

NUTRACEUTICALS AND HERBALS AS ADJUVANTS IN THE CHEMOTHERAPY OF CANCER? A REVIEW

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ABSTRACT

Cancer is the third leading cause of death worldwide. The current cancer treatments such as chemotherapy and radiotherapy resulting in the development of unintended adverse effects that reduce the quality of life and economic burden in oncology patients. Nutraceuticals along with food value have natural bioactive components that have reassuring therapeutic properties in several diseases. Herbs of significant interest have been proven to prevent and treat various types of cancer and also reduce the side effects of chemotherapy and radiotherapy. The efficacy of nutraceuticals and herbs such as chemopreventive and chemotherapy is highlighted. We conclude that further studies are required to countersign the targeted approaches and efficacy of herbs and nutraceuticals in cancer patients as adjuvant therapy.

Keywords: Nutraceuticals, Herbals, Chemotherapy, Cancer, Adjuvant therapy.

INTRODUCTION

The world's third leading cause of death, especially in the middle-aged group inhabiting established realms. Compared to other fatal morbidity diseases, it is superior due to the revolution in routine, food customs, and treatment for significant disorders and diseases [1]. Such high death percentage climaxes the quandary of conventional chemotherapy and radiotherapy practiced in controlling this deadly disorder. These treatment regimens develop an increase in resistance, adding to the unadorned side effects of radiotherapy and chemotherapy; such treatment options additionally develop modern resistance of most cancerous cells toward the treatment [2].

Conversion of a normal cell into an invasive malignant phenotype necessitates tiers of initiation, development, and promotion through changing the unique genetic code. Although a single factor cannot reject the predisposition, people are at higher risk due to other additional factors, such as few high-risk cases, which may have a similar genetic context, nutritional, and dietary adoptions, which may determine the outcome of health [3].

Evolving revisions advocate that few plants originated intermediaries might influence molecular and cellular cascades of primary fundamental lump advance. However, some of these molecules may hurt traditional therapeutic standards. Numeral revisions by researchers steer onto herbals, anti-oxidants, unreal (synthetic) moieties to fix their corresponding characters in the supervision of countless forms of malignancy as adjuvants to chemotherapy and radiotherapy; meanwhile, assuming that they may advance the feat of malignancy treatment, though this view is debatable. Although this area is under exploration for over 40 years, even today there are still many qualms about their ultimate role.

CANCER STAND IN INDIA

"National Cancer Registry Program" is active since 1991 in reporting about the epidemiological subjects who are Indian inhabitants. The predictable cancer prevalence was a tad more in women. Certain types of cancer such as the esophageal, pharyngeal, stomach, lung, and oral cancers are more intricate in man, on the other hand, cervical and breast cancer stand at high incidence in females, followed by oral, gastric, and esophagus.

The intensifying figure of novel malignancy cases denotes the status of cancer exploration across India. The present research image ranges from basic studies required in governing the carcinogens to the research techniques to evaluate different molecular pathways and new drugs for treatment.

MOST NOTED ANTICANCER TREATMENTS WITH ADVERSE EFFECTS

The chemotherapeutic agents are well-recognized agents that are associated with severe adverse effects leading to the decreased quality of life and economic burden. In India, there are no extensive published data regarding the adverse effects of anticancer agents [4]. The cancer patients immensely suffered from adverse effects since chemotherapy regimens are highly complicated, and oncology patients are the inclined population with little tolerance [5]. The most common anticancer drugs causing adverse effects are imatinib, docetaxel, gemcitabine, paclitaxel, oxaliplatin, capecitabine, 5-fluorouracil, vincristine, 6-mercaptopurine, and gefitinib [6] which can cause cardiovascular toxicity, hepatotoxicity, neurotoxicity, nephrotoxicity gastrointestinal toxicity, and dermatological toxicity [7]. Radiation therapy can have specific or other side effects depending on which area of the body is being treated. Radiation to the brain can also have side effects that show up usually from 6 months to several years after treatment ends. Serious delayed effects can include memory loss, stroke-like symptoms, and poor brain function. Radiation to the breast can affect heart or lungs as well causing other side effects such as chemobrain, lymphedema, and some side effects of radiation therapy such as skin problems and fatigue can happen no matter at which part of the body is being treated [8].

NUTRACEUTICALS

Plentiful epidemiological, biological, and clinical revisions direct a stable connection among dietetic factors and lesser peril for developing malignancy. Dietary factors can prevent cancers, and they, on the other hand, can induce cancers [9]. The usual (natural) bioactive foods which deem to have nutritional value and used in numerous ailments based on their beneficial effects are termed to be nutraceuticals. In trend cancer remedy approaches, which include chemotherapy and radiotherapy, induce unintended extra effects negotiating the lifetime of sufferers [10].

A massive sum of revisions has confirmed that dietary routine stands as one of the top vital determining factors of enduring diseases such as diabetes, cardiovascular disorder, neurodegenerative diseases, and different types of malignancy [11]. such connotations between disease and the dietary habit displays that nutrition has a straight effect on healthiness. The increasing desire for longevity, growing urbanization, subsequent environmental changes, and lifestyle has made cancer a steadily growing health problem globally. Therefore, many research papers and surveys show the influence of environmental surroundings and food regimen on the cellular function and health of an individual.

Some nutritional dietary supplements protect the body from most cancers through cleansing, even as others resource in lowering the noxious effects of radiotherapy and chemotherapy. The unfavorable side effects related to chemotherapy aggravate the dietary issues, and the right amount of nutrient supplement must be a critical part of chemotherapy. Nutraceuticals save you from the side effects of both with the aid of intervening or editing the biologic response [12].

The primary belief of nutraceuticals was well-thought-out as organic foods to deliver strength and was advised daily for consumption within the body for well-being until the year 1990. For instance, quite a lot of food industries initiated to augment iodine in the table salt to avoid goiter during the early 19th century, which epitomizes the efforts on the way to making purposeful components [13].

In the new 21st century, the earlier concept of nutraceuticals as effective therapeutic supplements and their enormous budding awareness is shown, leading to the recognized idea of nutraceutical medicine as a new branch of "complementary and alternative medicine". Around two millennia past, hippocrates, the father of western medicine, advised: "Let food be thy medicine and medicine be thy food" accentuating the affiliation among human health and nutrition, in actual it is among the precise vitamins for health and their healing paybacks. Plant food products can be defined as food supplements, functional foods, and nutraceuticals on the basis of the isolation step. Where unadulterated and purely extracted plant molecules are referred to as nutraceuticals, semi-purified plant products, which are not considered regular food, are referred to as functional food [14].

Foods that can be taken recurrently as a diet to uphold the overall health are termed to be food supplements. Plant food features many ingredients such as phytonutrients, polyunsaturated lipids, and secondary metabolites such as flavonoids, glucosinolates, lignans, phytosterols, polyphenols, phytoestrogens, phytates, and terpenes [15].

CURRENT SCENARIO

Since the ancient humankind, the extracts of herbals and natural materials are still under use for various purposes. At present, around 470 nutraceutical and functional food products are available with documented health benefits. In the process of pharmaceutical development, clinical test results from animal tests and studies to ascertain the effects are legally required; for now, there is no documentation strategy for foods used to prevent diseases in the ancient era.

Nutraceuticals used for cancer usually are as follows:

- Soyfoods are a source of isoflavones that possess cancer chemopreventive properties.
- Lycopene concentrates on the testes, skin, prostate, and adrenal protecting against cancer.
- Saponins possess antitumor and antimutagenic activity.
- Curcumin, a polyphenol of turmeric possess anticarcinogenic, antioxidative, and anti-inflammatory properties and so on.
- There have been reports of anti-tumor activity in vegetables and fruits such as beetroots, cucumber fruits, and spinach leaves.

Coming to India's nutraceutical scenario, poor eating habits and sedentary lifestyles have indeed led to an increase in the incidence

of diet and health complications, although there is growing public awareness of the importance and value of proper nutrition and diet for good health and longevity.

It has been reported that many nutraceuticals are incredibly active and also have a profound effect on cell metabolism and sometimes have a little adverse effect. They have always been new and competed against India's underdeveloped pharmaceutical industries. The French oncologist reported that high doses of nutrients were used in conjunction with conventional chemotherapy in patients with lung cancer, which reduced the recurrence of the tumor to half, which also reduced cytotoxic levels [16].

Vitamin C

It reduced the formation of nitrosamine in the intestinal tract, which reduced the incidence of stomach and esophageal cancers significantly. The survival time of people treated for terminal cancers has increased. Epidemiological studies appear to point to ascorbate as a possible chemopreventive for breast cancer. A Latin American study compared nutrient intake and dietary patterns of 748 cervical cancer patients with 1411 controls [17]. The results supported a protective effect of Vitamin C against invasive cervical cancer. An inverse relationship between Vitamin C status and risk for cervical dysplasia was observed. The relationships of dietary and supplemental factors with esophageal cancer were examined in 147 males with esophageal cancer and 264 males with other diagnoses at Roswell Park Memorial Institute. Vitamins C, A, and intakes of fruits and vegetables were associated with decreased risks of esophageal cancer [18].

Fish oil

In hyperthermia and chemotherapy, eicosapentaenoic acid improved tumor inhibition by altering the cancer cell membranes, which increased vulnerability [19].

Selenium

A trace element is known for its antitumor genic effects. It is a powerful antioxidant found in enriched white rice, seafood, and whole wheat. Glutathione peroxidase, an antioxidant enzyme that protects against free radical damage, constitutes selenium. Increased risk of cancer is reported in the world's soil which is deficient in selenium resulting in low selenium intake. People need very little selenium to protect their health [20].

Ginseng

Panax ginseng improves the use of mitomycin (anticancer and antibiotic) to increase the anticancer drug's potency. Nutrition therapy enables medical therapy to make the most selective toxins (anticancer drugs) on the tumor cells [21].

Avemar™

Avemar is a formulated and "Approved dietary food for special medical purposes of cancer patients," it is fermented wheat gram extract that is highly recommended into adjuvant protocols (supported by the clinical study) of high-risk skin cancer patients [22].

HERBALS

Herbal drugs include plants, plant mix, and green complexes. In allopathic and traditional medicine, herbal plants were used across the ecosphere in a variety of ways. Herbal medicines are recognized for their efficacy, affordability, convenience, and safety. Regardless of advancements in synthetic chemistry, approximately 80% of the ecosphere's inhabitants still hang onto medicinal plants for the treatment of disease [23]. The biological activity of any plant is due to its components, i.e., phytochemicals, flavonoids, and phenols. They are plant-based constituents that directly arbitrate their positive health benefits by changing precise molecular objectives directly or indirectly as stabilized conjugates affecting metabolic cascades [24]. Natural anticancer products offer valuable means of increasing cancer treatment to a new level of success with less or no adverse side effects [25]. The

precise use of phytochemicals in this era of medicines may provide us with new dimensions in improving the outcome of chemotherapy. For the past 30 years, natural products, especially those from the plant kingdom, have been a vital source of chemotherapy [26]. "Cancer is hostile to the human body, and hostile environment is cancerous to plants" which means that the plants which can proliferate in multiple but diverse environments may naturally provide us with a vital source of anticancer agents [27].

Herbs are usually classified according to their behavior, herbs alter the immune system and chemoprotective herbs. Herbs that modify the immune system show a significant increase in cancer patient's resistance [28]. Malignant cells subsequently decline the immune system's potency by truncated immunogenicity in people with cancer. Most herbal medicines stimulate immunity and improve it [29] and also protect the bone marrow against chemotherapy's myelosuppressive side effects. Herbal medicines prevent the progression of oncogenic apoptosis. Instance, the apoptosis in cancer cells is bought by curcumin, which blocks the NF-KB signaling pathway through the regulatory phosphorylation of the IKB enzyme [30].

HEALTH BENEFITS OF DIFFERENT HERBS AND HERBALS DURING CANCER

Ellagic acid

Ellagic acid is a polyphenol compound extant in many nuts, seeds, and fruits, such as black raspberries, pomegranates, walnuts, strawberries, raspberries, and almonds. In another study, Baradaran et al. showed that ellagic acid has a chemoprotective effect due to strong antioxidant properties, which lead to reducing OS [31]. Some studies in the past also indicated that ellagic acid showed chemoprotective, anti-apoptotic, and anticarcinogenic properties that make it interesting for further studies in different disorders particularly cancer cell systems [32].

Vinca rosea (periwinkle)

Periwinkle, also called *Catharanthus roseus*, is the foremost antitumor herb. The components of this are vinca alkaloids such as vincristine (leurocristine), vinblastine, and reserpine. To display their anticancer property, it is essential for the alkaloids to bind with tubulin (microtubule protein), resulting in the halt of microtubules and constraint in the construction of spindles during the metaphase hence, halt the division of malignant cells [33]. Vinblastine is used in treating Hodgkin's disease, a malignancy of kidney, and non-Hodgkin's lymphoma. Nevertheless, vincristine is prescribed with a combination of other anticancer agents for the effective treatment of various cancers such as lung, breast, cervix, and liver [34]. As of now,

periwinkle's herbal compounds were legalized by the FDA for treating the neoplasm. In general, vincristine has used the drug during breast cancer [33].

Limitations

It has aftereffects like a loss of the need to eat, bone ache, unhappiness, giddiness, constipation, intestinal pain, and hair loss [35].

Curcuma longa (turmeric)

Curcuma Longa confirms the full gamut of therapeutic effects. It is antitumor, anti-inflammatory, antioxidant, antimutagenic, antifungal, antiviral, antibacterial, and hepatoprotective. Constituted curcumin averts the making of eicosanoid (injurious) like PGE-2, henceforth, hinders the cancer cell's progress [36]. Curcuminoids extracted from turmeric like curcumin (Di-feruloyl-methane) suppressed cancer cells at each step, i.e., initiation, growth, and metastasis by hindering the malignant cell propagation in G₂/S phase and inducing apoptosis. It also hinders angiogenesis, a rate-limiting step in the metastasis and growth of malignancy [37].

Limitations

1 g/day ingestion of turmeric till 9 months exerted substantial effects on the worsening of precancerous lesion of palatal malignancies. Although, after administering turmeric powder of dose up to 10 g/kg, no acute toxic signs are observed [38].

Nigella sativa (Kalonji or black cumin)

Known as Kalonji in South Asia used to promote health and fight diseases. By tradition, it is used in the promotion of overall health conditions besides during a headache, cold, and microbial infections [39] and it also stimulates the immune system by increasing helper T cells (T4) to suppressor T cells (T8) ratio and literature also states that is also refined the natural killer cell activity by decreasing the immune globulin (IgA, IgM, and also IgG) levels [40].

Anticancer activity

N. sativa is immune-modulating, immune-potentiating, and acts like interferon. Ethanolic extract of *N. sativa* was found to inhibit cancer cell progression of endothelial cells *in vitro* [41]. Thymoquinone and di-thymoquinone, active constituents of *N. sativa* were found to have potent anticancer activity at odds with various cancers they have shown their strong cytotoxic actions even on the multidrug resilient humanoid tumors which were 10-fold more resistant to etoposide and doxorubicin [39]. MCF-7 breast cancer cell line *in vitro* was inactivated after the treatment with alcoholic extract or in combination with hydrogen peroxide. *N. sativa* terminates malignant cells by attaching

Table 1: Health benefits of certain nutraceuticals and herbals during cancer treatment

Nutraceuticals/herbals	Health benefits during cancer treatment
Vitamin C	Chemoprotective in the treatment of esophageal and breast cancer
Fish oil	Improved tumor inhibition by altering cancer cell membranes
Selenium	Antitumor genetic effect
Ginseng	Nutrition therapy enables anticancer drug's (like mitomycin) potency
Avemar	Dietary food for cancer patients specifically for high-risk skin cancer patients
Ellagic acid (found in many nuts and fruits such as black raspberry, pomegranates, walnuts, strawberries, and almond)	Chemoprotective, anti-apoptotic, anticarcinogenic
Vinca rosea	Antitumor herb, effective in the treatment of lungs, breast, and cervix cancer
Curcuma longa	Antitumor, anti-inflammatory, antioxidant, antimutagenic, antifungal, antiviral, antibacteria, and hepatoprotective
Nigella sativa	Inhibit cancer cell proliferation, immune-modulating, and immune-potentiating
Cannabis (marijuana)	Herb that relieves from pain, depression, nausea caused during chemotherapeutic treatment of cancer
Allium sativum	Antiproliferative effects and act as anticancer for intestinal cancer chemotherapy
Carica papaya	Anticancer activity
Ganoderma lucidum	Anticancer agent due to its role as an activator of the immune system response
Mangifera indica	Chemoprotective properties and as nutrition therapy enables anticancer drug's potency
Solanum torvum	Act as a natural antibiotic, antimicrobial, antibacterial, and hepatoprotective activity
Crateva magna	Antitumor activity
Azadirachta indica	Enables anticancer drug's potency

to the asialofetuin (lectin) superficially, instigating their clumping and aggregation [42].

Limitations of *N. sativa*

Acutely toxic once administered 25 g/kg orally. However, noxious indications appear once administered 25 g/kg intravenously [43].

Cannabis (marijuana)

Cannabis sativa is a magic herbal that relieves from pain, depression, and nausea caused during chemotherapeutic treatment of cancer. "Δ9-tetrahydrocannabinol (THC)" is the core integral moiety found in cannabis that is accountable for its pharmacological activity in the curative medicinal ground [44-47]. Researchers sign post the upsurge of weight gain and appetite after the ingestion of marijuana (*cannabis*) for AIDS-associated anorexia and cancer patients [45]. "Nabilone (Cesamet)," a synthetic derivative of THC, was active in governing chemotherapy brought vomiting and nausea [46]. Moreover, it is also effective in treating the children undergoing chemotherapy [47].

Limitations of cannabis

Although the side effects of cannabis are not every so often understood in the bodily facets, cognitive, or mental domain, like powerlessness to recognize the time interval and distant objects and memory thought manners [48].

Allium sativum (garlic)

The beneficial use of *A. sativum* for the treatment of cancer was first endorsed by the father of western medicine, i.e., Hippocrates. It has defensive possibilities and partakes in enhancing the immune system [49]. "Allicin, S-allyl cysteine, di-allyl-di-sulfide, and di-allyl-tri-sulfide cristine" possess anticancer activity. It plays an important role in intestinal cancer chemotherapy. Metabolic by-products of organic-sulfur constituents of garlic are responsible for its antiproliferative effects [50].

Carica papaya

C. papaya (fruitless type) extract inhibited the cell growth when tested against the MCF-7 cell line at different concentrations (25, 50, 100, 200, and 400 µg/ml). It exhibited exponential growth in inhibiting the cell growth on increasing the concentrations, the lowest growth inhibition being 9.38% at 25 µg/ml, and the highest growth inhibition was 71.76% at 400 µg/ml. The IC₅₀ value was more than 233.01 µg/ml. This study reveals that *C. papaya* extract possesses anticancer activity [51].

Ganoderma lucidum

It has been a substantial source of natural mycological remedies for many years. Nevertheless, the usage of *Ganoderma* is poorly depicted in the field of cancer immunotherapy. *Ganoderma*'s beta-glucan polysaccharide plays a significant role in immune surveillance and chemoprevention of cancer [52]. The most comprehensively investigated important pathways are NF-κB and MAPK. The broad-spectrum application of *Ganoderma* enables us to use it for the treatment of cancer and immune disorders and as an adjunct to modern cancer therapies due to its regulatory actions of the immune system [53]. Available evidence suggests that the efficacy of *Ganoderma* species as an anticancer agent due to its role as an activator of the immune system responses. Much literature is available about the other natural sources such as microorganisms and marine, which can be used as chemotherapeutic agents directly or indirectly [54].

Mangifera indica (Mango)

Mango pulp extract (MPE) and lupeol were evaluated for chemopreventive properties against 7, 12-dimethylbenz (a) anthracene induced alteration in the liver of Swiss albino mice. MPE was found to be effective in combating cellular injury of mouse liver by modulating cell-growth regulators which were induced through oxidative stress [55]. Prasad *et al.* reported that mangiferin increased the efficacy of doxorubicin in MCF-7 [56].

Solanum torvum Sw. (night berries)

Solanum torvum Sw. is a member of the family Solanaceae, and its fruits are commonly called night berries which are useful for treating liver and spleen enlargement, cough and also used as a hematopoietic, antimicrobial, and analgesic agent. The leaf extract has been reported to have antiviral and antiulcerogenic properties. The fruit coat exhibited significant antibacterial activity against pathogenic bacteria when compared to standard antibiotics and hence acted as a natural antibiotic. Recently, it has been reported that this fruit extract has hepatoprotective activity [57,58]; therefore, apparently this fruit extract can be used as adjuvant therapy for chemotherapy-induced hepatotoxicity.

Crateva magna

C. magna belongs to the family Capparaceae commonly used in the treatment of urinary disorders. Currently, *in vivo* and *in vitro* antitumor activity of leaves *C. magna* has been reported [59]. This study reveals that the ethanolic extract of *C. magna* has antitumor activity [60].

Azadirachta indica (neem)

Studies of extracts from all major parts of neem plant, including leaves, flowers, fruits, and seeds, have shown promising chemopreventive and therapeutic effects in pre-clinical research [61]. The underlying mechanisms of such anticancer effects of neem have begun to unravel with accumulating studies. As a natural resource, neem extract has the advantages of easy availability, low cost, and safety to humans, which collectively make neem-derived compounds valuable candidates for anticancer therapy [62]. Preclinical studies have primarily established neem as a potential preventive and therapeutic agent against various types of cancer [63].

Interestingly, neem has been shown to improve the efficacy of other anticancer drugs besides its anticancer functions as a single agent [64-66]. The combination of neem-derived gedunin and cisplatin further decreases the proliferation of treated ovarian cancer cells by almost 50% compared to the cells treated with only cisplatin [61]. The combination of a sub-lethal dose of ethanolic NLE and cisplatin also provides synergistic effects in decreasing the viability of breast and cervical cancer cells compared to individual compounds alone [67,68]. Further investigation is warranted to determine whether neem could sensitize cancer cells to the cytotoxic effects of other therapeutic regimens and whether combination therapy could offer potential clinical benefits.

ADJUVANT THERAPY – HOW IMPORTANT IS IT?

All the therapies to fight cancer are advanced into the age of specific molecular targets, yet the current therapies are inadequate because of the severe side effects of antitumorigenic agents and cell-signaling complexity. It is evident that a few types of cancers are resistant to conventional chemotherapeutic agents. Desired results with the least number of side effects have been obtained with adjuvant therapies that have also improved the quality of life. Although, it is associated with dose-relationships. Therefore, it is necessary for mechanistic and targeted approaches for improving the quality, efficacy, and minimizing unwanted effects, which is crucial during the chemotherapeutic treatment. Although, shortlisting the appropriate adjuvant will always be the rate-limiting step to achieve effective adjuvant synergism.

Over the past few years, many nutraceuticals and few dietary agents are deemed to imitate the actions of anticancer drugs, which can be used as adjuvants during chemotherapy refer Table 1. Few agents act through regulation of various cell signaling pathways which in turn changes the fate of biological systems. For the fact, many of such agents were proven to be nontoxic and synergistic when used along with the different classes of anticancer drugs. Therefore, it is evident that these agents can be combined with anticancer drugs which could be of profitable use in dealing with cancer and its side effects.

CONCLUSION

The use of herbs and nutraceuticals is growing rapidly every day, but the molecular and mechanistic actions of respective classes from natural sources are still lacking profound clinical data. Therefore, there is a need for practices like adjuvant therapy in addition to conventional chemotherapy. Adjuvant therapy not only renders the effectiveness of conventional chemotherapy but also increases the quality of life of patients, for which awareness should be created among the public regarding the promising use of certain herbs and nutraceuticals as an adjuvant which might be helpful in the critical need of the hour.

AUTHORS' CONTRIBUTIONS

All authors have equally contributed to reviewing the preparation and editing of the manuscript.

CONFLICTS OF INTEREST

We declare that there are no conflicts of interest.

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