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Ayurvedic intervention in breast cancer patients reduces adverse effects of chemotherapy, modulates systemic immune response and improves quality of life: A non-randomised controlled study

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Abstract

Background: 65-97% of cancer patients experience one or more chemotherapy-induced adverse effects, which hampers the quality of life (QoL) of cancer patients. One of the studies carried out at our centre regarding the use of adjunct Ayurvedic medicine in alleviating the chemotherapy adverse effects showed significant improvement in lessening the adverse effects and improving QoL.

Objective: To assess the efficacy of combinations of Ayurvedic drugs in alleviating the toxicity of chemotherapy, and improving systemic immune response and QoL of breast cancer (BC) patients.

Methods: Participants: A total of 135 BC patients undergoing chemotherapy were screened in this study. Among them, 120 patients were included in the study. The Study group (n=63) completed the chemotherapy with Oral Ayurvedic Medicines (OAM) while the Control group (n=57) received no OAM.
Intervention: The Study group received OAM in the form of herbo-mineral metallic formulations for 10 months, initiating at the start of chemotherapy. The Control group received no OAM along with chemotherapy. Both groups were followed for 4 years.

Outcome measures: All the patients were assessed for adverse effects based on Common Terminology Criteria (designed by the National Institute of Health-National Cancer Institute), physical examination including Karnofsky performance score and QoL Questionnaire C-30 and BR-23 (designed by European Organisation for Research and Treatment of Cancer). Additionally, complete blood count, liver function test, kidney function test, inflammatory and tumour markers, cytokines and oxidative stress markers were also evaluated at definite time points.

Results: The standardized and OAM tests for chronic toxicity ensured quality and safety. Study subjects experienced significant improvements in side effects such as anorexia, nausea, mucositis, and fatigue ($p<0.01$). Clinical haematological and biochemical parameters within normal limits suggested the protective effects of OAM on vital organs like the liver and kidneys during chemotherapy drug metabolism. CRP levels, cytokine markers, and oxidative stress markers partially responded during chemotherapy. Notably, 65% of patients in the study group could complete chemotherapy without delays, compared to 37% in the control group. The survival analysis at the end of 4 years showed no significant difference between the two groups, indicating non-interference of OAM in the efficacy of chemotherapy drugs but a better quality of life in breast cancer patients taking OAM.

Conclusions: OAM appeared to be safe and effective in reducing the toxic adverse effects of chemotherapy drugs in breast

cancer patients, if administered simultaneously with chemotherapy for the short-term and continued after completion of conventional treatment for long-term adverse effects. No statistical difference in the survival pattern after four years signifies no adverse interaction with chemotherapeutic drugs used as a conventional treatment for cancer. Clinical Trial: CTRI/2017/01/007687

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Trial Registration: CTRI/2017/01/007687

Keywords

Anti-cancer drugs toxicity; Adverse-effects; Chemotherapy; Oral Ayurvedic Medicines; Quality of Life; Survival analysis.

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Introduction

Cancer ranks second leading global cause of death, with almost 10 million deaths in 2020, constituting one in six death [1]. The prevalence of cancer has surged notably in developing nations [2].

BC, a significant contributor to global cancer incidence, recorded an estimated 2.3 million new cases in 2020, making up 11.7% of all cancer cases [3]. In India, BC accounted for 13.5% (1,78,361) of cases and 10.6% (90,408) of all deaths, with a cumulative risk ratio of 2.81 [4]. The incidence of BC in India has exhibited an upward trend, as reported by various registries of the National Cancer Registry Programme [5].

The primary treatment for BC involves surgery, followed by chemotherapy and/or radiotherapy. Although chemotherapy has substantially enhanced overall cancer survival, its cytotoxic adverse effects pose significant obstacles, hindering the clinical application of otherwise beneficial therapies [6]. Chemotherapeutic drugs often induce adverse effects because of their inability to differentiate between dividing cancer cells and normal cells. This indiscriminate action results in heightened oxidative stress and compromised immune status [7].

These adverse effects, well-documented in Common Terminology Criteria, encompass immediate and early effects, with gastrointestinal adverse effects being major obstacles causing delays, dose modifications, and treatment discontinuation [8,9]. Delayed adverse effects, occurring post-chemotherapy completion, include fatigue, peripheral neuropathy, cognitive impairment, ovarian failure, infertility, and cardiotoxicity [10]. An observational study conducted revealed that 97.4% of chemotherapy patients experienced at least one adverse effect, with approximately 66.7% of patients experiencing six or more adverse effects. These findings highlight the importance of identifying even minimal adverse effects at an early stage and managing them promptly to improve the quality of life for patients undergoing chemotherapy [11].

In response to these challenges, an integrative approach combining conventional chemotherapy with Ayurvedic formulations has been developed to mitigate adverse effects [12]. Ayurveda, with its *Rasayana* and *Panchakarma* practices, offers immunomodulatory and detoxifying benefits, respectively; while modification of diet and lifestyle to achieve anti-inflammatory activity provides symptomatic relief where conventional treatment (palliative) has limitations [13]. This integrative approach aims not only to alleviate adverse effects but also to prevent cancer recurrence or metastasis. The present study describes a case-control

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clinical trial conducted to evaluate the efficacy of prudently selected Ayurvedic formulations in alleviating chemotherapy-induced adverse effects.

Methods

Study design

A prospective, interventional, non-randomized controlled study was conducted at our centre in collaboration with other centres. Patients were informed about the research and those willing to participate were enrolled after fulfilling the eligibility criteria. All the patients were assessed at five time points within the study period of 10 months i.e., t1- at the beginning of chemotherapy, t2- mid-chemotherapy, t3- end of chemotherapy, t4- one month after completion of chemotherapy and t5- one year after starting the chemotherapy. The survival status of the recruited patients was determined at the end of 4 years (Figure 1).

Figure 1. Flowchart of patient allocation. Analysis was done at t1: before chemotherapy at enrolment, t2: mid-chemotherapy, t3: End of chemotherapy, t4: One month after chemotherapy and t5: One year from enrolment. Survival analysis was done after 4 years from enrolment. Patients who did not complete the chemotherapy were excluded from the analysis. Absent for follow-up denotes patients who were absent for a particular follow-up but continued later.

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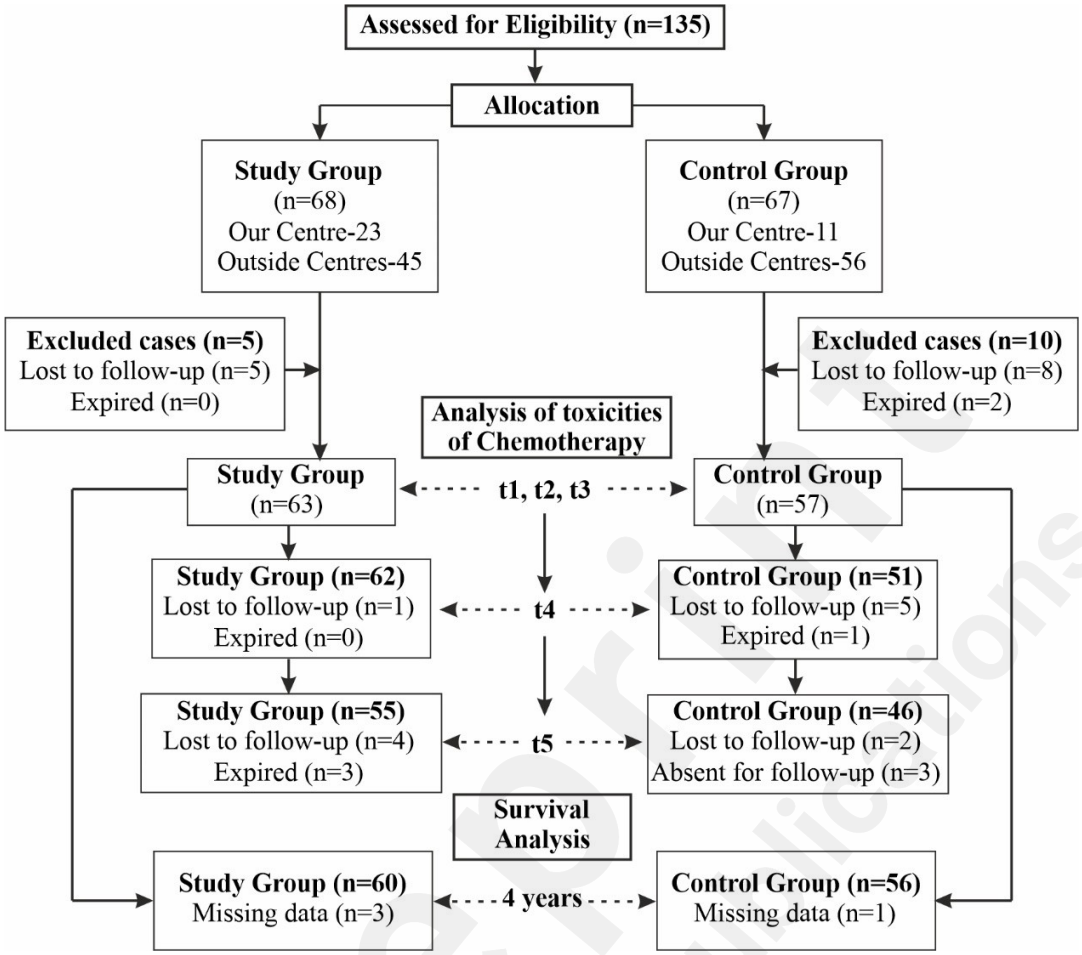

Patient population

Patients aged 25 to 75 years with recently diagnosed BC, preferably stage I to III, were enrolled irrespective of their surgery status, immunohistochemistry findings, and subsequent line of treatment after chemotherapy. Patients with co-morbidities like hypertension, diabetes, and hypothyroidism were enrolled only after assuring that their respective parameters were within normal limits. Metastatic patients (stage 4) or those already taking Ayurvedic formulations for BC or any other ailment in the last 3 months were excluded from the study.

Ethics statement

The Institutional Ethics Committees of all centers approved the study. The trial was registered under the Clinical Trial Registry of India (No. CTRI/2017/01/007687). Signed written informed consent was obtained before enrolment from all the trial participants. The study followed the Declaration of Helsinki and International Conference on Harmonization—Good Clinical Practice guidelines.

Allocation

A total of 135 potential patients from all three centers were enrolled into two groups- a study group that received OAM along with chemotherapy (n=68) and a control group that received chemotherapy alone (n=67) (Figure 1). All the patients underwent several laboratory investigations at various time points, however, the actual sample size after noting down the missing data for any parameter due to technical difficulties such as patient's blood non-withdrawal, and blood hemolysis after withdrawal is specified in Multimedia appendix 1.

Fifty healthy females aged between 25-75 years, with no co-morbidities or any acute infection, and those not under any treatment for the last three months were separately delegated to ascertain the normal range of cytokine markers.

Ayurvedic formulations

OAM were manufactured by Atharva Healthcare Pvt Ltd, Pune, India (Food and Drug Administration Department, Maharashtra State, India-approved, GMP certified). These products collectively as a kit have been applied for a patent and published as Indian and US Patents. It consisted *Athava Suvarnabhasmadi Vati* (ASBV), *Kamdudha* (*Mauktikyukta*) *Vati* (MKD), *Atharva Padmakadi Ghruta* (APG), and *Atharva Ananta Vati* (AAV). The details of ingredients, doses and vehicles are provided in Multimedia appendix 2. The tablets as well as lipid-based semi-solid formulations were standardized based on physicochemical and safety parameters at the Indian Drug Research Association & Laboratory, Pune as well as the in-house Ayurvedic Drug Testing and Standardization Laboratory.

Chronic toxicity study of OAM

Chronic toxicity study of OAM as a regime was conducted at the Laboratory Animal Facility of Advanced Centre for Treatment, Research and Education in Cancer, Navi Mumbai, India; after approval from the Institutional Animal Ethics Committee as per the Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India guidelines (Sanction no. 22/2018). Six to eight weeks Sprague Dawley (SD) rats were maintained at 23±1°C and relative humidity of 50±10% in 12 h light-dark cycle. The animal dose was extrapolated from the human dose based on body surface area. A total of 24 animals were divided into two groups (study and vehicle control-VC) for 7, 30- and 90-day study as detailed in Multimedia appendix 3. After dosing, animals were weighed on alternate days and observed for physical activity and behavioral changes. Blood samples were collected before and after treatment while the vital organs of sacrificed animals were fixed in 10% buffered

formalin for histopathological study.

Drug intervention and follow-ups

OAM intervention was initiated in the study group from the beginning of chemotherapy up to 10 months. The medicines were dispensed after each follow-up of 1-2 weeks and medication adherence was assured and strengthened by regular telephonic follow-ups (weekly). In addition, patients were advised to maintain daily records of medicine intake or any missed dose. Along with OAM, they were also provided with a specific diet regime to be followed during and after the completion of chemotherapy.

Both the groups were treated with Anthracycline and/or Taxane-based chemotherapy (dose based on height, weight and Sr. creatinine clearance of the patients) protocols, along with pre- and post-chemotherapy drugs. Pre-medications included Granisetron, Dexamethasone and Aprepitant (wherever applicable), while Pheniramine and Ranitidine additionally for Taxane. Post-medications in both groups included allopathic medicines like antacids, anti-emetics and prophylactic medicines for leukopenia. The survival data of the patients with discontinued follow-ups was collected telephonically at the end of the four years.

Outcome measures and assessment

All patients were assessed based on clinical, hematological and radiological investigations, as detailed in Table 1.

Table 1. Outcome measures of the study.

Characters	Parameters
Clinical	**a)** Commonly observed 12 adverse effects of chemotherapy graded using CTCAE Version 4.03 [Scale of grade 1-5, except for fatigue (grade 1 – 4) and taste disturbance (grade 1 and 2). Grade '0' denotes absence of symptom] **b)** KPS- Grading for well-being on a 0 to 100 scale, a higher score denotes better performance **c)** QoL Questionnaire-C30 and QLQ-BR23 (specially designed for breast cancer patients) based on patients' perspectives about their well-being. Further, QLQ C30 is interpreted as a Symptom, Functional and Global scale while BR-23 as Functional and Symptom scale
Clinical laboratory	**a)** Hemogram (Hb, WBC, RBC, Platelet) **b)** Liver Function Test[a] (Sr. bilirubin, SGOT, SGPT, Alkaline phosphatase) **c)** Renal Function Test (Sr. creatinine, Blood urea), **d)** Tumor marker[b]-CA 15.3

	e) C-reactive protein- CRP **f)** Cytokines viz., IL-1β, IL-6, IL-8 and IL-10 measured by ELISA method, using commercial kits (BD Biosciences, India) **g)** Oxidative stress measured by estimating two enzymes viz., Superoxide dismutase (SOD) and Catalase; and one protein Glutathione using commercial kits (Caymen Chemicals, USA).
Radiological	**a)** CT (Abdomen and Pelvis) and Mammography[c] **b)** 2D Echo Test[d] **c)** X-ray (Chest)[e] **d)** Ultrasonography (Abdomen and Pelvis) [f]

[a] Liver function test was not assessed at t2; [b] tumour marker was not assessed at t2 and t3; [c] CT was assessed at t1 and t5; [d] 2D Echo test was done at t1 and t4; [e] X-ray chest was done at t1, t2 and t5; [f] Ultrasonography was done at t2, if the chemotherapy drugs were changed; CTCAE: Common Terminology Criteria for Adverse Events, KPS: Karnofsky Performance Score, QoL: Quality of life.

Data analysis

In the animal toxicity study, data were presented as Mean ± SEM, and group differences were assessed with Paired t-tests. Karnofsky Performance Score (KPS), and Quality of Life Questionnaire (QLQ)-C30 (version 3.0) and BR-23 (version 1.0) data in both groups were analyzed by comparing mean scores and the percentage of patients with >0 score differences at t1 (before starting OAM). All scales and items were linearly transformed to a 0-100 scale. Chemotherapy adverse effects were categorized as low and high, and the % of the population with high adverse effects at all time points in both groups were compared. Statistical significance set at $p<0.05$. Objective data viz., hematological, clinical biochemistry, cytokines, and oxidative stress markers were compared using independent t-tests. Cytokine concentration difference between basal level at t1 and disease stage-wise distribution was compared. Population variance was measured by a two-sample Z-test. Analyses were performed using IBM SPSS Statistics Version 27 and Kaplan-Meier Survival curves with GraphPad Prism Version 8.

Results

Standardization study of OAM

All four medicines of OAM were tested for quality control and assurance. The results of various parameters are specific to these formulations and can be considered monographs (Multimedia appendix 4,5).

Chronic toxicity study

No behavioral changes, mortality, or visible toxicity were observed in OAM-administered SD rats after 7, 30, and 90 days and their relative organ weights remained unchanged (Multimedia appendix 6). OAM-treated rats displayed significant changes in hemoglobin (p=0.007), Sr. bilirubin, Sr. creatinine, platelets, and alkaline phosphatase on respective days. Other hematological and biochemical parameters varied non-significantly from Day 0. Conversely, VC-treated rats exhibited a significant decrease in platelets and serum glutamic pyruvic transaminase (SGPT) on the 7th day, and only SGPT on the 90th day (Multimedia appendix 10). Histopathology revealed no significant change in organs of OAM-treated as compared to VC group at 7, 30, and 90th day. Details of cytoarchitectural changes are tabulated in Multimedia appendix 7.

Analysis of recruited patients

Out of 135 enrolled patients, 120 who completed chemotherapy were included in the analysis as detailed in Figure 1.

Demographic characteristics

In the study (n=63) and control (n=57) groups, the median age in years was 54 (Range = 34 to 71) and 50 (Range = 32 to 71), while the median weight was 60.7 (Range = 37 to 93) Kg and 58 (Range = 32 to 88) Kg, respectively. Other demographic details are provided in Table 2. Clinicopathological analysis depicted that major patients were in stage II followed by stage III, grade II and Invasive Ductal Carcinoma. Most patients received adjuvant chemotherapy, radiotherapy and hormonal therapy as first-line treatment (Table 3).

Table 2. Demographic characteristics of the Study and Control Groups of Breast Cancer (BC) patients.

Characteristics	All [n (%)] (n=120)	Study group [n (%)] (n=63)	Control group [n (%)] (n=57)
Age (year)			
<45	30 (25)	13 (20.6)	17 (29.8)
45-60	55 (45.8)	27 (42.9)	28 (49.1)
>60	35 (29.2)	23 (36.5)	12 (21.1)
Education			
Illiterate	35 (29.2)	20 (31.7)	15 (26.3)
Up to high school	59 (49.2)	28 (44.4)	31 (54.4)
>High school	26 (21.6)	15 (23.9)	11 (19.3)
Occupation			
Housewife	69 (57.5)	39 (61.9)	30 (52.6)

Service	15 (12.5)	8 (12.7)	7(12.3)
Labor	36 (30)	16 (25.4)	20 (35.1)
Income			
<1.5 lacs	91(75.8)	43 (68.3)	48 (84.2)
1.5-2.5 lacs	12 (10)	6 (9.5)	6 (10.5)
>2.5 lacs	23 (19.2)	14 (22.2)	9 (5.3)
Marital status			
Married	82 (68.3)	40 (63.5)	42 (73.7)
Divorce/ Widow	38 (31.7)	23 (36.5)	15 (26.3)

Table 3. Clinicopathological parameters of Study and Control Groups of BC patients.

Characteristics	**All [n (%)] (n=120)**	**Study group [n (%)] (n=63)**	**Control group [n (%)] (n=57)**
Stage			
I	9 (7.5)	5 (7.9)	4 (7.0)
IIA	41 (34.2)	18 (28.6)	23 (40.4)
IIB	25 (20.8)	16 (25.4)	9 (15.8)
IIIA	21 (17.5)	8 (12.7)	13 (22.8)
IIIB	2 (1.7)	2 (3.2)	0 (0.0)
IIIC	20 (16.7)	13 (20.6)	7 (12.3)
IV	2 (1.6)	1 (1.6)	1 (1.8)
Grade			
I	12 (10)	3 (4.8)	9 (15.8)
II	56 (46.7)	28 (44.4)	28 (49.1)
III	52 (43.3)	32 (50.8)	20 (35.1)
Types of Cancer			
HPR			
IDC	107 (89.2)	56 (88.9)	51 (89.5)
Others	13 (10.8)	7 (11.1)	6 (10.5)
IHC			
TNBC	31 (25.8)	16 (25.4)	15 (26.3)
Non-TNBC	89 (74.2)	47 (74.6)	42 (73.7)
Chemotherapy			
Neoadjuvant	5 (4.2)	2 (3.2)	3 (5.3)
Adjunct	115 (95.8)	61 (96.8)	54 (94.7)
Radiotherapy			
Yes	77 (64.2)	45 (71.4)	32 (56.1)
No	28 (23.3)	11 (17.5)	17 (29.8)
ND	15 (12.5)	7 (11.1)	8 (14.0)
Hormonal therapy			
Yes	59 (49.2)	34 (54)	25 (43.9)
No	49 (40.8)	23 (36.5)	26 (45.6)
ND	12 (10)	6 (9.5)	6 (10.5)

HPR: Histopathology Report, IDC: Invasive Ductal Carcinoma, IHC: Immunohistochemistry, TNBC: Triple Negative Breast Cancer, ND: No Data

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Effect of OAM on the schedule of chemotherapy cycles

In this study, 34.92% of patients receiving OAM experienced chemotherapy schedule delays, compared to 63.16% in the control group. The maximum delay was 7 and 12 cycles in the study and control group, respectively. Most delays were of 5 days (22.22% in the Study group, 57.89% in the Control group), with some control patients experiencing delays up to 80 days. About 10% of patients in both groups required hospitalization for chemotherapy-induced adverse effects. Oral conventional medications (other than the OAM protocol) were needed by 5% of the study patients and 16% of control patients during chemotherapy (Table 4).

Table 4. Status of chemotherapy cycles in both groups.

Characteristics	Study (n=63) [n (%)]	Control (n=57) [n (%)]
Chemotherapy cycles delayed		
Yes	22 (34.92)	36 (63.16)
12 cycles	0 (0.00)	1 (1.75)
7 cycles	1 (1.59)	0 (0.00)
6 cycles	1 (1.59)	1 (1.75)
5 cycles	0 (0.00)	2 (3.51)
4 cycles	2 (3.17)	6 (10.53)
3 cycles	5 (7.94)	9 (15.79)
2 cycles	7 (11.11)	14 (24.56)
1 cycle	6 (9.52)	3 (5.26)
No	41 (65.08)	21 (36.84)
No. of days delayed		
1-5 days	14 (22.22)	33 (57.89)
6-10 days	10 (15.87)	11 (19.30)
11-15 days	5 (7.94)	2 (3.51)
16-20 days	2 (3.17)	0 (0.00)
< 20 days	6 (9.52)	6 (10.53)
- 21-40 days	6	3
- 41-60 days	0	2
- 61-80 days	0	1
Hospitalisation required during chemotherapy		
Yes	6 (9.52)	5 (8.77)
No	57 (90.48)	52 (91.23)
Oral medications (other than OAM) required during chemotherapy		
Yes	3 (4.76)	9 (15.79)
No	60 (95.24)	48 (84.21)

Effect of OAM on various performance, functional and well-being

The impact of OAM on several scales (KPS, C-30 FS, GS, SS; BR-23 FS, SS) is shown in Figures 2 and 3. In the study group, the KPS trend was found to be ascending after completion of chemotherapy, while in the control group, it was significantly higher at the end

of chemotherapy (Figure 2A). GS was statistically significant in the study group at mid-chemo and one year after starting chemotherapy (Figure 2B). Both groups had similar physical functioning trends, except for a significant increase in the control group at one year of chemotherapy. Role functioning was higher in the study group till mid-chemo, but the control group scored significantly higher at one year of chemotherapy. Emotional and social functioning were consistently higher in the study group. Cognitive functioning linearly improved over time in the study group but in the control group, it decreased at the end of chemotherapy. Later, it significantly increased one month after chemotherapy and was the same as the study group at the end of one year of chemotherapy (Figure 2B).

For the symptom scales (Figure 2C), nausea and vomiting were significantly increased and decreased, at t3 and t5, respectively in the study group. Dyspnoea was higher in the study group at t1 and t5. Constipation was notably higher in the study group at t1, t4, and t5, but decreased after t3. Diarrhoea was significantly higher at mid-chemotherapy in the study while higher at the end of the chemotherapy in the control group. Fatigue, pain, insomnia, and financial difficulty were lower with a descending trend in the study group compared to the control group.

In BR-23 scales, the study group showed significantly higher scores at mid-chemo and one year after chemotherapy in Body image while the future perspective score was higher during and end of the chemotherapy (Figure 2D). Systemic side effects increased during chemotherapy and returned to baseline at one year in both groups. Breast and arm symptom scores were generally similar across groups, except at t1. Hair loss concerns showed unique patterns in each group (Figure 2D).

Figure 4 illustrates the proportion of patients with >0 (positive changes) in KPS, FS, and GS. KPS showed an ascending trend and increased significantly at the end of one year in the study group while the GS score increased after completion of chemotherapy in the study group while it was ascending throughout in the control group. Physical and role functioning improved in the study group, while emotional and social functioning scored higher, in an ascending pattern. Cognitive functioning in the study group improved till one year while it improved until one month and remained stable at one year after starting chemotherapy in the control group (Figure 3A, B). For symptom scales (Figure 3C), symptoms like nausea, vomiting, and insomnia decreased after one year in both groups. Appetite loss, constipation, and diarrhoea had similar scores between both groups at all time points. Dyspnoea, financial difficulty, and pain were highly scored in the control group at various time points.

Body image scores were stable initially but diverged after one month and one year after

starting chemotherapy. Future perspective score remained stable in the study group but increased slightly at the end of chemotherapy in the control group (Figure 3D). Systemic side effects decreased at one year in both groups, with higher proportions in the study group. Breast and arm symptoms scored significantly higher in the control group at different time points (Figure 3D) (Multimedia appendix 8, 9).

Figure 2. Clinical assessment at all-time points in both the groups expressed as mean score **A:** Karnofsky Performance Status Score, **B:** QLQ-C30-Global health status scores and QLQ-C30-Functional scales score, **C:** QLQ-C30-Symptom scales score, **D:** QLQ-BR-23 Functional and Symptom scales score. The difference of means was compared by independent t test. * and ** denote $p<0.05$ and $p<0.01$, respectively.

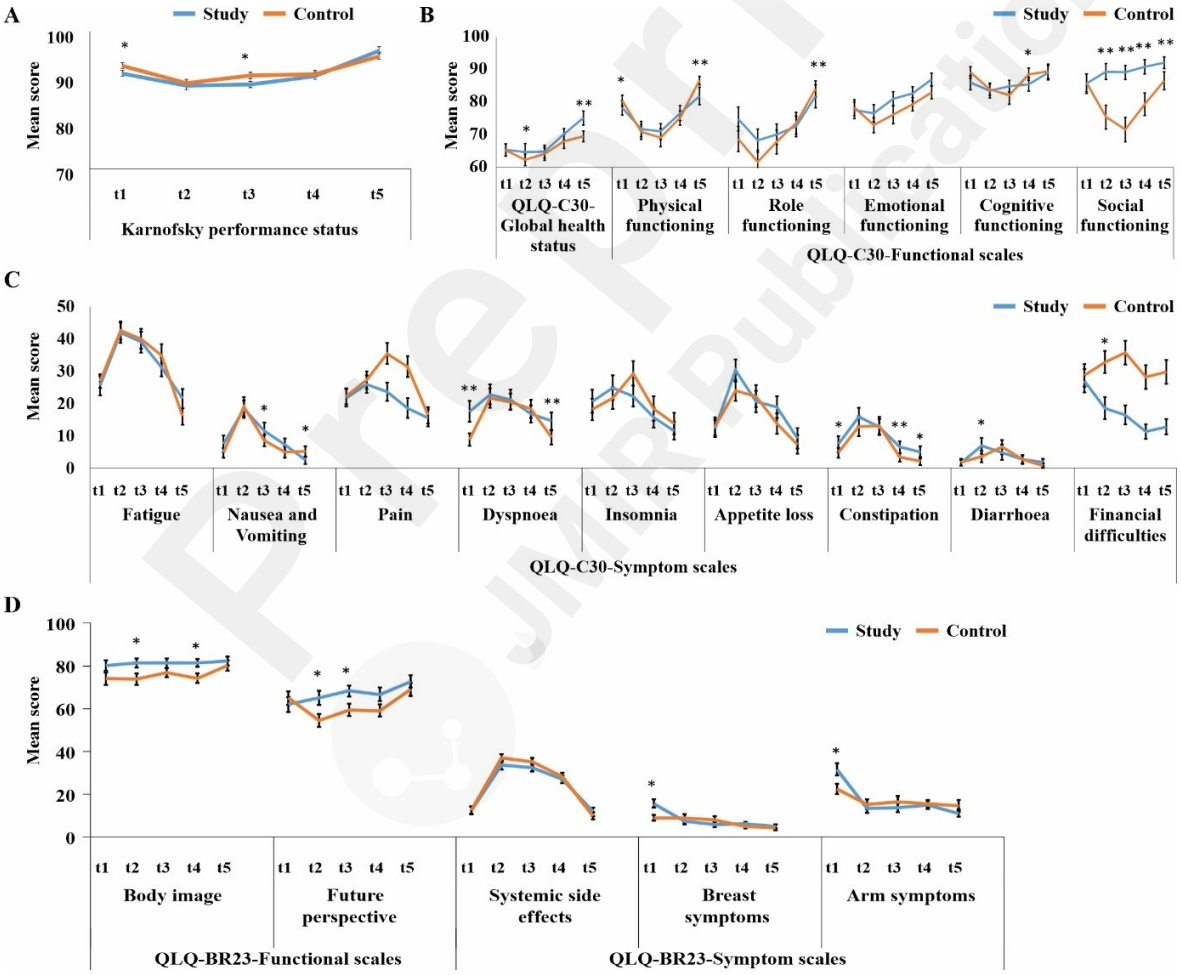
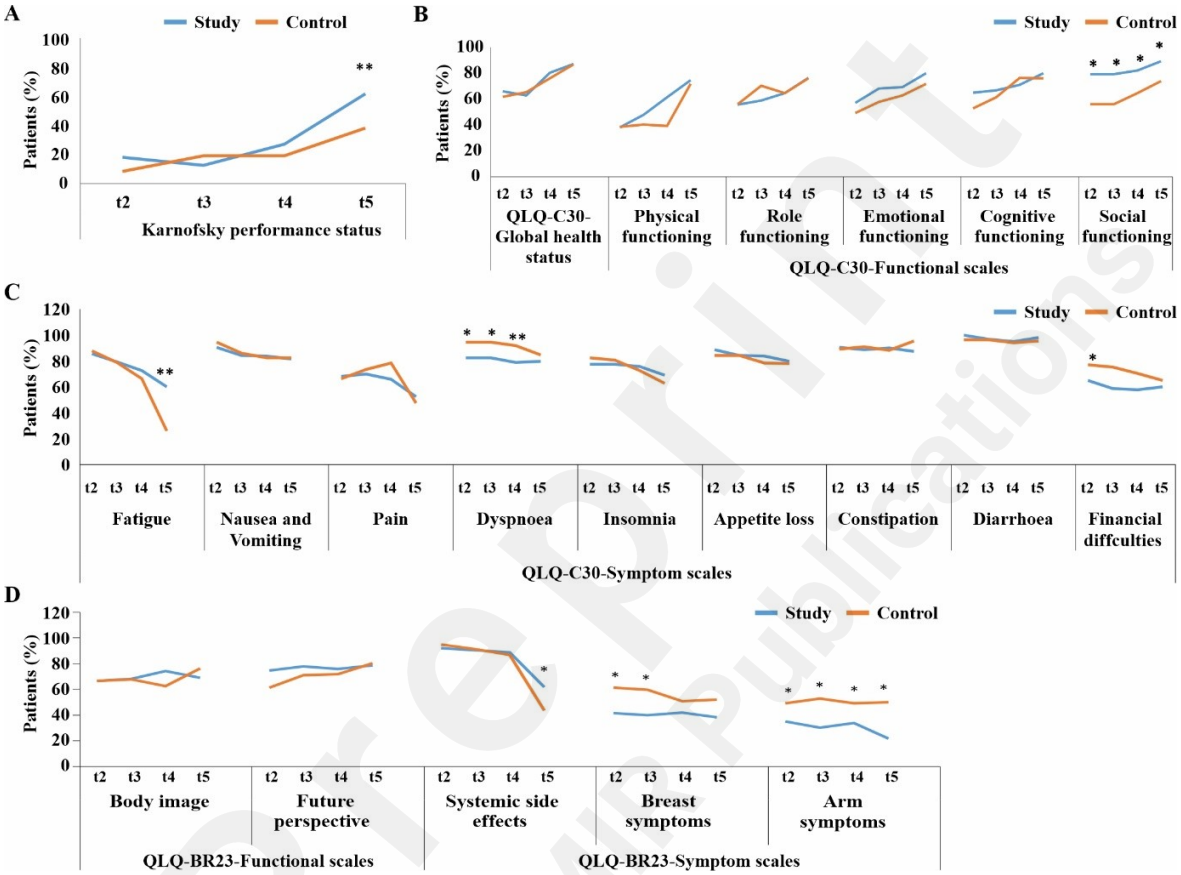


Figure 3. Clinical assessment at all-time points in both the groups expressed as the proportion of patients (%) with positive change (>0) in scores from the initial score at

subsequent time points **A:** Karnofsky performance status score, **B:** QLQ-C30-Global health status scores and QLQ-C30-Functional scales score, **C:** QLQ-C30-Symptom scales score, **D:** QLQ-BR-23 Functional and Symptom scales score**.** The difference in two population was calculated by Z test. * and ** denote p<0.05 and p<0.01, respectively.

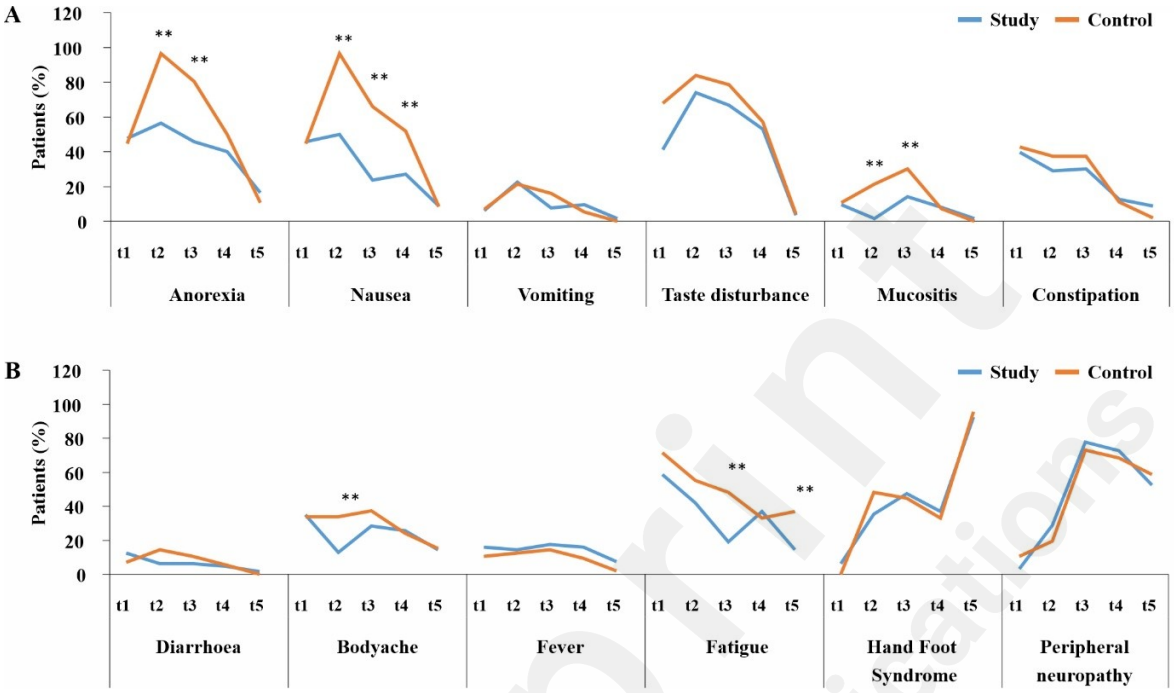


Effect of OAM on chemotherapy-induced adverse effects

Adverse events were graded as per Common Terminology Criteria for Adverse Events at each time point, categorizing low and high adverse effects based on scores. For anorexia, nausea, vomiting, taste disturbance, mucositis, constipation, diarrhoea, fever, hand-foot syndrome, and peripheral neuropathy, a score <1 was low, and ≥1 was high while for fatigue and body ache, a score <2 was low, and ≥2 was high. The percentage of patients with high scores of symptoms was lower in the study group than in the control group. The detailed patterns of symptoms in patients at all time points are given in Figure 4A-B.

Figure 4(A-B). Trend of the percentage of patients in study and control groups with high adverse effects graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The difference in percentages of both the groups was calculated by Z test. * and

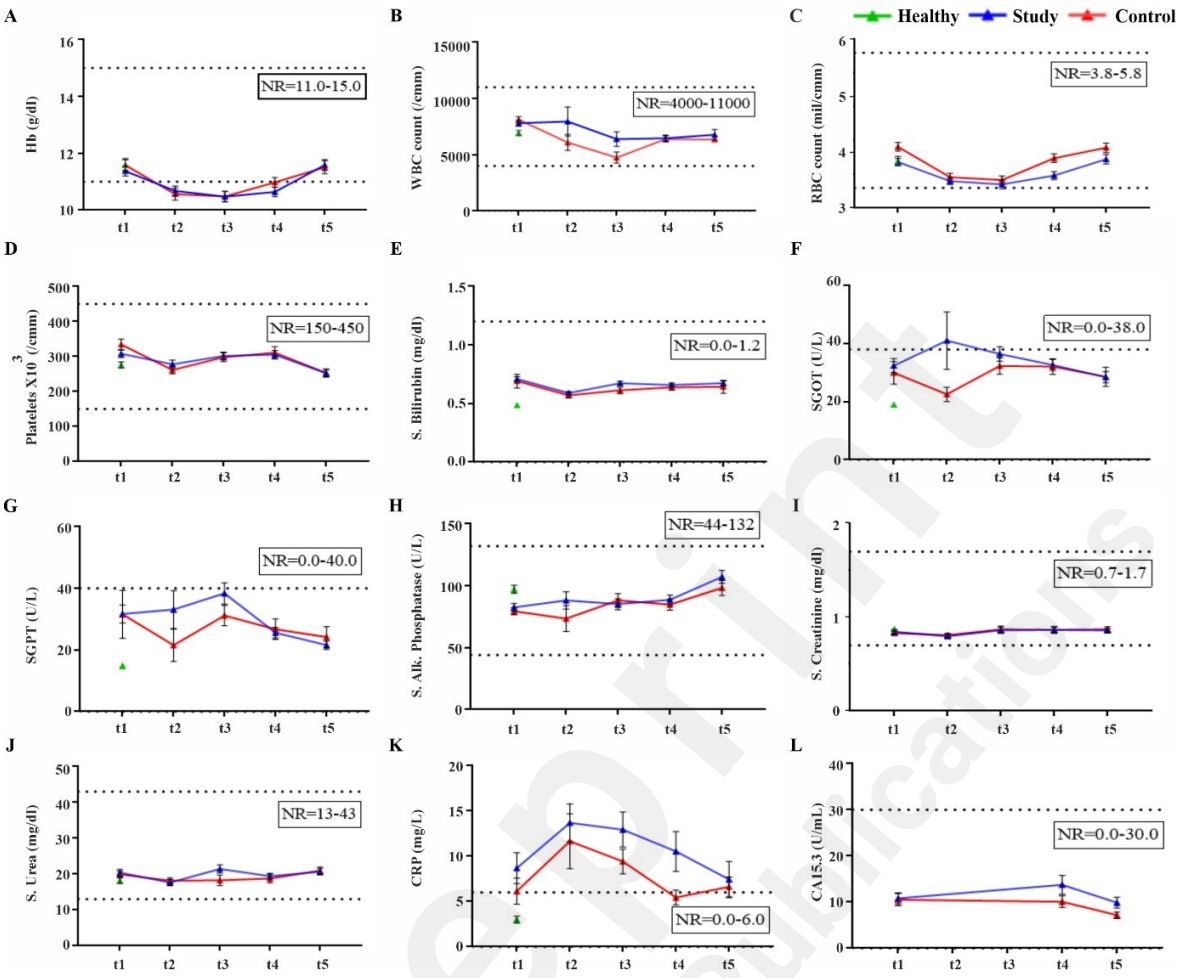
** denote p<0.05 and p<0.01, respectively.



Effect of OAM on clinical laboratory parameters

During chemotherapy, hemoglobin decreased below normal but normalized at one year for both groups (Figure 6A). WBC, RBC, platelet count, and other biochemical parameters (Sr. bilirubin, SGPT, SGOT, Sr. alkaline phosphatase) remained within the normal range. Tumour marker CA 15.3 also fluctuated within normal limits. A detailed pattern is depicted in Figure 5 (A-L).

Figure 5 (A-L). Effect of Oral Ayurvedic Medicines (OAM) on hematological and clinical biochemical parameters of the study and control groups at various time points. NR= Normal Range. The difference in mean values compared by independent ‘t’ test.



Effect of OAM on pro-inflammatory and oxidative stress markers

The trends of mean and difference of the mean of pro-inflammatory cytokines and oxidative stress markers in both the groups are presented in Multimedia appendix 11 and Table 5. Further, the disease stage-wise analysis of cytokine markers for both groups and the trends for individual cytokines are depicted in Multimedia appendix 11. For each studied cytokine, the level increased notably at different time points for each stage in both the groups (Multimedia appendix 12). Accordingly, the concentration difference of individual cytokines from the baseline also varied at different time points in patients of several disease stages from both groups (Multimedia appendix 12).

Effect of OAM on the survival of the BC patients

The Disease-Free Survival (DFS in %), Overall Survival (OS in %) and mortality rate (%) were compared at the end of 4 years and their proportions were observed to be similar in both groups. Kaplan-Meier survival analysis for both groups indicated no significant difference in survival at the end of 4 years (Multimedia appendix 13).

Discussion

Comparison with Prior Work

The literature review revealed that no comprehensive prospective research on the use of herbo-mineral-metallic Ayurvedic drugs to alleviate the adverse effects of chemotherapy has been reported so far by evaluating clinical and immunological responses. However, a case-control retrospective study has been reported on herbo-mineral-metallic Ayurvedic formulations for alleviating the chemotherapy-induced adverse effects. Elaborately, the control group patients completed six chemotherapy cycles while the study group consisted 3 interventional sub-groups. Sub-Group 1 received herbo-mineral formulations: MKD and MPP during and after the chemotherapy; Sub-Group 2 received MKD and MPP only after completion of the chemotherapy and Sub-Group 3 received herbo-mineral-metallic formulations: ASBV, MKD and MPP after completion of chemotherapy. Post-chemotherapy, all the study sub-groups received 16 weeks of treatment. Both groups were assessed for 6 months at specific time points with outcome measures viz., physical examination, common toxicity criteria, radiological investigations, pathological investigations, KPS, and QoL questionnaire. The data recommended simultaneous consumption of herbo-mineral/-metallic Ayurvedic drugs from the beginning of the chemotherapy to impart desired effects in alleviating adverse effects [14]. Hence, the present study was planned as prospective case-control clinical trial to evaluate the efficacy of herbo-mineral metallic OAM administered in breast cancer patients to alleviate the chemotherapy adverse effects. OAM was administered from the beginning of chemotherapy up to a long period of 10 months. Both the groups were assessed at periodic time points (6 monthly) with common toxicity criteria, pathological investigations, radiological investigations, KPS, and QoL questionnaires up to 5 years after diagnosis.

Principal Results

Analogy of chemotherapeutic drugs and toxins in Ayurveda

Ayurvedic concept of toxins (*Visha*) [15] is analogous to the qualities and adverse effects of chemotherapeutic drugs. This analogy has been aptly used to select OAM in the present study to mitigate the adverse effects of chemotherapeutics in BC patients.

Acharya Caraka has mentioned qualities of *Visha* as easy to digest (*Laghu*), dry (*Ruksha*), fast acting (*Ashu*), penetrating (*Tikshna*), can reach up to deep tissues (*Vyavayi-Vikasi-*

Sukshma), hot (*Ushna*). The *Ruksha* and *Ushna* qualities vitiate *Vata* and *Pitta dosha* while the *Tikshna* and *Ushna* qualities vitiate *Rakta dosha*. *Ashu, Vyavayi* and *Sukshma* qualities instantly circulate the drug all over the body. It harms the vital organs (*Marma*) like the heart due to its *Tikshna*, *Vyavayi* and *Vikashi* qualities and thus turns fatal. Further, toxic effects are difficult to treat due to *Laghu* quality [15]. These properties lead to pathological aggravation of three *dosha*, vitiation of seven tissues (*Saptadhatu- Rasa to Shukra*) and their channels of circulations (13 *Srotasa*) showing symptoms similar to side-effects of chemotherapy such as nausea (*Hrullas*), vomiting (*Chhardi*), anorexia (*Agnimandya*), constipation (*Malavibandha*), diarrhea (*Atisar*), skin changes (*Twak vaivarnya*), hair fall (*Khalitya*), peripheral neuropathy (*Hasta – Pada Chimachimayan, Supti* and *Daha*), fatigue (*Klama*) and body ache (*Angamarda*). Hence, to overcome these adverse effects, drugs possessing sweet, bitter or astringent tastes, cold potency (*Madhura rasa*, *Tikta rasa, Kashaya rasa*, *Sheeta veerya*); and showing activities like an appetizer (*Deepana*), digestive (*Pachana*), physical strength enhancer (*Balya*), rejuvenator (*Rasayana),* burning sensation pacifier (*Dahashamana*), *and* toxin eliminator (*Vishaghna*) can be the drug of choice. The OAM collectively holds these properties that alleviate *Tridosha*, mainly *Pittadosha*, and is prescriptible for symptoms such as loss of appetite (*Agnimandya*), anorexia (*Aruchi*), burning sensation (*Daha*), cachexia (*Kshaya*), vomiting (*Chhardi*) and skin diseases (*Kushtha*). According to modern pharmacology, the components of OAM possess activities viz., free radical scavenging, antioxidant, immunomodulatory, and anti-hepatotoxic [16–23]. Their detailed correlation and mode of action of OAM is given in the Multimedia appendix 2,14.

Quality and safety assurance of OAM

The efficacy of any drug depends on its quality, non-toxicity and safety, hence the standardization and characterization of OAM used was carried out to establish identity, purity, and strength through quality control and assurance by adopting the Central Council of Research in Ayurvedic Science guidelines[24]. The average weight, dimensions, and disintegration parameters of tablets were within the permissible range for proper dosing and minimal interference in the bioavailability of active ingredients [25] while the herbo-lipid formulation, APG, indicated lesser rancidity and higher stability of the lipids. Microbial load and heavy metals were within the permissible limits, thus reciprocating Good Manufacturing Practices.

These OAM were further tested for chronic toxicity in animals. Animal organ weight [26] and hematological/ biochemical assessment indicating physiological, nutritional, and

pathological status under environmental, nutritional, and/or pathological factors [27] were within normal limits. Decreased Hb, WBC, and platelet while disturbed Sr. bilirubin, ALP, SGPT, and Sr. creatinine were also within the normal range [28]. Focal degenerative alterations and necrosis in liver tissue of all groups were consistent with previous findings related to ghee consumption in rats. Rats lacking a gallbladder face challenges in fat digestion, disrupting liver function and leading to observed liver changes. The gallbladder's crucial role in concentrating and releasing bile in response to food intake, facilitating the emulsification and digestion of fats, underscores its significance [29,30]. As rats were administered with 2 ml ghee alone or with Ayurvedic formulation every day for 7, 30 and 90 days, normal liver function was disrupted in all the rats, leading to observed changes. These imbalances may be attributed to changes in hepatocyte membrane integrity, increased free radicals and lipid peroxidation, or a combination. Fat metabolism hampers hepatocytes' ability to eliminate excess fat through their association with proteins by forming lipoproteins, leading to the accumulation of fat droplets in hepatocytes' cytoplasm and subsequent vacuolar degeneration, along with congestion of the central vein [31].

Renal tubular cell thinning and necrosis were also observed in all groups, likely due to metabolic disturbances and oxidative stress from ghee administration. The renal tubular cells, being highly susceptible to oxidative damage, can undergo structural alterations and necrosis [32]. Thus, many biochemical and histological changes observed in both VC and OAM groups resulted from a high ghee content used as the vehicle. Ayurvedic formulations alone did not show toxicity beyond the VC, indicating their safety. However, such toxicities are less likely in humans due to lower ghee quantities and a functional gallbladder for fat digestion.

Efficacy of OAM in reducing chemotherapy-induced adverse effects and improving QoL in BC patients

Most enrolled patients in this study were from Stage II (IIA, IIB) and Stage III (IIIA, IIIC) and treated with Anthracycline and Taxane-based chemotherapy. These drugs exhibited Gastrointestinal tract-related adverse effects like nausea, vomiting, sore mouth and lips, loss of appetite, abdominal pain, diarrhea; respiratory-related cough and dyspnea; musculoskeletal related-joint pain, low backache, swelling on feet; neurological- tingling and numbness; skin-related rash, change in skin colour, itching; and hair loss [33]. The patients treated with OAM exhibited lower adverse effects than the control patients. Further, the adverse effects like anorexia, nausea, mucositis, body ache, and fatigue showed remarkable improvement in the study group as compared to the control group.

Moreover, in the study group that received OAM, 65% of the patients followed a regular chemotherapy schedule while 63% of control patients faced difficulty. Secondly, only 4.76% of study patients required any other oral medication support apart from OAM, indicating a good response to OAM.

The effect of OAM on adverse events of chemotherapy was measured clinically with symptoms gradation throughout the treatment. KPS, a determinant of the ability of patients to tolerate the therapy [34], while the items included in C30 [35] as well as BR23 [36], were analyzed to evaluate the QoL. In this study, the parameters – Sexual functioning, sexual enjoyment (BR23-FS) and upset by hair loss (BR23-SS) were not considered since OAM was not intended to treat sexual ability and alopecia. Overall, the trend of C30-SS showed a lower range in the study group compared to the control group, indicating less symptom load due to OAM. Physical and role functioning worsened during chemotherapy, however, both the parameters recovered to baseline at the end of chemotherapy in both groups. Emotional and cognitive functioning was marginally impaired during chemotherapy in the study group; however, cognitive functioning was worse up to the end of the chemotherapy and recovered after one year in the control group. Social functioning was worse in the control group till the end of chemotherapy.

QLQ BR-23 assessed the disease symptoms, adverse effects of the chemotherapy, body image, and future perspectives [37]. The trend of functional scale in the study patients was maintained throughout the chemotherapy denoted by body image and future perspective. Though the systemic adverse effects increased during chemotherapy in study patients, they decreased later and remained marginally lower compared to the control group, denoting the effects of OAM on adverse events of chemotherapy. The baseline symptom load in breast and arm symptoms of the study group was higher than the control group, they decreased at t2 and t3 compared to the control group due to OAM interventions, showing significant improvement during follow-ups. Also, the study group tolerated chemotherapy as denoted by improved KPS.

Efficacy of OAM on laboratory, cytokines and oxidative stress parameters

In the present study, multiple parameters viz., hematological, biochemical, immunological and clinical were evaluated that lead to QoL of the cancer patients.

The hematological parameters of the study group did not cross the lower limit of the normal range during the chemotherapy, except Hb, indicating the effect of OAM on maintaining blood cell counts. Liver and kidney function parameters did not express any remarkable

change signifying its protective effect and safety to these two vital organs. CRP, an inflammatory marker, depicted a higher range in both groups indicating an inflammatory response to the chemotherapy drugs [38]. CA 15.3 was within the normal limit in both the groups during and after chemotherapy revealing a good response to chemotherapy to eliminate the residual tumour mass [39]. Further, the patients from both groups did not suffer from any cardiotoxicity as evaluated by 2-D Echocardiogram one month after the end of the chemotherapy.

Four cytokines were quantified at various time points in both groups. Interleukin-10, which has an important coordinated role in breast carcinogenesis [40], is an anti-inflammatory cytokine that regulates the immune response [41]. Its low expression is associated with poor survival outcomes [42]. Our data revealed higher IL-10 levels in the study patients with a declining pattern at subsequent time points, suggesting chemotherapy drug-induced inflammatory response. Many studies report that higher expression of serum IL-1β, IL-6 and IL-8 levels in BC patients are associated with poor outcomes [43–45]. The pro-inflammatory IL-8 levels presented lower inflammatory response and IL-1β and IL-6 presented higher responses in the study patients compared to the control group. These markers followed a similar pattern at all time points in both groups. The oxidative stress marker, SOD, depicted below normal level activity in both the groups at all the time points showing low antioxidant response, while catalase demonstrated higher than the normal range indicating moderate antioxidant activity in the study group as compared to the control group. However, glutathione activity was remarkably higher in the study patients during and after chemotherapy, denoting antioxidant response to OAM [46].

The Kaplan-Meier survival analysis for both groups indicated no significant difference in the survival proportion at the end of four years. Thus, the alleviation of adverse effects in the study group was observed during chemotherapy due to adjunct Ayurvedic medicines without deteriorating the effect of chemotherapy drugs and the survival of the patients. It was further interesting to note that the percentage of women with co-morbidities like Diabetes Mellitus, hypertension, thyroid disease, epilepsy, rheumatoid disease, and asthma was higher in the study group (51%) as compared to the control group (44%). Despite this, the study group patients tolerated chemotherapy with minimal adverse effects and improved QoL. Moreover, the patients did not report any adverse effects during the 10-month treatment duration and four-year post-treatment surveillance period. This, especially, is an important outcome since the safety of long-term use of herbo-mineral metallic formulations is a concern. This advantage may motivate the long-term use of standardized mineral-metallic combinations

without many toxic effects for better outcomes.

Overall, the subjective and objective responses of OAM-treated patients varied during and after completion of the chemotherapy. The subjective parameter response was positively in favour of the study group while the clinical, hematological, and biochemical parameters exhibited protective effects on vital organs like the liver and kidney during chemotherapy drug metabolism. The CRP level, proinflammatory markers, and oxidative stress markers revealed partial response during chemotherapy in the study group, hence there is a need to explore other markers to elucidate the mechanism of action of OAM.

Present research further recommends supportive therapy for managing chemotherapy-induced adverse effects. Complementary and alternative therapies support the management of cancer treatment-induced adverse effects. A paradigm shift through integrating conventional medicine with evidence-based CAM is essential. Educating patients and healthcare workers about the supportive role of Ayurveda is crucial for maximizing benefits from both contemporary medicine and Ayurveda [47–50].

Limitations and future scope

In this non-randomized active-controlled trial, we have chosen only BC patients undergoing chemotherapy (irrespective of drugs/ protocol) and treated them with only OAM for 10 months. This study can be done with other types of cancer patients undergoing chemotherapy and can be treated up to one year after completion of chemotherapy. The investigators have preserved important organs of rats exposed to these mineral-metallic formulations for the detection of possible metal deposition. This may be one of the future aspects of this study.

Conclusions

In conclusion, the study demonstrates that the administration of OAM containing herbo-mineral and metallic drugs, when given alongside chemotherapy and continued post-treatment, appears to be safe and effective in reducing the toxic adverse effects due to chemotherapy in BC patients. The OAM treatment showed a positive impact on subjective parameters of QoL and indicated a protective effect on vital organs such as the liver and kidneys, as evaluated by clinical and biochemical parameters. Additionally, partial improvements in inflammatory markers and oxidative stress were observed, suggesting a potential role in enhancing the systemic immune response and improving the overall quality of life for patients undergoing chemotherapy.

Preprint JMIR Publications

Authorship Contributions Statement

SPS, VD and VSG: Conceptualization, Methodology, Resources; **TP and RN**: Resources, Methodology, Supervision; **SG, VRG, and SJK**: Resources, Supervision, Software, Visualisation; **SP**: Software, Visualisation, Data curation, Statistical analysis; **DD, NS**, **VA, DK and SA**: Collection and assembly of data; **NP, SK, PP**: Resources; **SB**: Data curation, Software, Writing- Original draft; **VG**: Resources, Project administration; **KB and KG**: Data curating, Formal analysis; **SC**: Visualisation and critical revision of article. All the authors have reviewed the original draft before submission.

Sources of funding

The study is funded by Tata Trusts (Grant ID: Health-BSDT-20151007).

Authorship disclosure

The medicines (OAM) used in this study have been filed and published as Indian (Application no. 201921018276) and US (Filing no. 17/609,673) patents.

Data Availability

Data generated during and/or analysed during this study are available from the corresponding author on reasonable request.

Abbreviations

AAV: *Atharva Ananta Vati*, **APG:** *Atharva Padmakadi Ghruta*, **ASBV:** *Atharva Suvarnabhasmadi Vati*, **BC:** Breast Cancer, **BR23-FS:** BR23 Functional Scale, **BR23-SS:** BR23 Symptom Scale, **BRAS:** BR23 Arm Symptoms, **BRBI:** BR23 Body Image, **BRBS:** BR23 Breast Symptoms, **BRFU:** BR23 Future Perspective, **BRHL:** BR23 Upset by Hair loss, **BRST:** BR23 Systemic therapy side effects, **CAM:** Complementary and Alternative Medicines, **CF:** Cognitive Functioning, **CRP:** C-reactive protein, **EF:** Emotional Functioning, **FS:** Functional Scale, **GS:** Global Scale, **IL:** Interleukin, M**KD:** *Mauktik Kamdudha Rasa*, **KPS:** Karnofsky Performance Score, **MPP:** *Mauktik Praval Panchamruta*, **OAM:** Oral Ayurvedic Medicines, **PF:** Physical Functioning, **QLQ:** Quality of life questionnaire, **QoL:** Quality of life, **RF:** Role Functioning, **SD:** Sprague Dawley, **SF:** Social Functioning, **SGOT:** serum glutamic-oxaloacetic transaminase, **SGPT:** serum glutamic pyruvic transaminase, **SOD:** Superoxide dismutase, **SPSS:** Statistical Package for Social Sciences, **SS:** Symptom Scale, **VC:** Vehicle Control.

Multimedia Appendix

Multimedia appendix Table 1-9 and Figures 10-14.

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Multimedia Appendixes

Number of patients (n) tested for various Haematological and Biochemical parameters as well as Immunological and Oxidative markers.
URL: http://asset.jmir.pub/assets/193aeebddbe4f3a7f31a8fc6a1cb53c2.docx

Details of oral Ayurvedic medicines (OAM).
URL: http://asset.jmir.pub/assets/79f1136927968cc9fc704ec191545274.docx

Grouping and experiment protocol of chronic toxicity study in Sprague Dawley (SD) rats.
URL: http://asset.jmir.pub/assets/ff71bf3df5aedefd19caba22386c8b79.docx

Basic physicochemical parameters of OAM in tablet form.
URL: http://asset.jmir.pub/assets/0916ffbdbde07bb67c0f5bcbbf5a4adc.docx

Basic physicochemical parameters of OAM in medicated ghee form.
URL: http://asset.jmir.pub/assets/eb87553f4152bcbc78ae3d1d80dc1e15.docx

Effect of OAM and Vehicle on vital organ weight (g) of SD Rats.
URL: http://asset.jmir.pub/assets/fc1df6470a2f1ca7ff7b9c9425a03e47.docx

Histopathological changes in SD rats after 7, 30 and 90 days of OAM and Cow’s ghee administration.
URL: http://asset.jmir.pub/assets/694d13203edbd87c93fae819aac0e7c6.docx

Clinical assessment at all-time points in both groups expressed as the mean score.
URL: http://asset.jmir.pub/assets/1dda117d10496292e38072708c5e90ee.docx

Clinical assessment at all-time points in both the groups expressed as the proportion of patients (%) with positive change (>0) in scores from the initial score at subsequent time points.
URL: http://asset.jmir.pub/assets/b9e5021e8cf552e28f20b023f30ab0c1.docx

Effect of OAM on hematological and biochemical parameters of SD rats on 7, 30 and 90th Day. VC denotes the group of Vehicle Control while CH represents the OAM-treated group. The differences of mean values before and after treatment of both the groups was calculated by Paired t test. *p
URL: http://asset.jmir.pub/assets/64f8b84f0335e06b3d51105941e0b003.png

Mean values (A, C, E, G, I, K, M) and differences of the mean (B, D, F, H, J, L, N) of immunological and oxidative stress markers from the baseline of study and control group patients at all time points. HR= Healthy Range. The difference in mean values of both the groups was calculated by independent ‘t’ test and difference of means measured by Z test. * and ** denote p

URL: http://asset.jmir.pub/assets/f0f3090f167e2cfef7e6133cc6561d65.png

Mean values (A, C, E, G) and differences in concentration (B, D, F, H) of the cytokine markers in control and study group patients of different disease stages, at all-time points. The difference in mean values of both the groups was calculated by the independent ‘t’ test and the difference in means was measured by Z test. * and ** denote p
URL: http://asset.jmir.pub/assets/751769fca11bf25c1510c0cfc12cf5a7.png

Survival analysis (4 years), A: Status of both study and control groups at the end of 4 years, B: Kaplan-Meier Survival curve.
URL: http://asset.jmir.pub/assets/c881aee0caee212227ba43c4c96796e0.png

Analogy of chemotherapeutic drugs with toxins in Ayurveda and probable mode of action of OAM over their side effects.
URL: http://asset.jmir.pub/assets/c8635e29abcab662473f567567c99360.png

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