present study, it is noted that IS enhanced the endogenous NOx levels within 48 h. BR treatment showed dose-dependent reduction of NOx levels in serum and thereby it is hypothesized that it may have the ability to diminish the genesis of high amount of NOx radicals by preventing membrane bound tissue damage. The significant increase observed in the levels of LPO in rats with IS-induced MI compared with the normal control, was in accordance with the observation of previous reports[26]. While, BR-treated rats showed a significant decrease in LPO level in cardiac tissues compared with the MI model rats. Previous investigations have shown that herbal formulations could exhibit cardioprotective effect against MI injury by inhibiting LPO and thus enhancing the recovery of cardiac function[28, 32].

In hypertensive patients, the platelets are hyperactive and responsible for thrombogenesis and if left untreated may aggravate and complicate the hypertensive disorders[3]. Platelet aggregation is enhanced in presence of ADP, collagen or adrenaline in vascular bed and may cause fatalities[7]. ADP is contained within the platelet in storage organelles and released from the platelet during formation of primary haemostatic plug and thereby could induce further platelet aggregation[18]. In the present study, it indicates that BR has the ability to reduce platelet aggregation induced by ADP and also by collagen. The active principles of the plants present in BR have been reported to possess antioxidant, anti-inflammatory and cardioprotective properties[7-15]. The present study of platelet aggregation reflect that BR may at least partially inhibit prostaglandins synthesis pathway.

The therapeutic effect of BR may be due to its antioxidant, antilipidperoxidative, free radical-scavenging, immunomodulatory and cardiotonic property that could have prevented IS-induced tissue injury. Thus it could be concluded that BR could protect experimental MI and platelet aggregation which merit further detailed studies to develop it as a cardioprotective formulation.

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5 Competing interests

The authors declare that they have no competing interests.

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印度草药方 Body Revival 对人类血小板聚集及大鼠心肌缺血的作用

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目的:观察印度草药方 Body Revival (BR)对人类血小板聚集及异丙肾上腺素引起的大鼠心肌缺血的作用。
方法:BR 悬浮液(分别含 BR 10、20 和 30 μg)与富血小板血浆混合后,37 ℃下培养 30 min,分别将二磷酸腺苷(20 mmol/L)或胶原蛋白(2 μg)加入混合液中,与混合了等体积的 BR 悬浮液的贫血小板血浆对比观察 BR 对于血小板凝集的作用。Wistar 大鼠分为 4 组以检测 BR 对于异丙肾上腺素引起的心肌缺血的作用。使用标准的商业化试剂盒测量大鼠血清中肌酐激酶、天冬氨酸氨基转移酶及丙氨酸氨基转移酶的水平,同时测量大鼠血清中氮氧化物的含量及大鼠心肌中脂质过氧化物及蛋白质的含量。
结果:BR 能够剂量依赖性地抑制二磷酸腺苷或胶原蛋白引起的人类血小板聚集。此外,BR 对于异丙肾上腺素引起的大鼠心肌缺血具有保护作用。与对照组比较,BR 能够显著降低大鼠血清中肌酐激酶、天冬氨酸氨基转移酶、丙氨酸氨基转移酶和氮氧化物的含量以及大鼠心肌中脂质过氧化物的含量($P<0.01$)。
结论:BR 能够抑制人类血小板聚集并对异丙肾上腺素引起的大鼠心肌缺血具有保护作用。
关键词:血小板聚集抑制剂;心肌缺血;脂质过氧化反应;一氧化氮;植物提取物;大鼠

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Indian Medicine Can Improve Quality of Life in Breast Cancer Patients: Case Studies

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Case Report

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Abstract

The present study was evaluated the QoL of breast cancer patients who were taking Body Revival, an Indian polyherbal medicine. A case study was conducted among 5 breast cancer patients, who were voluntarily treated with Body Revival for ≥6 months. The average age of 5 breast cancer patients was 48.6 yrs (range 35-64 yrs), out of them 3 suffered in Stage II and 2 in Stage IV with metastasis. 3 patients undergo surgery, 4 under chemotherapy treatment and 1 did not received any chemotherapy or surgery. All of them used Body Revival (average 13.2 months). A structured and validated interview schedule was used to gather data from cancer patients. The QOL of all the patient symptoms was significantly improved ($p<0.001$) with Body Revival supplementation. It improved both the psychological and physical domains of day-to-day life, either by attenuating the adverse events of regular treatments for cancer or by enhancing vital energy in the body. Conclusions: With Body Revival supplements with routine medical care improve their day to day life. To strengthen the present findings, more research is required.

Keywords: Breast Cancer; Quality of Life; Indian Medicine; Herbs; Chemotherapy

Introduction

Most cancer patients who have been diagnosed and are undergoing treatment, report that they have difficulty in sleeping, feel depressed, and have a poor quality of life (QoL). The World Health Organization (WHO) defines quality of life as "an individual's perception of their position in life in relation to their goals, expectations, standards, and concerns in the context of the culture and value systems in which they live." It includes subjective evaluations of both positive and negative aspects of life [1]. Many nations, including India, suggest using nutritional and herbal supplements with medicinal properties as adjunct therapy for cancer patients [2]. There are also scientific evidences and clinical trial reports of using herbal formulations on cancers. Some of the marketed Indian medicines for cancers are Varunadi Ghritha for head and neck cancer [3], HUMA for oral cancer [4], HC-9 for breast cancer [5], BASANT for cervical cancer [6] and Body Revival to all cancers [7].

Breast cancer is the most prevalent types of cancer in India, accounting for 12.5% of all new registered cases [8]. The usual course of treatment for breast cancer is surgery, which is then followed by various treatment combinations like chemotherapy, radiotherapy, and hormone therapy. Chemotherapy medications have serious side effects, including anorexia, vomiting, abdominal pain, diarrhea, hot flashes, headache, dyspnea, skin rash, fever, back pain,

muscle cramps, fatigue, vertigo, and edema. To the best of our knowledge, there are very few studies examining the QoL of Indian breast cancer patients employing herbal supplements; hence, this questionnaire based case report was conducted to find out the QoL of breast cancer patients who were consuming voluntarily Body Revival.

Materials and Methods

This case study was carried out during June 2022 to August 2022, among 5 breast cancer patients, diagnosed to be in Stage II-IV and who used Body Revival voluntarily. The adult participants were selected randomly from the registered of patients to continuously use Body Revival medicine through online for at least 6 months. QoL-tool designed and validated by Latha, et al. [9] was used through telecommunications (telephone/Internet). Present tool has 20 structured items, including 4 negative (score 4 to 1) and 16 positive (score 1 to 4) questions with a maximum total score of 80. QoL of breast cancer patients was categorized into five according to scoring pattern: very high (above 60), high (59-50), average (49-36), low (35-27) and very low (below 27). The respond of breast cancer patient to individual question was marked and recorded in the prescribed format by the rater (physicians) over telecommunication after receiving their verbal consent for their willingness to participate. Moreover, demographic information, including age, gender, height, weight, cancer stage, and treatment, as well as the duration of Body Revival use, were taken. The collected information from the allotted questions was analysed statistically using SPSS software (version 20; IBM, Chicago, USA). Categorical variables were presented as frequencies. Qol score was presented as mean and standard deviation (SD) and statistically analysed by single t-test and 95% Confidence Interval. P-value ≤0.05 was considered significant.

Variables	Category	Patients
Number of patients	N	5
Age (years)	Mean ± SD	48.60±11.58
Age (years)	<40	1
	40-60	3
	>60	1
BMI	Low (≥18)	2
	Normal (18-25)	3
	High (≤25)	0
Stage	I	0
	II	3
	III	0
	IV	2
Duration (m)	<12	1
	12-24	3
	>24	1
Modern treatment	Chemotherapy	4
	Surgery	3
Body Revival use (m)	<6	0
	6-12	4
	>12	1

Table 1: Frequency distribution of demographic variables.

Results and Discussion

The present case study was done in 5 breast cancer patients. Table 1 describes the demographic details of selected breast cancer participants. The average age group was 48.6 yrs. Majority of them suffered from cancer for more than 12 months from stage IV with metastasis. Chemotherapy was used in 4 patients and surgery with chemotherapy was done in 3 patients.

QoL variables (Qs. No)	Quality of Life Score (N=5)					
	Mean ± SD	Best Score	95% CI		One Sample Test	
			Lower	Upper	t-Value	p-Value
Qs.1	2.8±0.83	4	1.76	3.83	7.48	<0.001
Qs.2	3.4±0.54	4	2.71	4.08	13.88	<0.001
Qs.3	3.0±0.70	1	2.12	3.87	9.48	<0.001
Qs.4	1.6±0.54	1	0.91	2.28	6.53	<0.001
Qs.5	1.8±0.44	1	1.24	2.35	9.00	<0.001
Qs.6	1.6±0.54	1	0.91	2.28	6.53	<0.001
Qs.7	3.2±0.83	4	2.16	4.23	8.55	<0.001
Qs.8	2.0±0.70	1	1.12	2.87	6.32	<0.001
Qs.9	1.8±0.83	1	0.76	2.83	4.81	<0.001
Qs.10	1.6±0.54	1	0.91	2.28	6.53	<0.001
Qs.11	2.8±0.83	4	1.76	3.83	7.48	<0.001
Qs.12	1.2±0.44	1	0.64	1.75	6.00	<0.001
Qs.13	2.6±0.98	4	1.48	3.71	6.50	<0.001
Qs.14	2.0±0.89	1	1.16	3.23	5.88	<0.001
Qs.15	2.2-0.10	1	1.48	3.71	6.50	<0.001
Qs.16	2.6±0.83	1	0.91	2.28	6.53	<0.001
Qs.17	1.6±0.89	1	1.91	3.28	10.61	<0.001
Qs.18	2.6±0.54	1	1.76	3.83	7.48	<0.001
Qs.19	2.8±0.83	1	2.71	4.08	13.88	<0.001
Qs.20	3.4±0.54	4	1.76	3.83	7.48	<0.001

Table 2: Quality of Life of breast cancer patients treated with Body Revival.

Table 2 describes the QoL details of 5 breast cancer participants with t-test and 95% Confidence Interval. In this case series there were significant ($p<0.001$) improvement in QoL life of breast cancer patients who were using Body Revival supplement. Body Revival is composed with nine natural ingredients including water extract of Aegle marmelos fruit pulp (150 mg), Acorus calamus rhizome (175 mg), Withania somnifera root (325 mg), Blumea lacera fruit (115 mg), Rumex vesicarius whole plant (240 mg), Rubia cordifolia root (200 mg), Cucumis melo seed (200 mg), Symplocos racemosa stem bark (95 mg) and honey (Q.s). Body Revival therapy unquestionably reported to better the health condition in general and mental disabilities and illness due to weak immune circumstances by modulating signalling pathways or/and cellular functions [7,10].

Compared to the general community, cancer patients typically have a lower quality of life. Multidimensional types of patient-reported outcomes are perceived by patients that encompass their social, financial, psychosocial, and physical activities [11]. Moreover, in many cases, breast cancer patients experience loss of appetite, pain, muscular cramps, exhaustion, sleep disturbances, depression, and a poor quality of life after being diagnosed and treated for cancer. The present study assessed QoL in patients after receiving the Body Revival supplement to enhance health benefits as a prognostic medical factor and predict survival. Although, no participant gained sufficient scores to qualify for the very high QoL category, however, all of them reported (Figure 1) average quality of life (total score 45-49). Hence, by combining Body Revival supplements with regular medical care, breast cancer patients may be better able to manage their unpleasant symptoms, take control of their illness and medical care, and live healthier lives.

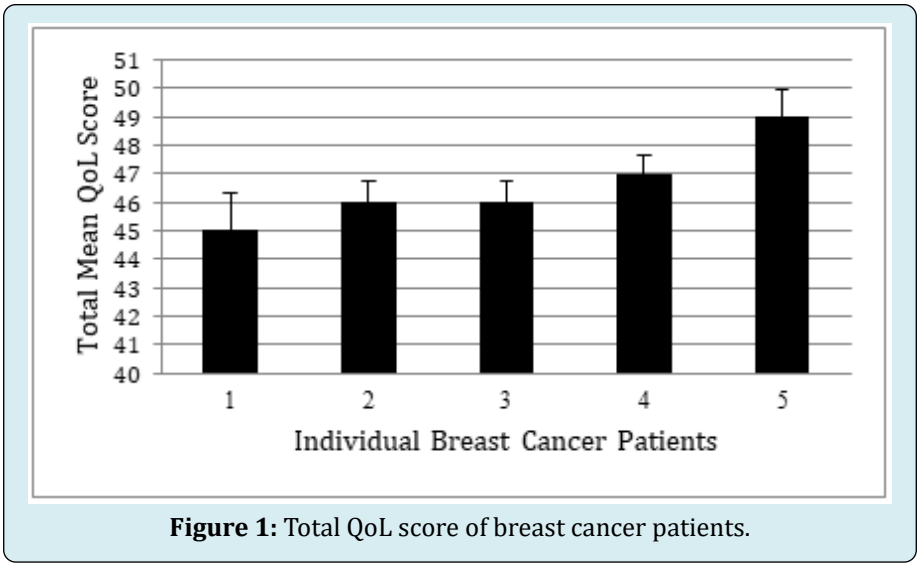

Figure 1: Total QoL score of breast cancer patients.

Conclusion

From the case reports, it may be concluded that Body Revival supplements taken during conventional therapy and palliative care can improve the quality of life of breast cancer patients. To confirm the current outcomes, further investigation is needed.

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Effect of Indian Herbal Formulation on Hepatomegaly: An Evidence Based Case Report

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Abstract

Enlargement of the liver, or hepatomegaly, occurs due to fatty liver disease, liver abscess, hepatitis, liver fibrosis, and carcinoma. Clinical diagnosis and PET CT scan revealed hepatomegaly with abscess in a 60-year-old male patient with a history of left laparoscopic radial nephrectomy due to cancer. The patient's blood contained somewhat elevated levels of hepatic enzymes, including gamma glutamyl transferase (γ-GT), alkaline phosphatase (AKP) and alanine transaminase (ALT), which were indicative of damage to the liver cells. Diabetes, high blood pressure, obesity, and viral hepatitis were not reported. For a period of 12 weeks, the patient consumed oral Body Revival® liquid (BR) at a dose of 5 ml on alternate days. Physical, clinical, and laboratory examinations were conducted every four weeks. The patient's liver enzymes were found to be within normal range following a 12-week course of BR treatment, and a CT scan examination showed that the patient's liver had neither a confluent nor an abscess. At that time, there were no signs of liver abscess, hepatomegaly, or NAFLD.The patient had a full recovery after receiving Body Revival®.

Keywords: Hepatomegaly; Liver Abscess; Non-alcoholic Fatty Liver Disease; PET CT Scan; USG; Herbs

Introduction

Hepatomegaly is enlargement of the liver beyond its normal size. The most common causes of hepatomegaly include fatty liver, liver abscess, hepatitis and liver carcinoma [1]. Accumulation of excessive fat in the liver is the common denominator underlying the two most common and emerging causes of chronic liver disease, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), that are emerging public health issues globally [2]. NAFLD is characterised by hepatic steatosis detected by either imaging or histology without secondary causes. It spans a spectrum of the disease from non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH) and ultimately to cirrhosis and its complications. The pooled overall prevalence of NAFLD in the general population was 26.9% [3]. The prevalence of adult NAFLD in India has been reported between 6.7% and 55.1% [4]. An expanded, dysfunctional, insulin resistant adipose tissue with ectopic fat deposition and hepatic storage due to an imbalance is the hallmark of NAFLD with lipotoxicity as the primary driver of hepatocyte injury [5]. On the other hand, NASH fibrosis is associated with an excess all-cause mortality

and also liver related mortality in general population [6]. Moreover, the highest incident of liver abscess observed in Asia, where rates can be as high as 21 per 100000 inhabitants per year. The common clinical symptoms of liver abscess are fever, pain in abdomen, jaundice and hepatomegaly [7]. CT scan and USG Imaging is the preferred modality to diagnose liver diseases including hepatomegaly, NAFLD, abscesses, hepatitis and liver carcinoma [8].

Herbal medicines have been widely used for the management of hepatic diseases, including hepatomegaly, NAFLD, jaundice, hepatitis and liver carcinoma. Clinical trials of single herbs, such as *Crataegus pinnatifida and Salvia miltiorrhiza*, are effective in treating fatty liver disease [9]. Silymarin, berberine, resveratrol, curcumin, quercetin and other polyphenols have been reported for supportive and combination therapy of liver diseases [10,11]. In earlier studies, Indian herbal formulation Body Revival® (BR) reported for the improvement of quality of life in cancers including hepatic carcinoma [12,13]. BR contains with 9 ingredients including water extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Rubia cordifolia* root (200 mg), *Cucumis melo* seed (200 mg), *Symplocos racemosa* stem bark (95 mg) and honey q.s [14]. Scientific reports confirmed that most of the ingredients of BR have hepatoprotective actions including the supportive treatment of hepatic malignancies [15]. Although, BR is available in market, but its usefulness in targeted interventions are essential to ascertain. Therefore, the therapeutic role of BR was assessed in the following evidence based case study.

Case Report

A 60-year-old man with past history of left laparoscopic radial nephrectomy due to renal cell carcinoma, diagnosed and operated before three years (Nov 9, 2020), initially presented to the medical emergency with a two-week history of nausea, vomiting, right upper quadrant abdominal pain and distension, but no documented history of hepatomegaly on physical examination, although remarkable for abdominal tenderness on palpation. After nephrectomy, Sunitinib (protein kinase inhibitor), a targeted anticancer drug was continued to impede the existing metastatic cells (if any) as treatment regimen. Preliminary clinical examination revealed an enlargement of the left supraclavicular node (Troisier sign). The patient was thoroughly examined and diagnosed. His body mass index was 24.2 kg/m^{2}and vitals were stable and as follows: blood pressure 132/89 mm of Hg, pulse rate 88 and respiratory rate 23/min. He never consumed alcoholic and did not smoke or chewing tobacco. He was vegetarian in diet. His only medication was a proton pump inhibitor (Pantoprazole, 40 mg/day). A through blood examination reported: Hb 12.7 g/dl (14-17 g/dl), RBC 4.25 million/mm^3 (4.35-5.65 million/mm^3) WBC 6270/mm^3 (4500-11000 per mm^3), fasting glucose 112.1 mg/dl (70-80 mg/dl), PP glucose 125 mg/dl (110-120 mg/dl), albumin 35 g/l (34-54 g/l) , alanine transaminase 94 IU/l (4-36 IU/l), alkaline phosphatase 285 IU/l (44-147 IU/l), total bilirubin 1.6 mg/dl (0.1-1.2 mg/dl), gamma glutamyl transferase 122 IU/l (5-40 IU/l), lactate dehydrogenase 193.7 U/l (140-280 U/l), urea 7.9 mg/dl (6-14 mg/dl) and creatinine 1.13 mg/dl (0.7-1.3 mg/dl). Viral hepatitis (HBsAg) serology was negative.

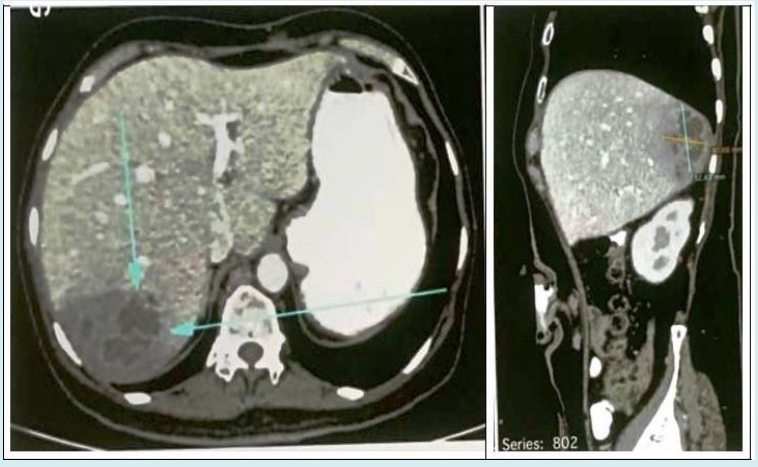

Figure 1: CT scan of abdomen and pelvic (baseline).

Furthermore, the patient went on to have an ultrafast multi-slice computed tomographic (CT) scan of the abdomen and pelvis after administration of oral and IV contrast and confirmed hepatomegaly and liver abscess (Figure 1). The posterior superior segment of the right lobe of liver reveals extensive confluent necrotic peripheral host oedema. The

entire confluent, measuring approximately 5.2x4x6.2 cm, extends up to the posterior capsular surface of the liver (segment 7), with immediate adjacent perihepatic inflammation and fluid. Flow within the portal vein and hepatic vein was normal. The intra-hepatic bile duct and common bile ducts were not dilated. Gall bladder was collapsed, and no CT evidence of gall bladder calculi was noted. Spleen, pancreas, and adrenals were normal in size, thickness, morphology, outline and attenuation. The right kidney was normal in size (11.9 cm), shape, outlines and revealed prompt symmetrical contrast enhancement and excretion of contrast. Urinary bladder was normal. The results of the laboratory test and clinical evaluations indicated hepatomegaly with major abscess and suggested that NAFLD or NASH would likely result if the condition was not well addressed.

Treatment

As part of his disease management regimen, the patient was instructed to apply Body Revival® liquid (BR). It is used to treat liver fibrosis, cirrhosis, NAFLD, hepatitis, and jaundice. Following the medical professional's recommendation, the patient ingested BR orally for 12 weeks at a dose of 5 ml on alternate days. During this therapy phase, the patient received extra attention through close monitoring. Every four weeks, physical, clinical, and laboratory tests were performed. The patient was also advices to restrict and control food habits including changes to follow lifestyle.

Results

After 12 week treatment with BR, laboratory investigations of the patient blood showed haemoglobin level 13.1 g/dl, RBC count 4.4 million/mm^3, leukocyte count 6500 /mm^3, glucose fasting 86 mg/dl and PP 103 mg/dl, albumin 36 g/l, ALT 32 IU/l, AKP 140 IU/l, total bilirubin 0.9 mg/dl, γ-GT 36 IU/l, LDH 162 U/l, urea 7.1 mg/dl (6-14 mg/dl) and creatinine 1.11 mg/dl (0.7-1.3 mg/dl). His liver function tests were within the normal limit.

Additionally, a CT scan assessment of the pelvis and abdomen revealed that the liver's intrahepatic vascular systems, size, and outline were all normal. There was no confluent and no abscess (Figure 2). Pericocelescystic collection was not seen. The gall bladder, common bile duct, and hepatic bile ducts were among the other hepatic structures that were found to be normal. The size, shape, and attenuation of the spleen, pancreas, adrenal glands, prostates, right kidney, and ureters were all normal. There were no indications of NAFLD, hepatomegaly, or liver abscess at the time.

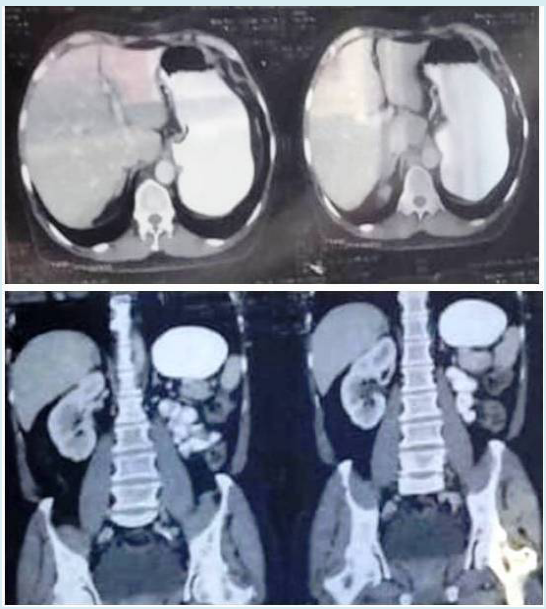

Figure 2: CT scan of abdomen and pelvic (after treatment).

Discussion

There is no direct medication available for chronic liver disease; instead, non-pharmacological treatments including a balanced diet and/or regular exercise can be helpful. However, several herbal medicines and nutritional supplements are used in complementary and alternative medicine to treat chronic liver problems, such as cirrhosis,

hepatitis, hepatomegaly, and liver abscesses. It has been claimed that the components of BR perform liver protection through a variety of mechanisms, including modulating metabolisms and absorption rates, facilitating the elimination of toxic metabolites, minimizing oxidative stress and inflammation, or retrieving the activities of hepatic cells [16-22].

A recent comprehensive review elucidates the thirteen clinical trials involving herbal medicines and chronic liver illnesses, such as hepatomegaly, ascites, cirrhosis, and liver abscesses [11]. While the duration between the onset of BR and the remission of symptoms and the elimination of clinical hepatomegaly may vary from week to months. Depending on the severity of the liver disease, improvement or normalization of blood indicators could take place one to three months later. Despite achieving non-diabetic glycemic control, our patient's glycogenic hepatopathy did not worsen in response to treatment. NAFLD can lead to fibrosis and cirrhosis, although it is typically a rather benign condition when there is no indication of non-alcoholic steatohepatitis, as in his case. However, more investigation is advised to validate the curative effects of BR in NAFLD and related hepatomegaly.

Conclusion

In this critical instance, the herbal remedy known as Body Revival contributes to the treatment of clinical hepatomegaly with abscess. Future research is expected to determine the therapeutic role of Body Revival in NAFLD.

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Assessment of Quality of Life in Cancer Patients Supplemented with Ayurvedic Medicine (Body Revival): Case Reports

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Abstract

Background: Cancer patients experience a wide range of symptoms, which can affect their daily performance and quality of life (QoL).
Objectives: The study's goal was to evaluate the QoL of cancer patients who were taking natural polyherbal supplement (Body Revival).
Methods: A small survey was conducted among 38 cancer patients, who were supplemented with Body Revival for ≥3 months. A structured and validated interview schedule was used to gather data from cancer patients.
Results: Out of 38 cancer patients, 58.8% were male and 55% were in the age group of above 60, the majority with cancers in the breast (35%) and the reproductive system (male 27.8% and female 30%), and 44.4% male and 40% female had stage II disease. The QOL of the majority of patient symptoms was significantly improved ($p<0.001$) with Body Revival supplementation. It improved both the psychological and physical domains of day-to-day life, either by attenuating the adverse events of regular treatments for cancer or by enhancing vital energy in the body.
Conclusions: Combining Body Revival supplements with routine medical care may help patients better control their negative symptoms, take initiative with their disease and treatment, and lead healthier lives. To strengthen the present findings, more research is required.

Keywords: Cancer; Chemotherapy; Radiotherapy; Quality of Life; Herbs

Abbreviations: QoL: Quality Of Life; SD: Standard Deviation.

Introduction

The Cancer Registry specifies 18.1 million new cases and 10 million global deaths due to cancer in 2020. Breast, lung, colon, and prostate cancers are the most prevalent types of cancer, accounting for 12.5%, 12.2%, 10.7%, and 7.8% of all new cases, respectively [1]. One in nine Indians has a lifelong risk of developing cancer. The most common malignancies among men and women, respectively, were lung and breast cancers [2]. Studies on cancer survivorship aim to investigate a wide range of subjects related to cancer diagnosis and treatment-related outcomes, such as medical status, late effects of treatment, supplemental diet

or medications, second cancers, and quality of life (QoL). The World Health Organization defines quality of life as "an individual's perception of their position in life in relation to their goals, expectations, standards, and concerns in the context of the culture and value systems in which they live." It includes subjective evaluations of both positive and negative aspects of life [3]. After receiving a cancer diagnosis and receiving treatment, most cancer patients report having trouble sleeping, feeling depressed, and having a bad quality of life.

Depending on the type and stage of the cancer being treated, "*chemotherapy*" usually refers to treatments given orally, intravenously, or subcutaneously with the goal of slowing or preventing the development of cancer cells. The majority of chemotherapeutic drugs have severe side effects, such as anorexia, vomiting, abdominal pain, diarrhea, hot flashes, headache, dyspnea, skin rash, fever, back pain, muscular cramps, exhaustion, vertigo, and oedema. The nutritional and performance state of patients is also affected by a variety of changes, such as changes in physiologic and psychological processes [4]. Many nations, including India, suggest using nutritional and herbal supplements with medicinal properties as adjunct therapy for cancer patients [5-7]. Body Revival, a formulated and marketed herbal liquid suspension (M/s Health Reactive, India) has been developed based on immunotherapy to treat cancers as mentioned in ancient Ayurvedic texts. Body Revival therapy unquestionably better the health condition in general and mental disabilities and illness due to weak immune circumstances by modulating signalling pathways or/and cellular functions [8,9].

To the best of our knowledge, there are very few studies examining the QoL of Indian cancer patients employing herbal supplements; hence, this questionnaire based survey (Case Report) was conducted to explore the QoL of adult cancer patients who were consuming voluntarily Body Revival adjunct to cancer therapy in India.

Materials and Methods

An exploratory survey was done during June 2022 to August 2022, among cancer patients who used Body Revival voluntarily for more than 3 months and diagnosed to be in Stage I-IV of cancer of any cancer and had undergone radiotherapy or chemotherapy or surgery or combination. The participants were selected randomly from the registered of patients to continuously use Body Revival medicine through online for at least 3 months. The participants aged less than 19 years and more than 85 years were excluded from the study. The maximum number of survey participants for this case series study was target to 50. Without a control group, a case series describes the traits and results among a number of people who have either an illness or an exposure (which could be an intervention) over time.

Modified QoL questionnaire version II, designed and validated by Latha, et al. was used to assess the QoL of volunteers/ participants through telecommunications (telephone/Internet) [10]. This modified tool has 20 structured items, including 4 negative (score 4 to 1) and 16 positive (score 1 to 4) questions with a maximum total score of 80 (Table 1). The modified tool for cancer patients is found to be a valid and reliable tool and feasible to administer at the clinical settings. QoL of cancer patients was categorized into five according to scoring pattern: very high (above 60), high (59-50), average (49-36), low (35-27) and very low (below 27). The respond of cancer patient to individual question was marked and recorded in the prescribed format by the rater (physicians) over telecommunication after receiving their verbal consent for their willingness to participate in the survey (Table 1). Moreover, demographic information, including age, gender, height, weight, number of family members, occupation, total family income, cancer location, stage, and treatment, as well as the duration of Body Revival use, were taken.

		Very much (4)	Moderate (3)	A little	Not at all (1)
Q1	How do you rate your overall quality of life during the past week?				
Q2	How would you rate your overall physical conditioning during the past week?				
Q3	Do you feel you are physically performing less than what you want to do?				
Q4	Do you get the kind of support you need from your friends and relatives?				
Q5	Do you experience any pain at present?				
Q6	Does your pain interfere in your day-to-day activity?				
Q7	Is your appetite normal?				
Q8	Do you have any problem in sleep?				
Q9	Do you feel you need more rest?				

Q10	Do you feel fatigued?				
Q11	Are you able to move around (physical) as usual?				
Q12	Do you feel depressed?				
Q13	Are you comfortable attending social functions as usual?				
Q14	Do you have a fear of functional disability?				
Q15	Do you feel very lonely or remote from other people?				
Q16	Do you feel free to share your problems with your family members?				
Q17	Do you have difficulty in remembering things?				
Q18	Do you need any assistance to do your day-to-day activities?				
Q19	Face the difficulties?				
Q20	Do you feel your doctor is cooperative?				

Table 1: Quality of Life questionnaire tool for cancer participants using Body Revival.

Statistical Analysis

The collected information of the survey was input in the electronic data-sheet for statistical analysis using SPSS version 20 (IBM, Chicago, USA). Categorical variables were presented as frequencies and percentages. Qol individual score (quantitative data) of male and female were presented as mean and standard deviation (SD) and statistically analysed by single t-test and 95% Confidence Interval. Qol between male and female individuals were compared statistically using two-tailed Person's correlation. P-value ≤ .005 was considered significant.

Results

Table 2 describes the demographic details of cancer participants. In this case series, out of 38 patients (18 male and 20 female), 61.2% of the males and 50% of the females were in the age group above 60 years, and 50% of them had a low BMI. Majority of them belonged to families with at least six members (55%) and a monthly family income above 50 thousand INR (males 72.2% and females 75%), and they had suffered from cancer for more than 12 years (males 71% and females 75%). In this survey, 27.8% of male participants and 35% of female participants were affected by prostate cancer and breast cancer, respectively. 44.4% of males and 40% of females were suffering from stage II, 22.2% and 30% in stage III and 33.3% and 30% in stage IV cancers. Chemotherapy was used in 44.4% of male patients and 65% of female patients, according to treatment history (Table 2). 55% of women and 66.6% of men continued to take the Body Revival product for a year.

Variables	Category	Male	Percentage	Female	Percentage
Number of participant	N	18	100	20	100
Age (years)	Mean ± SD	58.89±17.39	-	54.40±17.75	-
Age (years)	<40	3	16.6	5	25
	40-60	4	22.2	5	25
	>60	11	61.2	10	50
BMI	Low	9	50	10	50
	Normal	9	50	10	50
	High	0	0	0	0
Family member	≤6	8	44.4	9	45
	>6	10	55.6	11	55
Occupation	Paid worker	7	38.9	6	30
	Retired	6	33.3	0	0
	Business/others	5	27.8	0	0
	Unemployed	0	0	14	70
Income	<25,000	0	0	0	0
	25000-50000	5	28.8	5	25
	>50000	13	72.2	15	75

Cancer location	Breast	0	0	7	35
	Lower GI	2	11.1	2	10
	Upper GI	5	27.8	1	5
	Lungs	0		0	0
	Reproductive system	5	27.8	6	30
	Others	6	33.3	4	20
Stage	I	0	0	0	0
	II	8	44.4	8	40
	III	4	22.2	6	30
	IV	6	33.3	6	30
Duration (m)	<12	7	38.9	5	25
	24-Dec	10	55.6	12	60
	>24	1	5.5	3	15
Modern treatment	Chemotherapy	8	44.4	13	65
	Surgery	6	33.3	8	40
	Palliative	4	22.2	4	20
Body Revival use (m)	<6	4	22.2	5	25
	12-Jun	12	66.6	11	55
	>12	2	11.2	4	20

Table 2: The frequency and percent distribution of demographic variables among cancer participants.

Table 3 describes the QoL details of cancer participants. In this case series there were significant (p<0.001) improvement in QoL life of both male (48.38±4.66; 95% CI: 46.06-50.70) and females (48.75±5.98; 95% CI: 45.95-51.54) cancer patients, who were using Body Revival supplement. According to scoring, QoL was categorized in five categories (very high, high, average, low and very low). Overall, both men and females had average QoL scores (Figure 1). No participant gained sufficient scores to qualify for the very high QoL category. However, 10 (55.5%) men and 12 (60%) women who responded reported good quality of life, while 8 (45.5%) men and 8 (40%) women reported average quality of life (Table 3). Pearson Correlations (2-tailed) between male to female was r=0.330 and female to male was r=0.181.

QoL variables	Quality of Life Score					
(Qs. No)	Male(Mean ± SD)	95% CI	p-Value	Female(Mean ± SD)	95% CI	p-Value
Qs.1	2.83±0.70	2.48-3.18	<0.001	3.10±0.91	2.67-3.52	<0.001
Qs.2	3.50±0.51	3.24-3.75	<0.001	3.35±0.81	2.96-3.73	<0.001
Qs.3	2.72±0.83	2.31-3.12	<0.001	3.00±0.56	2.73-3.26	<0.001
Qs.4	2.50±0.78	2.10-2.89	<0.001	2.45±0.82	2.06-2.83	<0.001
Qs.5	1.94±0.87	1.51-2.37	<0.001	1.90±0.44	1.69-2.10	<0.001
Qs.6	2.88±0.75	2.51-3.26	<0.001	2.80±0.95	2.35-3.24	<0.001
Qs.7	2.77±0.94	2.30-3.24	<0.001	2.75±0.78	2.38-3.11	<0.001
Qs.8	1.77±0.80	1.37-2.17	<0.001	1.95±0.75	1.59-2.30	<0.001
Qs.9	1.55±0.51	1.30-1.80	<0.001	1.60±0.59	1.32-1.88	<0.001
Qs.10	1.83±0.61	1.52-2.14	<0.001	1.90±0.78	1.53-2.26	<0.001
Qs.11	2.83±0.51	2.57-3.08	<0.001	2.70±0.65	2.39-3.01	<0.001
Qs.12	1.55±0.70	1.20-1.90	<0.001	1.30±0.57	1.03-1.56	<0.001
Qs.13	1.16±0.98	1.67-2.65	<0.001	2.00±0.79	1.62-2.37	<0.001

Qs.14	2.72±0.66	2.38-3.05	<0.001	2.35±0.48	2.12-2.57	<0.001
Qs.15	1.66-0.84	1.24-2.08	<0.001	1.75±0.85	1.35-2.14	<0.001
Qs.16	2.55±0.98	2.06-3.04	<0.001	2.35±0.93	1.91-2.78	<0.001
Qs.17	2.22±0.95	1.75-2.69	<0.001	2.20±1.05	1.70-2.70	<0.001
Qs.18	2.61±1.24	1.99-3.22	<0.001	2.90±0.96	2.44-3.35	<0.001
Qs.19	2.38±1.19	1.79-2.98	<0.001	2.85±0.93	2.41-3.28	<0.001
Qs.20	3.33±0.84	2.91-3.75	<0.001	3.55±0.68	3.22-3.87	<0.001
Total Score	48.38±4.66	46.06-50.70	<0.001	48.75±5.98	45.95-51.54	<0.001

Table 3: Quality of Life of cancer patients treated with Body Revival Supplements.

Discussion

Our study aimed at exploring cancer patients' QoL status and sought their association with Body Revival, an herbal supplement. Body Revival is composed with nine natural ingredients including water extract of *Aegle marmelos* fruit pulp (150 mg), *Acorus calamus* rhizome (175 mg), *Withania somnifera* root (325 mg), *Blumea lacera* fruit (115 mg), *Rumex vesicarius* whole plant (240 mg), *Rubia cordifolia* root (200 mg), *Cucumis melo* seed (200 mg), *Symplocos racemosa* stem bark (95 mg) and honey (Q.s). With this effort, we were able to gather a variety of information on a number of significant parts of cancer patients' lives. The present study assessed QoL in patients after receiving the Body Revival supplement to enhance health benefits as a prognostic medical factor and predict survival.

Compared to the general community, cancer patients typically have a lower quality of life. It is a specific and multidimensional type of patient-reported outcomes which is perceived by patients as something that encompasses the patients' social, financial, psychosocial, and physical activities [11]. In contrast to the results of recent studies by Alam, et al. at only 17.5% [4], and Nayek, et al. At only 17.2% [12], we have observed that 55–60% of participants have good QoL after supplementing with Body Revival, demonstrated the beneficial role of Body Revival (Figure 1). Additionally, we noticed a statistically significant association in the patients' QoL between men and women.

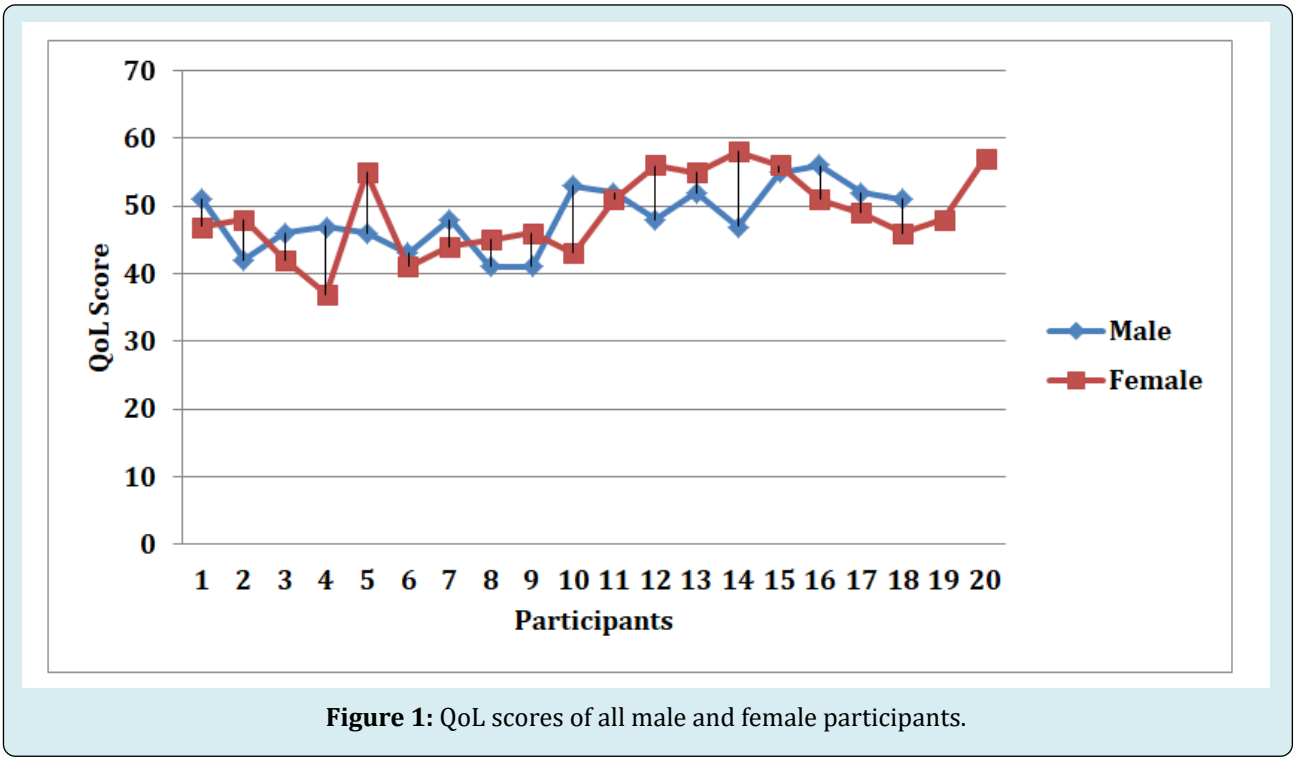

Figure 1: QoL scores of all male and female participants.

Moreover, in many cases, cancer patients experience loss of appetite, pain, muscular cramps, exhaustion, sleep disturbances, depression, and a poor quality of life after being diagnosed and treated for cancer. It is clear from this research that the number of ADRs has an effect on cancer patients' physical and mental health. Due to chemotherapy, the majority of patients complained of nausea, discomfort, and fatigue. Body Revival supplements improved both physical and mental condition and enhanced QoL in the participants. In the present study, the pain (Qs 5) and fatigue (Qs 10) scores were significantly lowered, while, physical activity (Qs 11) and cognitive score (Qs 17) were moderately enhanced in both male and female participants. Hence, by combining Body Revival supplements with regular medical care, patients may be better able to manage their unpleasant symptoms, take control of their illness and medical care, and live healthier lives.

Conclusion

From the case reports, it may be concluded that Body Revival supplements taken during conventional therapy and palliative care can improve the quality of life of cancer patients. To confirm the current outcomes, further investigation is needed.

Limitations

Our study has limitations with low sample size, non-homogeneous data, convenience approach and possibility of response related biases

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