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Research Article

EFFICACY AND SAFETY OF STANDARDIZED CINNAMON BARK EXTRACT FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED WEIGHT LOSS AND ALOPECIA IN PATIENTS WITH BREAST CANCER: A RANDOMIZED, DOUBLE-BLIND, AND PLACEBO-CONTROLLED STUDY

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ABSTRACT

Objective: The objective of the study was to evaluate the effects of IND02 (standardized Cinnamon bark extract) supplementation for the prevention of side effects of cancer chemotherapy in female patients with breast cancer.

Methods: The study was conducted using double-blind, placebo-controlled design in 34 female breast cancer patients during the first 4 consecutive 21-day cycles of the standard chemotherapy regimen. The active treatment (IND02 capsules, 400 mg, one capsule, and thrice a day) or matching placebo was orally administrated in randomized (1:1 ratio) patients. The efficacy outcome measures were reduction in chemotherapy-induced weight loss, alopecia (hair fall), and other side effects. The safety outcome measures were hematology, ECG, vital signs, adverse event monitoring, and laboratory safety measurements.

Results: The patients on the treatment with IND02 had shown significant protection from chemotherapy-induced severe weight loss (cachexia) and alopecia (reduced hair density and % hairs in the anagen phase, and increased % hairs in telogen phase) which was seen in the placebo group. IND02 treatment was found safe and well-tolerated during the study.

Conclusion: Concomitant use of IND02 in breast cancer patients during breast cancer chemotherapy showed a clinical promise regarding efficacy and safety in preventing chemotherapy-induced weight loss and alopecia.

Keywords: Cinnamon bark extract, Chemotherapy-induced alopecia, Weight loss, Side effects, Breast cancer patients.

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INTRODUCTION

The breast cancer is the second most common type of cancer after lung cancer worldwide (10.4% of all cancer incidence, both sexes counted) and the fifth most common cause of cancer death [1]. Breast cancer, a common form of cancer, usually starts in the inner lining of the milk ducts or lobules and goes in the uncontrolled growth stage (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes results into metastasis (spread to other locations in the body through lymph or blood). Cancer is caused by external factors (tobacco, chemicals, radiation, and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) [2].

The treatment of cancer has relied primarily on the use of various forms of cytotoxic chemotherapy and radiation therapy. Most chemotherapeutic drugs target fast-dividing cells and mitosis (cell division) impairment. These interventions have had profound positive results on many hematological malignancies and a few solid tumors, especially germ cell and some childhood malignancies. However, in most cases, the effectiveness of cytotoxic treatments has been limited by the side and immuno-suppression, with susceptibility to opportunistic pathogens [3,4] which remained as the major obstacles for the successful clinical use [5]. Toxicity of anticancer agents is the primary reason for patients to discontinue the treatment [5]. Typical chemotherapy side effects include severe weight loss (cachexia), alopecia (hair loss), nausea, vomiting, diarrhea, loss of appetite, mouth soars (mucositis), anemia, cardiotoxicity, hepatotoxicity, and nephrotoxicity.

Cachexia or severe weight loss and subsequent fatigue are the most debilitating side effects of most of the anticancer regimen. The primary causes include depression of the immune system, malnutrition, and dehydration caused by many chemotherapeutic agents. Chemotherapy-induced alopecia (CIA) or hair loss is another common side effect of chemotherapy regimens. The likelihood of alopecia is related to the type of drug used and its schedule of administration. Some chemotherapeutic drugs that kill rapidly dividing cells cause dramatic hair loss; other medications may cause hair to thin. These are temporary or permanent. After the temporary loss, the hair usually starts to regrow after the last treatment, sometimes with a tendency to curl, resulting in "chemo curls." Permanent hair loss can result from some standard chemotherapy regimens. As chemotherapy affects living, rapidly dividing cells, the hair loss from chemotherapy is associated with anagen effluvium (hair loss in the anagen or growth phase).

The nutritional approach may be the means of helping to raise cancer therapy to a new level of success as supplementing or supporting the body with natural phytochemicals not only reduce adverse side effects but also improve the effectiveness of chemotherapeutics [5-7]. However, most of the nutritional therapies have not been tested by rigorous clinical trials, and while some natural therapies have stood the test of time, very little information is available to validate their efficacy.

One such promising dietary ingredient described in many traditional and modern literature is Cinnamon (*Cinnamomum verum* and synonym *Cinnamomum zeylanicum*) bark [8-11]. Worldwide, cinnamon bark is used as a spice and flavoring agent due to its distinct flavor and aroma. The medicinal properties of cinnamon are mentioned in the

literature of traditional systems medicines of India, Sri Lanka, China, Egypt, and European countries. Moreover, cinnamon bark is a certified generally recognized as safe ingredient in the USA. Cinnamon bark is demonstrated immune stimulant and immunosuppressant activities depending on species, doses and nature of constituents [12,13]. Cinnamon-based supplements have demonstrated their ability as immuno-modulator [14] and anticancer [15]. Recently, sodium benzoate, a metabolite of cinnamon, has shown to have immunomodulatory activities through regulation of immune signaling pathways responsible for inflammation, and modulation of regulatory T cells, and cell-to-cell contact and implicated in amelioration the disease progression of immune disorders [13]. Furthermore, immunomodulatory activity of cinnamon bark extract on multiple arms of immunity to offer protection against side effects of chemotherapy (cyclophosphamide) in the presence [12] and absence [16] of pathogenic infections has been reported.

The multifaceted pharmacological activity profile of cinnamon bark is mainly attributed to its high polyphenol content [17,18]. Cinnamon bark PP (polyphenols) and TAPP-CZ (TAPP, type-A proanthocyanidins polyphenols) based standardized cinnamon bark extract have been demonstrated beneficial effects against immune inflammatory disorders such as rheumatoid arthritis [19,20], asthma [21], and allergic rhinitis [22]. The preparation, standardization and pharmacological efficacy and safety of IND02, a standardized cinnamon bark extract with PP as a marker compound has been reported in animal models of immune inflammatory disorders such as asthma [21] and allergic rhinitis [23]. The past studies have confirmed the safety of oral IND02 administration in laboratory animals [24]. The cinnamon extract has reported offering protection against side effects of cyclophosphamide-induced side effects on male sexual functions in laboratory animals [16]. However, clinical evidence for such immunological benefits for reduction of chemotherapy-induced side effects is lacking. In the light of these findings, the present study was undertaken with an objective to explore potential efficacy and safety of IND02 as a nutritional adjuvant to prevent side effects of breast cancer chemotherapy in randomized, placebo-controlled, and double-blind clinical study.

METHODS

Recruitment

The sample size to achieve 80% power was calculated. A total of 34 female patients with breast cancer undergoing chemotherapy before or after surgery were recruited at single center, namely, Central India Cancer Research Institute, Nagpur in India. The effects of IND02 were evaluated during four chemotherapy cycles (each of 21 days) were followed. The treatment was initiated 7 days before the start of the first chemotherapy cycle with a total duration of 91 days as per flowchart (Fig. 1). The study was performed according to the principles of Good Clinical Practice, the Declaration of Helsinki, and all local laws and regulations about clinical studies. The trial protocol was approved by the Independent Ethics Committee for Human ethics requirement and is registered with Clinical Trial Registry of India (CTRI), New Delhi, India (registration No. CTRI/2012/08/002883).

The inclusion criteria consisted of the patient's female breast cancer patients between the age of 18 and 70 years with confirmed primary carcinoma of the breast using core biopsy, needle biopsy or fine-needle aspiration cytology and who have undergone mastectomy and with indications for chemotherapy. Only patients with total leukocyte count ≥4000/mm, platelet count ≥100,000/mm^3, hemoglobin ≥10.0 g/dL and who are willing and able to comply with the study procedures and provide written informed consent to participate in the study were included in the study.

The exclusion criteria were as follows: (a) Patients received prior chemotherapy or hormonal therapy for the treatment of breast cancer within the past 6 months, (b) with existing mucositis or oral and throat pain condition before starting chemotherapy, (c) have already shaved the scalp hair before receiving chemotherapy, (d) have hypersensitivity

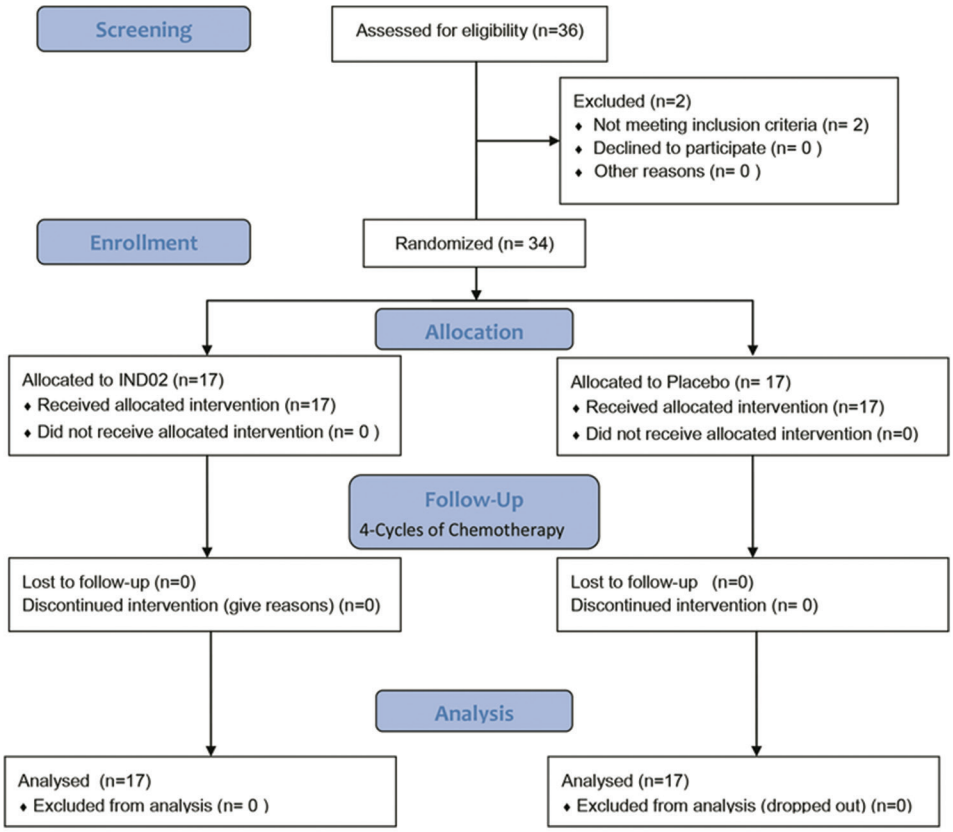

Fig. 1: Study flowchart (CONSORT diagram)

to the study medication, its excipients, its analogs, or any of the components of herbs, (e) diagnosed with active seropositive acquired immunodeficiency syndrome or Hepatitis B/C, (f) who are pregnant, lactating, pre-menopausal female patients with childbearing potential and/or not on contraceptives, (g) altered mental status precluding understanding of the informed consent process and/or completion of the necessary assessments, (h) with other severe diseases such as abnormal cardiac conditions, hepatic or renal disorder, uncontrolled diabetes or other medical conditions that are likely to interfere with the study in the investigator's judgment, (i) have participated in other cancer trials in the past 30 days, and (j) who, in the investigator's clinical judgment, are not suitable for this study.

Screening and randomization

Potential participants were screened, requested to attend an information session, informed of the trial process and were asked to provide their consent for trial participation. During visit 1 (screening visit), the medical history and demography of consenting subjects were taken, physical and clinical examinations and laboratory investigations were performed and recorded incase report forms. The medication was dispensed, and baseline values of outcome measures were also recorded. They were also randomized to 1:1 ratio to receive either active treatment, IND02 or placebo according to a computer-generated randomization list. Randomization was based on a total of 34 subjects, randomly allocated into two arms of equal numbers of subjects (n=17 for each group). Both the active treatment product and the placebo product were enclosed in bottles containing capsules that were identical in the appearance and function and individually coded. Patients were allocated a unique randomization number.

The treatments

Female breast cancer patients undergoing chemotherapy were on the standard chemotherapy for four cycles of intravenous CAF regimen. The regimen comprises cyclophosphamide (500 mg/m^2)+doxorubicin (adriamycin, 50 mg/m^2)+5-Fluoro Uracil (500 mg/m^2) on the 1st day of chemotherapy cycle (21-day cycle) [25]. The active treatment, IND02 was prepared and characterized as per reported procedure [14,19]. IND02 is a standardized extract of *C. zeylanicum* bark containing polymeric proanthocyanidins polyphenols as a marker compound. The patients were instructed to consume three capsules of 400 mg of IND02 matching placebo (di-calcium phosphate, IP grade) in a day during four chemotherapy cycles of CAF regimen as an adjuvant to chemotherapy.

Outcome measures

Efficacy outcome measures were a reduction in chemotherapy side effects caused by treatment regarding severe weight loss (cachexia), CIA, i.e., hair fall, mucositis, leukopenia, and anemia during each visit. CIA measurement was done using the TrichoScan®, a quantitative method, for the analysis of human hair growth and hair loss, is software-based that calculates hair growth parameters easily and rapidly. The digital images are taken from the scalp with a specially developed camera-optics system. TrichoScan® gives a quantitative result output for % anagen, telogen %, and hair densities (n/cm^2). Mucositis was measured with the help of the WHO Oral Mucositis Assessment Scale [26]. The severity of nausea, vomiting, and diarrhea was scored based on National Cancer Institute-Common Toxicity Criteria version 4.0. Each patient is supplied with the diary in which daily record of episodes of pain, nausea, vomiting, and diarrhea was recorded. The diaries were collected at the last visit and analysis of data was done. The safety criteria were the medication discontinuation due to adverse events (AEs), laboratory tests and AE reporting of the patient with its possible association with the drug under study. Concomitant medication data were also recorded. The laboratory assessment (hematology, biochemistry, and urinalysis) was performed at each visit. The AE monitoring including laboratory safety parameters, global assessment by physician and patients, was also performed. Participants were monitored for protocol compliance with the help of a telephone or face-to-face communications.

Data analysis

The data were presented as the mean and standard deviation. The data were analyzed by Analysis of variance followed by unpaired t-test for comparisons between the groups (IND02 vs. placebo group) or paired t-test for comparisons within the group (end of the study vs. baseline values). $p<0.05$ was considered significant.

RESULTS

Demographics and baseline characteristics

A total of 34 patients were enrolled in the study, 17 in either arm. All the patients enrolled completed the study. None of the patients was dropped out of the study. Unpaired "t"-test of demographic parameters was found to be uniform as mean age, weight, heart rate, and blood pressure (systolic and diastolic) were not found to be significantly different (Table 1).

Effects on chemotherapy-induced weight loss

The unpaired "t"-test of body weight data of the patient from the IND02 group was found to increased whereas that of the placebo group showed a decline in weight over the study period. The body weight changes (gain) were found to be significantly higher ($p<0.05$) in IND02 treated the patient (loss of weight) as compared placebo group at the end of cycle 2, 3, and 4 whereas such change was not the significant end of cycle 1 (Table 2).

Effects on CIA

Paired "t"-test of hair analysis data showed hair density of patients on placebo was significantly ($p<0.05$) reduced at the end of study (11.3 hairs/cm^3) as compared with baseline (37.12 hairs/cm^3). On the other hand, the reduction in hair density in IND02 treated patient was not significant (Table 3). Patients in the placebo group showed significantly ($p<0.05$) lower % anagen hairs at the end of study (39.09%) as compared to the baseline value (90.63%) whereas the corresponding change in IND02 treated the patient (from 74.29% to 50%) was not significant (Table 3). Patients in the placebo group showed significant ($p<0.05$) increase in % telogen hairs at the end of the study (57.27%) as compared with baseline values (10%). However, no significant change was observed in % telogen hairs in IND02 treated patients (Baseline: 21.43 %, End of study: 49.09 %) (Table 3).

Effects on chemotherapy-induced mucositis, nausea, vomiting, and diarrhea

No significant difference in the scores of oral mucositis, nausea, vomiting, and diarrhea or pain was observed in examinations during

Table 1: Demographic and clinical characteristics of enrolled patients at baseline

Variable	IND02 (n=17)	Placebo (n=17)	p-value
Age (years)	53.71±11.31	52.82±8.10	ns
Weight (kg)	58.29±11.70	64.19±13.44	ns
Heart rate (bpm)	78.76±3.80	78.12±3.43	ns
Systolic blood pressure (mmHg)	123.94±6.82	122.88±7.07	ns
Diastolic blood pressure (mmHg)	78.00±3.61	78.71±5.19	ns

Data were represented as Mean value±SD and were analyzed between the groups by unpaired "t"-test. ns: Not significant between the groups

Table 2: Effect of treatment on change in body weights from baseline

Visit (end of cycle)	IND02 (n=17)	Placebo (n=17)
Cycle 1	↑ 0.04±0.90	↓ 0.15±0.57
Cycle 2	↑ 0.38±1.15*	↓ 0.43±0.84
Cycle 3	↑ 0.28±1.28*	↓ 0.53±1.00
Cycle 4	↑ 0.63±1.03*	↓ 0.49±0.97

Data were represented as a change in body weight from baseline (kg) (mean±SD) and were analyzed by unpaired "t"-test. *$p<0.05$ as compared with the placebo group at the respective cycle

visits at the end of each chemotherapy cycles (data not presented). Similarly, no significant difference in the number of episodes of nausea vomiting or diarrhea was found between placebo and active treatment at baseline or at the end of the study (data not presented).These results can be explained by the same amount prophylactic treatment (for example, ondansetron injection and an antiemetic) that was received by all the patients in both the arms. Despite same dose of prophylactic treatment, a maximum number of vomiting episodes in placebo-treated patients was almost double as compared to the number of episodes in the IND02 group (18 vs. 10, respectively). Further, reduction in the number of episodes was observed in IND02 treated patients from 10 (baseline) to 7 (end of study) whereas the maximum number of episodes in placebo-treated patient did not show a significant change from baseline during the same period (18 vs. 17).

Safety evaluation

All the patients were evaluated for safety at baseline and the end of each chemotherapy cycle. The safety parameter data (hematology, biochemistry, liver function test, and kidney function test) are presented in Table 4. The differences between values at baseline and the end of the study were found non-significant. Vital signs and physical findings of patients were within the normal range during the study. There were no deaths or serious AEs the study which confirms the excellent safety profile of IND02.

DISCUSSION

Cancer chemotherapy-related symptoms such as cachexia and resultant fatigue, malaise, loss of interest in social activities, difficulty in concentration and changes in sleep patterns lead to treatment delays, dose reductions, or termination and affect the physical, psychosocial, and economic aspects of quality of life [27]. Therefore, the development of interventions to effectively manage chemotherapy-related side effects is one of the significant concerns in oncology.

Nutrition intervention, together with chemotherapy, has found to improve outcomes in patients with pancreatic and non-small-cell lung cancer [28]. Immune modulation is a major element of supportive care for many chemotherapy regimens [29,30]. The immunomodulatory potential of natural products was also explored as adjuvant therapy in cancer patients [31]. Recently, immune-modulating diet in combination with chemotherapy has reported preventing cancer cachexia without suppressing chemotherapeutic efficacy [32]. However, clinical evidence for such immunological benefits for reduction of chemotherapy side effects is lacking. The present study is aimed to evaluate potential efficacy and safety of IND02, an immunomodulatory nutritional ingredient, as an adjuvant to chemotherapy to breast cancer patients in randomized, placebo-controlled, and double-blind manner.

Clinicians have long suspected the symptoms of side effects similar to the "sickness behavior" (triggered by the inflammatory cytokines interleukin 1β [IL-1β], tumor necrosis factor α [TNF-α], and IL-6 by macrophages, and other cells of the innate immune system in response to immune challenge) [33]. Substantial evidence implicates the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 in the etiology of chemotherapy-related cachexia and related symptoms [27]. Furthermore, cytokine release in response to early side effects of paclitaxel chemotherapy results in joint pain and flu-like symptoms [34].

Immunomodulatory effect of cinnamon bark extract is known to be mediated through cytokines [35] and interferon γ (IFNγ), JNK, ERK1/2, and STAT4, p38, but not IL-2 production in activated T cells [36]. The body of evidence suggested that the presence of polyphenols in

Table 3: Effect of IND02 on CIA

Parameter	IND02 (n=17)		Placebo (n=17)	
	Baseline	End of study	Baseline	End of Study
Hair density (hair/cm^2)	44.53±16.09	21.5±23.15 ns	37.12±12.93	↓ 11.30±12.63*
Anagen hair (%)	74.29±33.45	50.0±45.61 ns	90.63±15.69	↓ 39.09±42.06*
Telogen hair (%)	21.43±28.78	49.09±45.49ns	10.00±16.33	↑ 57.27±41.01*

Data were represented as parameter Mean±SD and were analyzed by paired "t"-test for each parameter. ns: Not significant, *p<0.05 as compared with baseline for respective parameter. ↑ indicate a significant increase and ↓ indicate a significant decrease as compared with baseline values

Table 4: Hematology and biochemistry at baseline and end of treatment (safety)

Parameter	IND02 (n=17)		Placebo (n=17)	
	Baseline	End of study	Baseline	End of Study
Hematology				
RBC Count (million/mm^3)	3.97±0.47	↑ 4.06±0.35	4.36±0.47	↓ 4.20±0.40
Platelet count (/mm^3)	282823.53±76619.38	261823.53±88115.15	242529.41±39721.09	283294.12±82815.13
Total WBC (/mm^3)	7741.18±1736.40	6994.12±2801.67	7711.76±2102.94	6200.0±2855.91
Basophil (/mm^3)	00.00±0.00	00.00±0.00	0.12±0.49	0.00±0.00
Eosinophil (/mm^3)	2.88±0.99	3.06±0.90	3.53±1.23	3.53±1.74
Lymphocytes (/mm^3)	27.82±6.89	33.06±9.25	31.41±6.87	31.88±11.36
Monocytes (/mm^3)	2.12±0.33	2.06±0.90	2.24±0.56	2.24±0.97
Neutrophils (/mm^3)	68.12±6.36	61.82±9.58	62.88±7.33	62.24±12.42
Hemoglobin (%)	11.276±0.82	11.300±0.91	11.788±0.81	11.294±1.173
Biochemistry				
ALP (IU/L)	98.19±25.39	93.36±24.24	85.77±14.46	80.93±12.58
ALT (IU/L)	28.32±18.15	22.55±5.78	21.36±4.78	20.53±5.96
AST (IU/L)	33.22±20.63	24.59±5.73	26.34±6.03	23.74±7.28
Bilirubin direct (mg/dl)	0.31±0.07	0.31±0.12	0.31±0.11	0.29±0.08
Bilirubin total (mg/dl)	0.70±0.11	0.72±0.16	0.69±0.10	0.67±0.11
Serum creatinine (mg/dl)	0.83±0.26	0.82±0.11	0.77±0.25	0.83±0.15
Urea (mg/dl)	24.39±8.04	22.20±4.51	24.28±8.97	21.29±5.23
Uric acid (mg/dl)	3.78±1.39	3.91±0.67	4.01±0.71	4.22±1.32

The data are represented as the Mean±Standard deviation. Data were analyzed by paired "t"-test for each parameter within the group. No significant changes for any of the parameters within the groups (baseline vs. the end of study). RBC: Red blood cells, WBC: White blood cells, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase

cinnamon bark extract is responsible for anti-inflammatory effects through TNF-α gene modulation through NF-κB and mitogen-activated protein kinase [37]. Recently, the anti-inflammatory effects of a polyphenol fraction of cinnamon bark [19] and TAPP [20] in animal models of inflammation through cytokine (IL-2, IL-4, and IFNγ) inhibition have been reported. Therefore, the beneficial effects of IND02 on chemotherapy-induced cachexia in the present study can be attributed to cytokine inhibition action by the marker compound, TAPP from a cinnamon bark extract.

Chemotherapy is generally regarded as an immune suppressant if moderate cytotoxic doses are applied. However, the therapeutic effect of chemotherapy may, in turn, increase immunity due to the partial elimination of suppressive factors from tumor cells. Therefore, the immune function is affected by chemotherapy in the negative [38] and positive [39] manner. Therefore, a combination of chemotherapeutic and immunotherapeutic approaches are suggested in cancer treatment. Furthermore, immunity enhancement acts synergistically when chemotherapy has a positive effect on immunity [40]. The beneficial effect of prevention of weight loss as observed by IND02 supplementation with standard chemotherapy regimen in breast cancer patients during the present study is supporting the notion of a combination approach.

CIA affects various aspects of cancer patient's quality of life [41] and frequently ranked among top distressing/troublesome side effects of chemotherapy especially in female breast cancer patients [42,43] to the extent of refusal to chemotherapy [42,44]. The need to improve the management and measurement of CIA is emphasized in recent literature [45]. In the present study, the impact of TAPP-CZ supplementation on CIA using the modern, quantitative and precise technique (TrichoScan®) to measure hair density, and % hairs in anagen (growth) and telogen (fall) phases of patients as a measure of alopecia were evaluated. The outcome measures of CIA were found to be unchanged in IND02 supplementation group whereas placebo showed alopecia (decrease in hair density, % anagen hairs, and increase in % telogen hairs) and indicates beneficial effects of IND02 supplementation in CIA in breast cancer patients. To the best of our knowledge, our study is first clinical study to use such quantitative measures of CIA as an outcome measure.

Many anticancer drugs attack rapidly dividing cells, including not only malignant cells but also in hair follicle cells, and induce alopecia [46]. The role of apoptosis in CIA is also established [46]. Recently, cinnamon bark extract demonstrated its ability to promote apoptosis pathway and selective killing of tumor cells [47] in addition to suppression of tumor progression [48]. The proanthocyanidins content from grape seeds is known to demonstrate anticancer effects through apoptosis induction in many cancer cells including highly metastatic breast carcinoma cells [49,50]. Therefore, apoptosis-promoting effects of procyanidin content (a marker compound) of IND02 may be responsible for beneficial effects of IND02 supplementation in the prevention of alopecia. However, additional studies may be required to confirm the mechanism of the action.

CONCLUSION

Standardized cinnamon bark extract was found to be beneficial as an adjuvant in preventing breast cancer chemotherapy-induced weight loss and alopecia.

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AUTHORS' CONTRIBUTIONS

The author AM and SM were principal investigator coinvestigator of the study, respectively, and involved in the design, conduct, and analysis and report writing of the study. All authors contributed to the editing and review of the manuscript.

CONFLICTS OF INTEREST

The study was supported by Indus Biotech Private Limited, Pune, India, but has no role in data collection and analysis of the study.

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