Research Article Open Access

A comprehensive review of the preventive action of Natural Nutraceutical Ingredients in reducing Chemotherapy – Induced Side effects

Rajashri Gutte[1]* and Vijaya Deshmukh[2]

[1]Research Scholar, Institute of Management and Research, MGM university, Aurangabad, MH India 431001; [2]Director, Institute of Management and Research, MGM University, Aurangabad, MH India 431001

***Corresponding author:** Rajashri Gutte, Research Scholar, Institute of Management and Research, MGM university, Aurangabad, MH India 431001

Submission Date: January 5th, 2023; **Acceptance Date:** February 19th, 2022; **Publication Date:** February 28th, 2023

Please cite this article as: Gutte R., Deshmukh V. A comprehensive review of the preventive action of Natural Nutraceutical Ingredients in reducing Chemotherapy – Induced Side effects. *Functional Food Science* 2023; 3(2):1-14 DOI: https://www.doi.org/10.31989/ffs.v3i2.1051

ABSTRACT

Cancer is an umbrella term for more than 100 diseases, having the ability to access every part of the body. Chemotherapy drugs used to treat cancer can harm cells in the body including the nervous system and main functioning parts like the heart, lungs, and kidney, according to the American Cancer Society(2020).

This re-evaluation aims to give a detailed synopsis of the evidence supporting the effectiveness of natural nutraceutical ingredients and their role in minimizing chemotherapy-related side effects by reviewing several published studies.

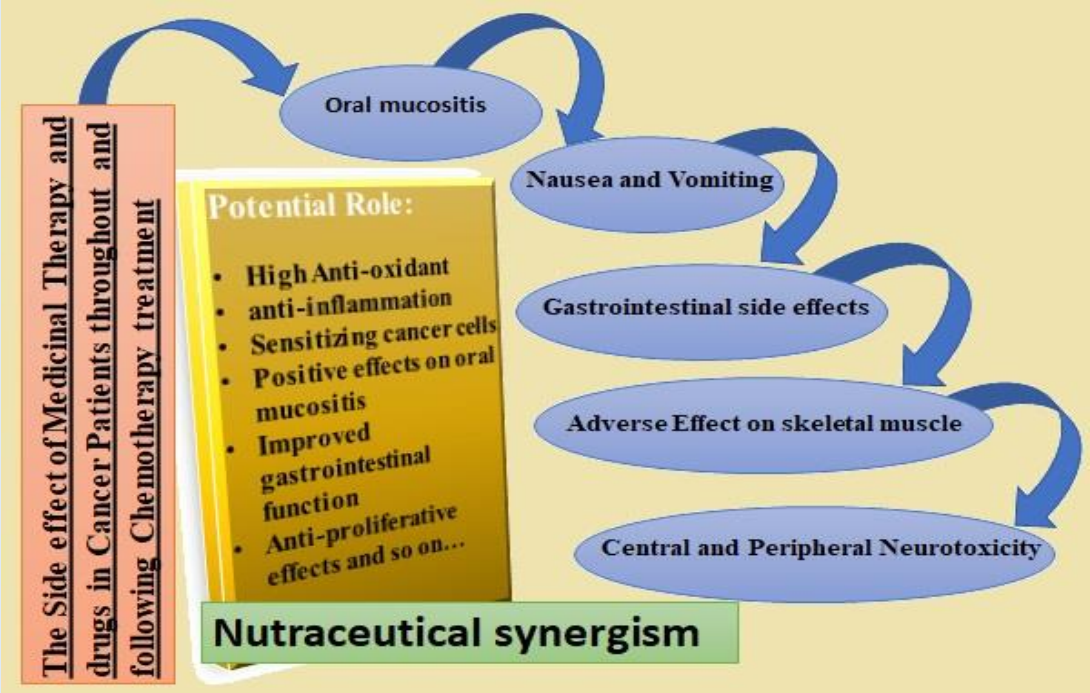
Research Gap gives ideas for searching for an ingredient with greater efficacy and fewer or no side effects.

This study focuses on natural nutraceutical ingredients as opposed to synthetic ingredients because the latter are poorly absorbed by the body and have more negative side effects. This study recommends using natural nutraceutical ingredients as supportive care supplements to treat chemo-related side effects and strengthen patients' immune systems to fight the disease by regenerating their tissues.

The main purpose of the study is to combine conventional medical practices with nutritionally enhanced autonomous human body recovery using natural ingredients in cancer patients.

This review will provide an overview based on the fact that natural ingredients, including bioactive components, enriched fractions, and extracts in both raw and pristine form, are shown as preventive measures for the treatment of cancer.

Keywords: Cancer, Chemotherapy-induced side effects, therapeutic benefits, Natural Nutraceutical ingredients, Supportive care, etc.



INTRODUCTION

Nutraceuticals are dietary supplements consumed for their physiological benefits and boosted immunity against diseases. They are made from dietary ingredients such as minerals, vitamins, and herbal products. The term "nutraceuticals" is derived from the combination of "nutrients" and "pharmaceutical," and its origins can be traced back to Dr. Stephen De Felice, a physician who introduced this area of medicine to mainstream medicine in 1989. Nutraceuticals are foods or components of foods that, in De Felice's words, "offer health or medical advantages, such as illness prevention and/or treatment" [1].

Let food be your medicine, advised Hippocrates, a Greek physician regarded as the father of medicine in the year 440 BC. "Focus on prevention" is the guiding principle. Nutritional supplements, health-beneficial foods, multi-functional foods, etc. are additional terms used in this context. Functional foods are regular foods with added components or ingredients that provide them with additional health benefits beyond their nutritional value. [2]

According to the National Cancer Institute, A bioactive compound is defined as A type of chemical found in small amounts in plants and certain foods (such as fruits, vegetables, nuts, oils, and whole grains). Bioactive compounds have actions in the body that may promote good health. They are being studied in the

prevention of cancer, heart disease, and other diseases. Examples of bioactive compounds include lycopene, resveratrol, lignan, tannins, and indoles.

South Australian Food Innovation Centre says**,** Functional foods and beverages provide extra health benefits to the consumer beyond basic nutrition and functional ingredients are bioactive compounds that are useful in manufacturing functional food products. Altogether, these bioactive compounds and functional ingredients are used in the preparation of nutraceuticals.

The FFC (Functional Food Center) put forward a definition for Functional Foods as “Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms'' [48]

The Functional Food Center proposed a new model multi-step process in categories A, B, or C. Classification A denotes the completion of aftermarket research, epidemiological studies, and certification. B denotes the completion of epidemiological studies and certification of functional food status. Lastly, C, indicates that the product has only been certified as functional for exact regulation of functional foods. [49]

Mizoram, Delhi, and Meghalaya states in India have had the highest cancer Disability Adjusted Life Years (DALYs) and the most vulnerable are people in the 65 to 69 years age group [3].

There are different types of cancer treatments available, which vary according to cancer type and advancement. Some patients may have multiple types of therapies, such as surgery along with chemotherapy and radiation. Chemotherapy treatment involves ingesting drugs that destroy malignant cells. The purpose of this therapy is to stop these cells from proliferating and dividing. It operates on living, rapidly expanding cells. Active cells are those that constantly grow and divide to create new cells of the same type. However, some healthy cells are also active and capable of rapid growth. These cells are also found in your blood, mouth, digestive system, and hair follicles. Chemotherapy damages these healthy cells, leading to side effects [4].

The most frequent adverse reactions of chemotherapy are nausea, hair loss, constipation, anemia, weight loss, issues with conception and reproduction, renal issues, and more. These negative consequences diminish the quality of life for cancer patients and might even cause them to stop receiving treatment [5].

Radiation and chemotherapy may save patient’s lives, but these therapies have side effects ranging from minor (dry mouth) to serious (vomiting). When using medication to treat a condition, a person may seek out complementary and alternative therapies (CAM) to treat their symptoms [8].

From person to person, side effects can range greatly in severity. After cancer treatment, care is crucial. The therapeutic branch of nutraceuticals offers a variety of advantages and can be used successfully to treat a variety of illnesses, including various cancers, having no side effects.

It has been demonstrated that several herbal formulations, including natural medicines made from raw extracts, fractions richer in bioactive components, and pure chemicals obtained from herbs can both prevent and cure cancer. [6]

Ingredients such as Curcumin, Piperine, anolides from Ashwagandha, and Resveratrol can be used as a potential treatment and as nourishing supplements for increasing immunity among severely immuno-compromised individuals who suffer from COVID-19. [7]

A handful of drugs are available in the market to reduce the side effects of chemotherapy but most of them contain synthetic/chemical base ingredients which also come up with their side effects and temporarily fix the problem.

Mostly used chemotherapy drugs/medications:

- An antibiotic and anthracyclines share a similar chemical structure. Cancer cells are killed by anthracyclines by damaging their genetic makeup. Anthracyclines include daunorubicin, Ellence, and Adriamycin.
- Taxanes interfere with the way how cancer cells divide. Taxol, Taxotere, and Abraxane are taxanes.
- Very common chemotherapy administrations include medicines from one or both of these combination groups.[9]

  Steven Douedi; Michael P. Carson (2021), has given side effects of Anthracycline Medications (Doxorubicin) given Side Effects of Anthracyclines
- Allergy symptoms (anaphylaxis), intense cough, darkening of the skin and nails, the voice becoming hoarse, the flush of the face, Fatigue, achy joints, Photosensitivity, Having a hard time urinating, chronic diarrhea, etc. [5]
- Severe cancer symptoms and chemo side effects might prevent a patient from receiving additional treatment by lowering their quality of life, mood, and sentiments.

According to the National Cancer Institute, emotions and cancer have a connection. After being diagnosed with cancer and while taking treatment the patient may feel loneliness, anger, depression, stress, and worry [10].

The majority of side effects go away after treatment but may linger, return, or even worsen over time. For example, many chemotherapy regimens can harm the heart, lungs, liver, kidneys, or reproductive system permanently. Following therapy, people may have trouble with thinking, focusing, and memory long term. Unfortunately, a cancer survivor is likely to develop secondary, or metastatic, cancer in later life.

Natural Ingredients with high quality and purity provide superior availability at the site of action, hence ensuring a speedy recovery. Consequently, this study focuses on complementary supplements of natural origin that can be taken in addition to medications. The ingredients in these supplements have all undergone extensive clinical testing.

The effects of natural ingredients last for a long time without negative side effects. So, in our traditional Ayurveda, if one wants to fully recover, their treatment should recognize the underlying causes and address those issues alone to ensure that metastasis doesn't occur.

New Approaches to the Cancer Therapy; Platinum-based chemotherapy: Pt-based anticancer medications have advanced cancer therapy in recent years thanks to developments of nanotechnology and chemical synthesis. Platinum-based nano-drugs, such as platinum nanoclusters, offer new anticancer mech-anisms. This has shown significant potential in tumor-targeted treatment and have demonstrated encouraging clinical outcomes.

Cisplatin, carboplatin, and oxaliplatin are three commonly used platinum-based medications for the chemotherapeutic treatment of cancer. Platinum medication's adverse effects, such as low selectivity, significant systemic toxicity, and drug resistance, severely restrict their clinical use [11].

Immunotherapy: More cancer patients are benefiting from immunotherapy treatments in recent years because they increase the immune system's ability to detect and destroy cancer. Researchers have learned more about the negative effects of immunotherapy as it has become a more popular cancer treatment, including certain issues that weren't previously connected to other cancer therapies. On the side effects of immunotherapy, more study is required. [42]

Starvation based chemotherapy: Raffaghello, L. et al. (2008) claim that despite research into medications that precisely target cancer cells, there must be a completely innovative strategy that selectively kills cancerous, unhealthy cells. According to research, starvation has the potential to save human cells leaving malignant cells to die [45]. Preliminary results given by the author showed that starvation-dependent differential chemotherapy is not only practical and safe for cancer patients, but also effective in reducing the adverse effects of chemotherapy that are usually observed [44].

Modern herbal Oncology settings: The ancient art of healing in Middle Eastern countries, traditional Chinese herbal medicine, and Indian ayurveda have their own significance in cancer treatment.

In Arabic regions, one herbal preparation called 'Hubel Haub' i.e., Fresh carob serotinous liquid extract is used on chemo-taking patients who are suffering from mouth ulcers. Also, this includes the use of sage, *Salvia Officinalis* leaves, and sesame tahini which is then sprayed with the carob extract. preparation can be directly applied to the sore areas of the mouth up to five times a day [46].

Different herbs containing functional benefits used for the treatment of cancer include sage, oregano, moringa peregrine, myrrh gum, propolis, achillea fragrantissima, etc.

With the use of sage polyphenolic compounds, mouth sprays relieve chemo-related side effects according to the National Cancer Institute.

In 2016, a group of researchers from the Middle East Cancer Consortium surveyed 340 oncology care practitioners from 16 Middle Eastern countries. The group identified 44 herbal and three non-herbal dietary supplements which were being used by oncology patients under their care. They also found that for 29 of these supplements, two-thirds were important safety-related.

These included 15 herbal remedies with the potential for negative herb-drug interactions, which can change the pharmacodynamics of chemotherapy agents and other anticancer drugs. The group also identified 18 herbs with directly toxic effects, and seven herbs with the potential to increase the cytotoxic response of cancer cells to conventional chemotherapy. Changing the pharmacodynamics of the anti-cancer activity of conventional oncology drugs can have significant implications on treatment outcomes [47].

The Side effect of Medicinal Therapy and drugs in Cancer Patients throughout and following Chemotherapy treatment: ALTUN et.al (2018): A convenience sample of patients tracked at the oncology outpatient clinic was used for the study. Participants were cancer patients receiving chemotherapy for the first time diagnosed with any type of cancer at various stages. He examined the adverse effects of cancer therapies, such as nausea and vomiting (79.3 %) as well as exhaustion (74.7%). these were most frequently reported during the first cycle of chemotherapy. Additionally, other side effects worth noting included reduced appetite (65.5%), altered tastes (60.9%), hair loss (60.0%), dry mouth (51.7%), and constipation (51.7%). [12].

Muhammad Shahbaz Aslam et. al. (2014) examined the adverse effects of chemotherapy on cancer patients as well as the patients' perceptions of differential treatment based on fasting. This study was carried out to examine the typical side effects of chemotherapy and the contribution of hunger to their amelioration in Pakistan. A total of 100 individuals with multiple carcinomas participated in the trial. Interviewers filled out a detailed questionnaire regarding the starving inquiry, chemotherapy side effects, and their general information based on information provided by patients. Breast cancer affects 48% of patients, whereas uterine cancer affects 11%. 30%, 28%, 9%, and 9% of these patients voluntarily agreed to go without food for 12, 24, 36, and 48 hours,

respectively. According to a survey on the side effects of chemotherapy, 43% of patients experienced headaches, 90% of them reported feeling tired or tired all the time, 95% reported feeling weak, 76% reported hair loss, 77% reported nausea, 77% reported vomiting, 31% reported diarrhea, 40% reported abdominal cramps, 47% reported mouth sores, 74% reported dry mouth, and 14% reported feeling numb. Breast cancer is the most prevalent kind of cancer in Pakistan. Only 18% of the patients consented to go without food for longer than a day. The adverse effects of chemotherapy can vary significantly and are not related to the kind of cancer being treated [44].

The US Food and Drug Administration has authorized 132 different cancer chemotherapy medicines, 56 of which have been linked to oxidative stress [43].

The most distressing side effects for cancer treatment patients include nausea and vomiting. Cancer-related nausea and vomiting can be prevented and treated using antihistamines, phenothiazines, anticholinergics, and butyrophenones. Consequently, these medications have undesirable side effects. Doctors frequently give dimenhydrinate, midazolam, and metoclopramide to treat and prevent cancer-induced nausea and vomiting (CINV) in cancer patients receiving chemotherapy [13].

According to different research, metoclopramide increases the activity threshold of CTZ chemical receptors, which lowers cancer-induced nausea and vomiting (CINV) in cancer patients receiving chemotherapy [14].

There are negative side effects associated with the widespread use of industrial anti-vomiting medications to treat CINV, such as extrapyramidal side effects, blood pressure decreases, and headaches.

Following cisplatin treatment, Yamamoto et al. (2017) observed the alterations in the facial expression of rats and measured the impact of anti-emetic medications in preventing these changes. Furthermore, the scientists concluded that cisplatin treatment lowered the ratio between longitudinal and axial eye dimensions, or the eye-opening index, with this effect being blocked by standard antiemetics [15].

Other common and distressing adverse effects of cancer chemotherapy are gastrointestinal side effects. Chemotherapy-induced constipation (CIC) and diarrhea (CID), both of which are prevalent and may necessitate dosage reduction, postponement, or even termination of treatment, were detailed by McQuade et al. (2016) in addition to current and novel therapies.

The authors further highlight that CIC is far more severe and prevalent than generally understood constipation. One common cause of CIC is the overuse of anti-diarrheal medications for CID; however, it is unclear how CIC is caused by other factors [16].

Herradón et al. (2017) used 5 weekly intraperitoneal injections of cisplatin in male Wistar rats to investigate the potential causes of cardiovascular changes brought on by various chronic cisplatin treatments. Their model demonstrated signs of arterial endothelial alterations at lower dosages, while heart function was affected at the highest levels of 2 and 3 mg/kg/week [17].

Other adverse effects of cancer chemotherapy impact skeletal muscle. A study by Sorensen et al. (2017) first describes the immediate effects of repeated oxaliplatin doses on skeletal muscle, including elements of skeletal muscle mitochondrial activity and the possible impact of anticancer drugs on skeletal muscle.

They are the first to draw attention to BGP-15 as a possible supplementary treatment for skeletal muscle and mitochondrial damage as a result of chemotherapy. Additionally, they demonstrated the use of male BALB/c mice given six intraperitoneal injections over a 12-day period. Here, the small molecule BGP-15 defends against oxaliplatin-induced muscle atrophy, muscle collagen deposition, and alterations in mitochondrial function [18].

Anticancer medication-induced central and peripheral neurotoxicity has long-lasting negative consequences on cancer survivors' quality of life. Chemotherapy-induced peripheral neuropathy is a common side effect of anticancer medications, such as proteasome and angiogenesis inhibitors, vinca alkaloids, taxanes, and platinum-based medicines (CIPN). High morbidity from long-term CIPN is linked to conditions including sleeplessness, ataxia, and depression.

According to McQuade et al. (2016), there is evidence that chemotherapy-induced enteric neuropathy may be a factor in cancer survivors developing chronic gastrointestinal dysfunction [16].

Researchers then search for compounds with greater efficacy and fewer negative effects.

The support of Natural Nutraceutical Ingredients in Chemotherapy-induced side effects in cancer Patients: Natural dietary supplements with natural ingredients may aid in the recovery from serious illness and may lessen the side effects of chemotherapy by enhancing general health.

The plant Curcuma longa, also known as turmeric, is the source of the polyphenol known as curcumin. According to reports, curcumin has anti-inflammatory, anti-carcinogenic, and antioxidant properties [19].

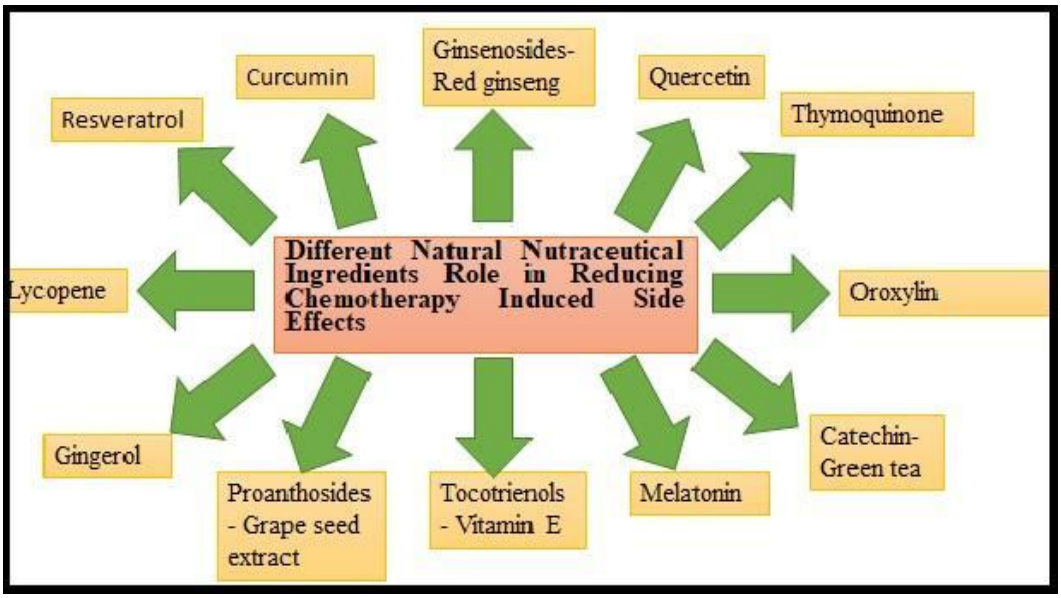


Figure 1. Different natural nutraceutical ingredient's role in reducing chemotherapy-induced side effects.

Numerous studies have demonstrated the benefits of complementary and alternative medicine when used in conjunction with chemotherapy or radiation therapy. For patients with prostate cancer, complementary therapy can be a dependable and practical responsive measure [20].

Citrus fruit flavonoids function as potent antioxidants and help prevent cancer. Isoflavones, polyphenolic phytochemicals that include curcumin from curry, epigallocatechin gallate from tea, and soya isoflavones with cancer-preventing qualities, are only found in soy foods [21].

Tannins are known anti-carcinogen that are used in alternative medicine to prevent cancer. They may be found in foods including tea, grapes, lentils, blackberries, blueberries, and cranberries. Ellagic acid is an anti-cancer compound found in red raspberry seeds, strawberries, cranberries, pecans, walnuts, and pecan products [22].

Chemotherapy-induced oral mucositis, a frequent side effect in chemotherapy patients, is partially brought about by inflammation and oxidative stress. The author claims that herbal remedies and other natural remedies can be used to treat this problem [23].

Chamomile, scientifically known as *Matricaria recutita*, is a medicinal value plant that has a wide range of properties like antioxidant, antimicrobial, and anti-inflammatory actions [24].

Curcumin has anticancer effects as shown by Hatcher et.al., 2008, who have demonstrated preclinical studies in phase 1 and phase 2 clinical trials [25].

Curcumin is an exceptional potential ingredient and quite helpful in manufacturing supplements including tablets, gummies, capsules, shakes, beverages, and functional foods.

In terms of fast wound healing, adult patients with oral mucositis brought on by chemotherapy and radiation had superior outcomes when using curcumin mouthwash [26].

Curcumin has immunomodulatory and anti-inflammatory functions which help in fighting various chronic conditions and cancer-like diseases [50].

Mahmoodnia et. al. (2017), double-blind, randomized clinical trials demonstrate that the ingredient lycopene has an antioxidative effect and can be used as adjuvant therapy. The side effect of nephrotoxicity in cancer patients can be alleviated by mouth administration between 24- and 72 hours following cisplatin administration [27].

Tocotrienols are Vitamin E analogs that are used to treat cancer by making cancer cells more susceptible to chemotherapy drugs [28].

Ranasinghe, et. al. (2022) Tocotrienol can be combined with standard chemotherapeutics or alone can achieve a viable strategy in cancer therapy by regulating cell cycle checkpoints [55].

Quercetin is a natural flavonoid, a highly potent antioxidant, and a potent anti-inflammatory action. The author administered 250mg of quercetin capsule twice daily for 4 weeks, which has shown positive effects on oral mucositis in patients undergoing high doses of chemotherapy for blood malignancy [29]

Table 1: Natural products in lowering CTX (Chemotherapy) and radiotherapy-induced intricacies.

No.	Name of Ingredient	Effect or mechanism of action	References
1	Curcumin	Rapid wound healing in oral mucositis	26
2	Ginsenosides from Red ginseng	Apoptosis or proptosis induction, and angiogenesis inhibition	35
3	Lycopene	High Antioxidant, effect on cisplatin-induced nephropathy	27
4	Gingerol	Antioxidant and anti-inflammation	40
5	Proanthosides- Grape seed extract	Oxidative stress, abatement of renal damage, the tumor suppressor protein p53 change, renal/kidney cells apoptosis.	41
6	Tocotrienols- Vit. E	Sensitizing cancer cells	28
7	Quercetin	Positive effects on oral mucositis	29
8	Thymoquinone	Improved gastrointestinal function	32
9	Oroxylin	Promotes hepatoma differentiation and halts cancer growth by activating PKM1/HNF4 alpha.	34
10	Melatonin	Protects against nephrotoxicity	36

The herb *bacopa monnieri* has a bacoside-rich content which reduces cisplatin-caused dry heave and vomiting [30].

According to research done on 576 individuals, ginger supplements can dramatically lessen acute chemotherapy-induced nausea in adult patients [31].

In rat models of cisplatin-induced intestinal damage following oral treatment, thymoquinone, a significant active component beneficial to gastrointestinal function, improved the redox and metabolic state of intestinal mucosal tissue [32].

Green tea contains catechin, which, when taken in

tablet form, has been demonstrated to lower the frequency and severity of radiotherapy-induced diarrhea when compared to a placebo group [33].

Oroxylin is a naturally occurring flavonoid and a patient-derived xenograft model for hepatoma. It has anticancer effects on human primary hepatocellular carcinoma cells. The author demonstrates that oroxylin A triggers PKM1/HNF4 alpha to cause hepatoma differentiation and stop the spread of malignancy [34].

Ginsenosides from red ginseng have anticancer mechanisms which show cell cycle arrest in the first Phase, then apoptosis or pyroptosis induction and angiogenesis inhibition [35].

Melatonin has anti-inflammatory characteristics. giving mice genistein and melatonin supplements before exposure to radiation protects them from nephrontoxicity [36].

The majority of studies have indicated that nutraceuticals help prevent cancer, although more thorough research is still needed.

G. Dranitsaris and others (2017) discussed up to 40% of cancer patients have the crippling side effect of chemotherapy-induced nausea and vomiting (CINV). 42.2% of patients had 4197 chemotherapy rounds and developed grade 2 CINV. Patients aged less than 60 years, the first two chemotherapy cycles, anticipatory nausea and vomiting, a history of morning sickness, and the number of hours of sleep the night before treatment were all found as risk factors [37].

According to Kristina Andrijauskaite et al. (2020), dietary supplements and natural substances are claimed to offer a variety of anticancer qualities and are frequently regarded as appealing innovative therapeutic approaches for combating chronic inflammation. Many of the natural remedies that have been described have also demonstrated neuro-cognitive benefits that, when combined with anti-inflammatory qualities, may have a double effect on lowering inflammation and PTSD-like symptoms in breast cancer patients. An astonishing list of foods with anti-inflammatory action has been supplied by research on the preventive effects of a fruit- and vegetable-rich diet [38].

By using several in vitro antioxidants, such as DPPH, ABTS, DMPD, O2, and H2O2 scavenging activities, total antioxidant activity, reducing capabilities, and Fe2+ chelating activities, Gulcin et. al. (2010) examined the antioxidant activity of resveratrol.

Resveratrol was discovered to have potent in vitro antioxidant and radical scavenging properties. Because of its antioxidant characteristics, it can be employed in the pharmaceutical and culinary industries. Resveratrol can be used as an alternative to BHA, BHT, and other antioxidant compounds for their safer usage to reduce or prevent lipid oxidation in pharmaceutical products. It does this by delaying the formation of toxic oxidation products, maintaining nutritive value, and extending the shelf life of food products and pharmaceuticals [39].

Sorayya Ghasemi et. al. (2021), Cancer stem cells (CSCs) are responsible for Re-Occurrence metastasis and have low therapeutic benefits for cancer. Phenolic compounds are a vast group of substances with anti-carcinogenic functions, and anti-inflammatory, and antioxidative activities [51]. They may help in preventing the side effects of chemotherapy as they are rich in antioxidative and anti-inflammatory properties.

Some natural compounds such as flavonoids, alkaloids, and saponins, can inhibit the de novo synthesis of lipids in GIC (gastrointestinal cancer therapy), reduce the level of lipid accumulation, and subsequently, inhibit the occurrence and development of GIC by regulating Sterol regulatory element-binding protein 1 (SREBP-1), adenosine monophosphate-activated protein kinase (AMPK), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), phosphatidylinositol-3-kinase/Akt and the mammalian target of rapamycin PI3K/Akt/mTOR, amongst other targets and pathways [52].

The natural compound resveratrol emerged as a very promising one and was widely recognized as a

chemo-preventive agent and potentiates the antitumor activity of conventional chemotherapeutics in several tumors, including prostate cancer [53]. Resveratrol is beneficial in colorectal cancer (CRC) treatment through the vital molecules and cancer signaling pathways, including SIRT1, P53, P21, AMPK, ROS, BMP7, COX-2, NO, caspases, Wnt, TNFs, NF-κB, EMT, and pentose phosphate pathway [54].

Limitations of Nutraceuticals in chemotherapy: Clinical research on natural nutraceutical ingredients and cancer treatment is less common. Formulations and comb-inations of natural ingredients require further study. Studies on natural ingredients and clinical trials in cancer patients involve complex molecular mechanisms. Hence need for more authentic data is necessary.

Some Nutraceutical ingredients can interfere with drug therapy so proper knowledge and re-search are required before giving it to any stage of cancer treatment and consistent positive results of herb-drug interactions.

Discussion and future outlook: In this era, people diagnosed with cancer have a long-term survival than past before because of novel cancer therapies and adjuvant therapy which also includes comp-lementary and supportive treatments like Nutraceutical supplements.

This report suggests priorities to the future goals and efforts to be taken for improvement in evidence-based-future recommendations for both natural nutritional ingredients and dietary supple-ments and adopt more qualitative strategies targeting chemotherapy treatment effects towards the health of cancer patients.

There is a current requirement for the proper framework by government bodies and other private or government organizations to significantly improve the health and quality of life of cancer patients and survivors.

Preventive action of Natural nutraceutical ingredients will benefit from the novel and precise measures for dietary supplements and their impact on the patients if the proper assessment of the database which will include the large range of ingredients and bioactive components research and presentation for future access.

Each and every bioactive ingredient has its own specialty, but precise clinical studies are required for addressing natural therapies more.

The search for relevant resources on the potential benefits of herbal medicine in cancer care should be directed at the more realistic goals which are related to patient quality-of-life-related concerns, and a secondary focus on curing the disease or strengthening the immune system.

This search needs to be conducted within the context of the doctor-patient interaction in which an environment of effective communication is esta-blished. The recommendations need to also recognize that any conclusions reached from the findings of herbal medicine research, whether clinical or pre-clinical have their limitations and need to be understood within the context of the integrity of cancer care.

In future directions, molecular-level studies of each Phyto ingredient are required for a better understanding of the human body before and after chemotherapy. A toxicity study is required before any health claims on priority and the future onset of nutraceuticals especially in cancer care is booming as nutraceutical industries are directing their research with regards to the health of cancer patients on focusing on improving their quality of life.

CONCLUSION

In this study, we combined conventional medical practices with nutritionally enhanced autonomous human body recovery using natural ingredients in cancer patients.

According to modern science, a fully functional

body has the majority of its curative power concentrated in its autonomous nervous system and blood circulation system, which also demonstrate natural ingredients with higher bioavailability that can aid in the healing process, would optimize the recovery without causing any collateral damage and would help reduce chemotherapy-induced side effects. Numerous studies have shown that natural substances might lessen the adverse effects of chemotherapy and radiation, including oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, nausea and vomiting, skeletal muscle issues, etc. Instead of using medicines, patients might utilize these components as dietary supplements.

Nutraceutical ingredients like Curcumin, Res-veratrol, Ginsenosides from Red Ginseng, Lycopene, Proanthosides- Grape seed extract, Thymoquinone, Oroxylin, Melatonin, Gingerol, etc. may be able to reduce the side effects of chemotherapy, according to several published studies.

However, efficacy and clinical trials have not yet reached their conclusions, and it is still unclear how these ingredients will be used in products that aim to reduce the side effects of chemotherapy.

Therefore, combining natural bioactive sub-stances with conventional chemotherapeutic medications might increase anticancer activity and minimize chemotherapy adverse effects.

Abbreviations: BC- Before Christ, FFC - Functional Food Center, DALYs - Disability Adjusted Life Years, COVID-19 - Coronavirus disease, CAM – Complementary and alternative therapies, Pt – Platinum, US – United States, CINV - Cancer-induced nausea and vomiting, CTZ - Chemoreceptor trigger zone, CIC – Chemotherapy-induced constipation, CID – Chemotherapy-induced diarrhea, BALB/c – Albino, CIPN - Chemotherapy-induced peripheral neuro-pathy, CTX – Chemotherapy, PKM1 - Pyruvate kinase muscle isozyme 1, HNF4 alpha - Hepatocyte nuclear factor-4 alpha, PTSD - Post-traumatic stress disorder, DPPH - 2,2-diphenyl-1-picrylhydrazyl, ABTS - 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid, DMPD – Dimethyl -4- phynalen-ediamine, O2 – Oxygen, H2O2 - Hydrogen peroxide, Fe2+ - Iron, BHA – Butylated hydroxy anisole , BHT – butylated hydroxytoluene, CSCs - Cancer stem cells, GIC - Gastrointestinal cancer therapy, SREBP-1- Sterol regulatory element-binding protein 1, AMPK- adenosine monophosphate-activated protein kinase, HMGCR- 3-hydroxy-3-meth-ylglutaryl-coenzyme A reductase,PI3K/Akt–phosph-atidylinositol-3 kinase/Akt, mTOR- mammalian target of rapamycin, CRC – Colorectal Cancer, SIRT1 - sirtuin (silent mating type information regulation 2 homolog, P53, P21- Tumor Proteins, AMPK - activated protein kinase, ROS - Reactive oxygen species, BMP7 – Bone Morphogenic Protein 7, COX-2 - Cyclooxygenase-2, Wnt - Wingless-related integration site, TNFs - Tumor necrosis factor, NF-κB - Nuclear factor-κB, EMT - Epithelial–Mesenchymal Transition

Data Availability: The data that support the findings of this study are openly available with DOI in references.

Conflicts of Interest: The author(s) declare(s) that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Trottier G, Bostrom PJ, Lawrentschuk N, Fleshner NE. Nutraceuticals and prostate cancer prevention: a current review. *Nat Rev Urol*. (2010);7(1):21-30. DOI: https://doi.org/10.1038/nrurol.2009.234.
2. Kalra EK. Nutraceutical--definition and introduction. *AAPS Pharm Sci*. (2003);5(3): E25. DOI: https://doi.org/10.1208/ps050325.
3. India's Cancer burden to rise to 29.8 million in 2025: ICMR Report (https://www.livemint.com/science/health/indias-cancer-burden-to-rise-to-29-8-million-in-2025-icmr-report-11652382169284.html) Updated 13 May 2022
4. Chemoprevention (https://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/chemoprevention) Retrieved on May 2019
5. Shapiro C. L: Highlights of Recent Findings on Quality-of-Life

Management for Patients with Cancer and Their Survivors, *JAMA oncology* (2016), *2*(11), 1401–1402. DOI: https://doi.org/10.1001/jamaoncol.2016.3620.

6. Sanders K., Moran Z., Shi Z., Paul R., Greenlee H.: Natural products for cancer prevention: clinical update (2016). *Semin. Oncol. Nurs.* 32, 215–240. DOI: https://doi.org/10.1016/j.soncn.2016.06.001.
7. Rajashri K. Mundhe, and Dr. Vijaya Deshmukh: role of natural nutraceutical ingredients in holistic recovery of affected human organs due to covid-19 infection and its treatment, *international engineering journal for research & development* (2022), *7*(MGM IOM & amp; R), 13. DOI: http://dx.doi.org/10.17605/OSF.IO/AVY3W.
8. Natural help for treatment side effects (https://www.webmd.com/cancer/cancer-natural-remedies-side-effects) Medically Reviewed by Melinda Ratini, MS, DO on February 10, 2023
9. Steven Douedi and Michael P.Carson: Side effects of Anthracycline Medications (Doxorubicin) (2021), https://www.ncbi.nlm.nih.gov/books/NBK551633/
10. Emotions and Cancer (https://www.cancer.gov/about-cancer/coping/feelings) Updated on Nov 23, 2021.
11. Zhang, C., Xu, C., Gao, X., and Yao, Q: Platinum-based drugs for cancer therapy and anti-tumor strategies (2022), *Theranostics*, *12*(5), 2115–2132. DOI: https://doi.org/10.7150/thno.69424.
12. Altun İ, Sonkaya A: The Most Common Side Effects Experienced by Patients Were Receiving First Cycle of Chemotherapy. *Iran J Public Health*. (2018);47(8):1218-1219. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc6123577/
13. F. Ekangaki and R. Chung: "Gastrointestinal pharmacology," in *Clinical Pharmacology for Anaesthetists*, J. G. Bovill and M. B. Howie, Eds., 1st edition, (2005), pp. 16–98, W.B. Saunders Company, London, UK.
14. V. Rosenthal, B. Radtke, M. Jordan, and S. Choararatana: Effect of metoclopramide on nausea and vomiting in cancer patients under chemotherapy, *European Journal of Cancer Care* (2010), vol. 42, no. 6, pp. 32–54.
15. Yamamoto, K., Tatsutani, S., and Ishida, T.: Detection of Nausea-Like Response in Rats by Monitoring Facial Expression. *Frontiers in pharmacology*, (2017), *7*, 534. DOI: https://doi.org/10.3389/fphar.2016.00534.
16. McQuade, R. M., Stojanovska, V., Abalo, R., Bornstein, J. C., and Nurgali, K.: Chemotherapy-Induced Constipation and Diarrhea: Pathophysiology, Current and Emerging Treatments (2016), *Frontiers in pharmacology*, *7*, 414. DOI: https://doi.org/10.3389/fphar.2016.00414.
17. Herradón, E., González, C., Uranga, J. A., Abalo, R., Martín, M. I., and López-Miranda, V. : Characterization of Cardiovascular Alterations Induced by Different Chronic Cisplatin Treatments (2017), *Frontiers in pharmacology*, *8*, 196. DOI: https://doi.org/10.3389/fphar.2017.00196.
18. Sorensen, J. C., Petersen, A. C., Timpani, C. A., Campelj, D. G., Cook, J., Trewin, A. J., Stojanovska, V., Stewart, M., Hayes, A., and Rybalka, E.: BGP-15 Protects against Oxaliplatin-Induced Skeletal Myopathy and Mitochondrial Reactive Oxygen Species Production in Mice, *Frontiers in pharmacology* (2017), *8*, 137. DOI: https://doi.org/10.3389/fphar.2017.00137.
19. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M.: New concepts in nutraceuticals as an alternative for pharmaceuticals. *Int J Prev Med*. (2014);5(12):1487-1499. DOI: https://pubmed.ncbi.nlm.nih.gov/25709784/.
20. Brouns F.: Soya isoflavones: A new and promising ingredient for the health foods sector. *Food Res Int.* (2002); 35:187–193. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4336979/
21. Thomasset SC, Berry DP, Garcea G, Marczylo T, Steward WP, Gescher A J.: Dietary polyphenolic phytochemicals – Promising cancer chemopreventive agents in humans? Are view of their clinical properties. *Int J Cancer.*2007; 120:451–8. DOI: https://doi.org/10.1002/ijc.22419.
22. Li H, Wang Z, Liu Y.: Review in the studies on tannins activity of cancer prevention and anticancer. *Zhong Yao Cai.* (2003); 26:444–8
23. Panahi Y., Saadat A., Shadboorestan A., Ahmadi A.: An updated review of natural products intended to prevent or treat oral mucositis in patients undergoing radio-chemotherapy. *Curr. Pharm. Biotechnol.* (2016), 17, 949–961. DOI: https://doi.org/10.2174/1389201017666160808094008.
24. Gomes V. T. S., Nonato Silva Gomes R., Gomes M. S., Joaquim W. M., Lago E. C., Nicolau R. A.: Effects of *Matricaria recutita* (L.) in the treatment of oral mucositis. *Sci. World J.* (2018):4392184. DOI: https://doi.org/10.1155/2018/4392184.
25. Hatcher H., Planalp R., Cho J., Torti F. M., Torti S. V: Curcumin: from ancient medicine to current clinical trials. *Cell. Mol. Life Sci.* (2008), 65, 1631–1652. DOI: https://doi.org/10.1007/s00018-008-7452-4.
26. Patil K, Guledgud MV, Kulkarni PK, Keshari D, Tayal S. Use of Curcumin Mouthrinse in Radio-Chemotherapy Induced Oral Mucositis Patients: A Pilot Study. *J Clin Diagn Res*. 2015;9(8): ZC59-ZC62. DOI: https://doi.org/10.7860/jcdr/2015/13034.6345.

27. Mahmoodnia L., Mohammadi K., Masumi R.: Ameliorative effect of lycopene effect on cisplatin-induced nephropathy in patients. *J. Nephropathol.* (2017), 6, 144–149. DOI: https://doi.org/10.15171/jnp.2017.25.
28. Sailo B. L., Banik K., Padmavathi G., Javadi M., Bordoloi D., Kunnumakkara A. B.: Tocotrienols: the promising analogues of vitamin E for cancer therapeutics. *Pharmacol. Res.* (2018), 130, 259–272.
29. Kooshyar M. M., Mozafari P. M., Amirchaghmaghi M., Pakfetrat A., Karoos P., Mohasel M. R., et al.: A randomized placebo-controlled double-blind clinical trial of quercetin in the prevention and treatment of chemotherapy-induced oral mucositis. *J Clin Diagn Res*. (2017) ;11(3): ZC46-ZC50. DOI: https://doi.org/10.7860%2FJCDR%2F2017%2F23975.9571.
30. Ullah I., Subhan F., Lu Z., Chan S. W., Rudd J. A.: The action of *Bacopa monnieri* to antagonize cisplatin-induced emesis in *Suncus murinus* (house musk shrew). *J. Pharmacol. Sci.* (2017), 133, 232–239. DOI: https://doi.org/10.1016/j.jphs.2017.03.001.
31. Ryan J. L., Heckler C. E., Roscoe J. A., Dakhil S. R., Kirshner J., Flynn P. J., et al.: Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. *Support. Care Cancer* 20 (2012), 1479–1489. DOI: https://doi.org/10.1007/s00520-011-1236-3.
32. Shahid F., Farooqui Z., Abidi S., Parwez I., Khan F.: Oral administration of thymoquinone mitigates the effect of cisplatin on brush border membrane enzymes, energy metabolism, and antioxidant system in rat intestines. *Biomed. Pharmacother.* (2017a), 94, 1111–1120. DOI: https://doi.org/10.1016/j.biopha.2017.08.044.
33. Emami H., Nikoobin F., Roayaei M., Ziya H. R.: Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of green tea in preventing acute gastrointestinal complications due to radiotherapy. *J. Res. Med. Sci.* (2014), 19, 445–450.
34. Wei L., Dai Y., Zhou Y., He Z., Yao J., Zhao L., et al.: Oroxylin A activates PKM1/HNF4 alpha to induce hepatoma differentiation and block cancer progression. *Cell Death Dis.* (2017), 8: e2944.
35. Wang C. Z., Anderson S., Du W., He T. C., Yuan C. S.: Red ginseng and cancer treatment. *Chin. J. Nat. Med.* (2016), 14, 7–16. DOI: https://doi.org/10.3724/sp.j.1009.2016.00007.
36. Canyilmaz E., Uslu G. H., Bahat Z., Kandaz M., Mungan S., Haciislamoglu E., et al.: Comparison of the effects of melatonin and genistein on radiation-induced nephrotoxicity: results of an experimental study. *Biomed. Rep.* (2016), 4, 45–50. DOI: https://doi.org/10.3892/br.2015.547.
37. Dranitsaris, G., Molassiotis, A., Clemons, M., Roeland, E., Schwartzberg, L., Dielenseger, P., Jordan, K., Young, A., and Aapro, M.: The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting, Ann.Oncol. (2017), 28(6) 1260–1267. DOI: https://doi.org/10.1093/annonc/mdx100.
38. Andrijauskaite K, Wargovich MJ. Role of natural products in breast cancer related symptomology: Targeting chronic inflammation. *Semin Cancer Biol*. 2022; 80:370-378. DOI: https://doi.org/10.1016/j.semcancer.2020.08.011.
39. İlhami Gülçin: Antioxidant properties of resveratrol: A structure-activity insight, Innovative Food Science & Emerging Technologies, , (2010), Volume 11, Issue 1, Pages 210-218, ISSN 1466-8564, DOI: https://doi.org/10.1016/j.ifset.2009.07.002.
40. Saberi H., Keshavarzi B., Shirpoor A., Gharalari F. H., Rasmi Y.: Rescue effects of ginger extract on dose-dependent radiation-induced histological and biochemical changes in the kidneys of male Wistar rats. *Biomed. Pharmacother.* (2017), 94, 569–576. DOI: https://doi.org/10.1016/j.biopha.2017.07.128.
41. Sano A.: Safety assessment of 4-week oral intake of proanthocyanin-rich grape seed extract in healthy subjects. *Food Chem. Toxicol.* (2017), 108, 519–523. 10.1016/j.fct.2016.11.021
42. New Drugs, New Side Effects: complications of cancer immunotherapy (https://www.cancer.gov/news-events/cancer-currents-blog/2019/cancer-immunotherapy-investigating-side-effects) May 10, 2019
43. Chen, Y., Jungsuwadee, P., Vore, M., Butterfield, D.A. and St Clair, D.K.: Collateral Damage in Cancer Chemotherapy: Oxidative Stress in Nontargeted Tissues. Molecular Interventions, (2007), 7, 147-156. DOI: https://doi.org/10.1124/mi.7.3.6.
44. Aslam, M., Naveed, S., Ahmed, A., Abbas, Z., Gull, I. and Athar, M.: Side Effects of Chemotherapy in Cancer Patients and Evaluation of Patients Opinion about Starvation Based Differential Chemotherapy. *Journal of Cancer Therapy*, (2014), **5**, 817-822. DOI: http://dx.doi.org/10.4236/jct.2014.58089.
45. Raffaghello, L., Lee, C., Safdie, F.M., Wei, M., Madia, F., Bianchi, G., et al.: Starvation-Dependent Differential Stress Resistance Protects Normal but Not Cancer Cells against High-Dose Chemotherapy. The National Academy of Sciences of the USA (2008), 105, 3305-3316. DOI: https://doi.org/10.1073/pnas.0708100105.
46. Gregoriou, G., Neophytou, C. M., Vasincu, A., Gregoriou, Y., Hadjipakkou, H., Pinakoulaki, E., Christodoulou, M. C., et. al.: Anti-Cancer Activity and Phenolic Content of Extracts Derived from Cypriot Carob (*Ceratonia siliqua* L.) Pods Using Different

Solvents. *Molecules (Basel, Switzerland)*, (2021), *26*(16), 5017. DOI: https://doi.org/10.3390/molecules26165017.

47. Ben-Arye, E., Samuels, N., Goldstein, et. al.: Potential risks associated with traditional herbal medicine use in cancer care: A study of Middle Eastern oncology health care professionals. *Cancer*, (2016), *122*(4), 598–610. DOI: https://doi.org/10.1002/cncr.29796.
48. Martirosyan D., Kanya H., Nadalet C.: Can functional foods reduce the risk of disease? Advancement of functional food definition and steps to create functional food products. Functional Foods in Health and Disease (2021); 11(5): 213-221. DOI: https://doi.org/10.31989/ffhd.v11i5.788.
49. Martirosyan D.M., Lampert T. and Ekblad M.: Classification and regulation of functional food proposed by the functional food center. Functional Food Science (2022); 2(2): 25-46. DOI: https://doi.org/10.31989/ffs.v2i2.890.
50. Chamani, Sajjad, et al. "Modulatory properties of curcumin in cancer: A narrative review on the role of interferons." *Phytotherapy research: PTR*, 2023, 10.1002/ptr.7734. 6 Feb. 2023, DOI: https://doi.org/10.1002/ptr.7734.
51. Ghasemi, Sorayya et al. "Epigenetic targeting of cancer stem cells by polyphenols (cancer stem cells targeting)." *Phytotherapy research: PTR* vol. 35,7 (2021): 3649-3664. DOI: https://doi.org/10.1002/ptr.7059.
52. Guo, Cui, et al. "Targeting lipid metabolism with natural products: A novel strategy for gastrointestinal cancer therapy." *Phytotherapy research: PTR*, 10.1002/ptr.7735. 7 Feb. 2023, DOI: https://doi.org/10.1002/ptr.7735.
53. Zaffaroni, Nadia, and Giovanni L Beretta. "Resveratrol and Prostate Cancer: The Power of Phytochemicals." *Current medicinal chemistry* vol. 28,24 (2021): 4845-4862. DOI: https://doi.org/10.2174/0929867328666201228124038.
54. Vernousfaderani, Eisa Kaveh et al. "Resveratrol and Colorectal Cancer: A Molecular Approach to Clinical Researches." *Current topics in medicinal chemistry* vol. 21,29 (2021): 2634-2646. DOI: https://doi.org/10.2174/1568026621666211105093658.
55. Ranasinghe, Ranmali et al. "Revisiting the therapeutic potential of tocotrienol." *Bio Factors (Oxford, England)* vol. 48,4 (2022): 813-856. DOI: https://doi.org/10.1002/biof.1873.