Role of Nutraceuticals in Treatment and Prevention of Cancer

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Abstract

One of the leading causes of mortality in the world, cancer has a number of pathologic components. The onset and progression of cancer disease states have been connected to genetic anomalies, infection or inflammation, poor dietary habits, radiation exposure, occupational stress, and/or toxin intake. Early cancer diagnosis and treatment have been found to increase the likelihood of survival and recovery, yet anticancer pharmaceutical side effects continue to have detrimental consequences that outweigh the advantages of therapy in terms of hospitalization and survival. Recently, it has been demonstrated that a number of naturally occurring bioactive compounds have anticancer properties, which means they may eliminate changed or cancerous cells without damaging their healthy counterparts. The investigation on four organic bioactive extracts, each of which has a unique polyphenolic profile, will be examined in this study. According to reports, the following activities in particular have been shown to support nutrition during cancer treatment: Suppression of cell growth, antioxidant activity, and anti-inflammatory activity. On the other hand, natural antioxidants may assist patients in adhering to anticancer therapy by minimizing the negative effects of currently available anticancer medications. In order to increase responsiveness and compliance in cancer patients, nutraceutical supplementation may be studied in conjunction with current anticancer medication therapy. It should be noted, however, that it is important to confirm that tests were conducted in accordance with protocol before presenting findings from research employing bioactive plant preparations.

Keywords: Polyphenols; bergamot; oleuropein; quercetin; curcumin; apoptosis; inflammation; antioxidant property.

Introduction

Recent epidemiological study has shown that food is a very effective way to maintain health and ward against sickness. Many neoplastic, autoimmune, and degenerative diseases are correlated with nutrition, and the interaction between nutrients and organisms may control the ratio of health to disease. Cancer is distinguished from other diseases by its uncontrolled cell growth and proliferation. It is a condition in which cells may divide and multiply endlessly without being controlled by the body's typical growth control systems, defying age and typical planned cell death. It is the end result of a multi-step process that took a long time and involved several genetic and epigenetic alterations. Many studies have revealed that dietary habits are one of the key contributors to the development of chronic diseases such as cataracts, diabetes, gallstones, neurological disorders, cardiovascular disease, and numerous forms of cancer. As demonstrated by the connection between dietary practices and disease, food has a direct influence on health [1].

Because to longer life expectancies, more urbanization, and the associated changes in lifestyle, cancer is becoming a more prevalent health issue worldwide. Despite the fact that the majority of high-risk cases are genetic, eating habits can have an impact on health. The most prevalent malignancies are those of the lung, bronchus, breast, colorectal, and prostate, according to epidemiological and demographic research. In general, the likelihood of survival and recovery is increased by early cancer discovery and appropriate treatment. The best course of treatment is determined by the kind of cancer and its stage; available choices include chemotherapy, surgery, radiation, hormone therapy, targeted therapy, etc. In order to guarantee the greatest efficacy and best results, a mix of therapeutic approaches is especially relevant nowadays [2]. Since every treatment has adverse effects on the patient, the oncologist should select the one with the best risk-benefit ratio. Despite being known to break DNA and harm both malignant and non-cancerous cells, chemotherapy is widely acknowledged as the gold standard of care and is still one of the major methods used to treat primary tumours [3].

A well-balanced diet with more fruits and vegetables and less meat and fat is popular in many Asian nations. Several hypotheses contend that nutrition and environment have a vital role in cellular health and function. In this study, we focused on the evolving theories and information about the use of nutraceutical supplements in cancer [4].

It came from the terms "pharmaceutical" and "nutrition". According to his definition of a nutraceutical, it is a food or component of a food that may be utilized for medical or health purposes, including the prevention and/or treatment of a disease or condition [5]. Functional foods were formerly included by this definition. Nevertheless, more recent definitions by various organizations and societies attempt to differentiate between functional foods and nutraceuticals. Any substance that is separated from herbal remedies, dietary supplements, certain diets, and processed foods like cereals, soups, and drinks that are used both as dietary supplements and as medicines is referred to as a nutraceutical [6].

Nutraceuticals

The terms "nutrition" and "pharmaceutical" were the source. According to him, a nutraceutical is a food or component of a food that has the potential to offer medical or health advantages, including the prevention and/or treatment of a disease or condition [7]. Formerly, this concept applied to functional foods. Nevertheless, more recent classifications made by

many institutions and groups attempt to distinguish between functional and nutraceutical foods. Any isolated herbal product, dietary supplement, particular diet, processed food (such as cereals, soups, and drinks), or dietary supplement that is utilized both as a food and a medicine is referred to as a nutraceutical [8]. Both non-food goods (such as medications and dietetics) and food products containing bioactive chemicals have seen a surge in demand over the last few years. These items cannot be categorized as "food" since they include extracts that have been enhanced with phytochemicals to exploit positive physiological benefits. In order to distinguish between nutrients and medications, a new word called nutraceuticals was created. Natural bioactive supplements known as nutraceuticals provide nutritional benefit and show promise as treatments for a number of ailments. Chemotherapy, radiation, and surgery are some of the current cancer therapies that have unwanted side effects that endanger the patients' health and wellbeing. Recent research indicates that several plant-based substances could affect the cellular and molecular mechanisms underpinning tumour growth. Some of these molecules may, however, also have antagonistic effects on conventional therapeutics. This article's goal is to summarize the most recent scientific research supporting the use of dietary supplements for both cancer treatment and prevention [9].

A substantial source of nutraceutical components includes bioactive phytochemicals such alkaloids, different terpenoids, and polyphenols (anthocyanins, flavones, flavanols, isoflavones, stilbenes, ellagic acid, etc.) [10] (Figure 1). In terms of human health, phytochemicals, which are primarily produced by plants, are non-essential nutrients that have either defensive or disease-protective properties [11]. Therapeutic substances known as nutraceuticals have drug-like qualities and can be used to treat illnesses with a high risk of death, including cancer, diabetes, atherosclerosis, and neurological and haematological problems. According to research findings, health food items include polyphenols, terpenoids, tannins, alkaloids, and flavonoids, all of which have a strong potential to combat these fatal diseases.

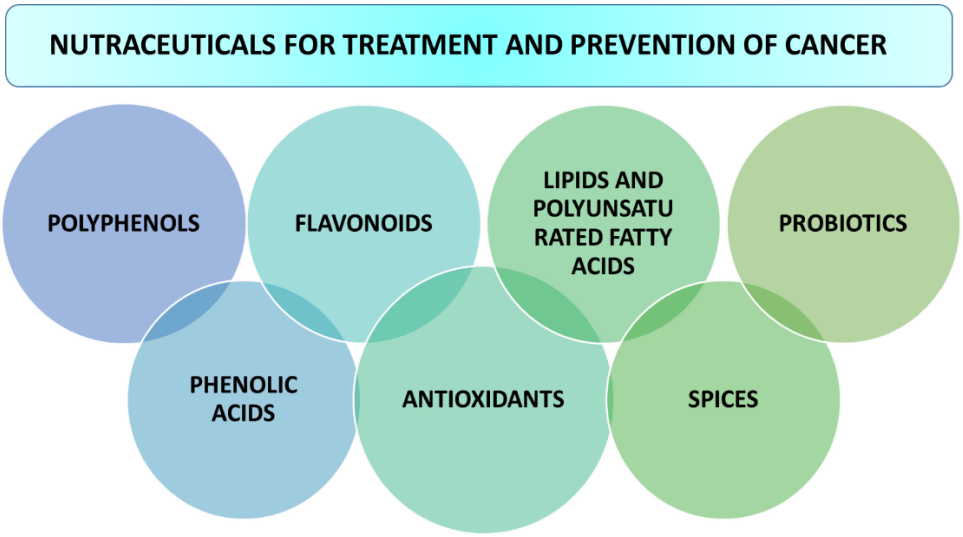

Figure 1: Nutraceuticals used for prevention of cancer

Nutraceuticals and Cancer

Epidemiology studies have repeatedly demonstrated that nutrition is a major risk factor for chronic conditions such cataract, type-II diabetes, gallstones, neurological illnesses, cardiovascular diseases, and a number of cancers (e.g., gastrointestinal cancer). A third of cancer-related fatalities are thought to be avoidable by dietary changes and other lifestyle modifications. As a result of the aforementioned, it can be claimed that nutraceutical oncology refers to the use of functional foods and nutraceuticals in the management, prevention, and treatment of cancer. Many scientific advancements have given the prospect of employing nutraceuticals and functional foods as a solo and complementary method in the prevention, treatment, and management of various types of cancer believability and credibility. Cancer patients benefit from consuming foods that are low in simple carbs and moderate in high-quality protein, fibre, and fat (particularly lipids of the omega-3 fatty acid family) [12].

Moreover, some additional micronutrients, nutraceuticals, and functional foods may be able to lower cancer risk or slow the growth and spread of pre-existing malignant diseases. They are crucial in lessening the side effects of chemotherapy and radiation treatment, and by lowering cancer cachexia, they may improve quality of life. They cause cancer cells to undergo apoptosis and suppress cell growth. Increased antioxidant consumption through diet may reduce the risk of illnesses like cancer. At various cellular levels, the phytochemicals have demonstrated a variety of distinct modes of action. The majority of them have become well-known as diverse sources of antioxidants that have an impact on the signalling pathway for redox-mediated transcription factors. Along the same lines, nutraceuticals could also be useful in lowering toxicity related to radiation and chemotherapy, and they might improve quality of life by lowering cancer cachexia. The ability to limit cancer cell proliferation and induce cancer cell death exists in nutraceuticals, functional foods, and supplementary micronutrients [13-15].

No mechanism-based preclinical investigations have been carried out despite good in vitro outcomes employing a number of cell types. Because to a dearth of preclinical evidence, the first extensive clinical studies of phytochemicals that were carried out in the 1990s were unsuccessful. There is a long history of the use of botanicals in the treatment of cancer. One of the numerous cancer treatment drugs made from plants is vincristine and vinblastine, two of the alkaloids from the Vinca species, as well as the Pacific yew *Taxus brevifolia* (Taxol). Several different methods were employed by ancient societies across the world to cure and prevent illness as well as to preserve health. Plant extracts are among these methods' subcategories. The fact that the same or very related plants are frequently used throughout cultures to treat the same symptoms or diseases suggests that they are probably extremely effective medicinally for those conditions [16].

Despite technological advancements, cancer is still a major worldwide health concern. Many plant extracts are used to treat and prevent cancer. For cancer patients, nutritional treatment may be helpful. There is proof that diets strong in high-quality protein, fibre, and fat (particularly omega-3 fatty acids) and relatively low in simple carbs are good for cancer patients. Nutraceuticals may also help lessen the side effects of chemotherapy and radiation treatment while also enhancing quality of life by lowering cancer cachexia. Several modes of action exist for phytochemicals at various cellular levels. The bulk of them have become

well-known as diverse sources of antioxidants with physiological effects [17].

Natural Compounds and Cancer

The main goal of cancer therapy is to eradicate cancer cells without harming healthy cells, and these drugs are successful because they act precisely on both cancer cells and healthy cells. It is imperative to develop treatments that have minimal side effects. Here, we examine the use of complementary medicine, which combines conventional and unorthodox methods, as an additional cancer treatment option for patients in addition to usual chemotherapy and radiotherapy. The phrase "alternative medicine" is used when unorthodox treatment entirely replaces traditional treatment modalities, emphasizing the patient's mental, emotional, spiritual, and social needs. Not only can lifestyle choices, such as food and nutrition, as well as genetic predisposition, exposure to toxic chemicals, and hormonal imbalance, contribute to the risk of developing cancer [18-21].

Dietary plans focused on consuming fruit, vegetables, selenium-rich foods, vitamins (B-12 or D), folic acid, and antioxidants on a regular basis, together with a high intake of fiber-rich foods and a moderate amount of milk and dairy products, can help prevent cancer. On the other hand, eating meat, animal products, or animal fats may raise the risk of developing cancer. The World Health Organization (WHO) specifically emphasizes that a balanced calorie intake that includes a higher intake of fruit and vegetables and minimal consumption of saturated fats, sugar, and salt significantly lowers the risk factors associated with the start of illnesses [19].

A strategy that strives to maintain healthy blood pressure, cholesterol, and triglyceride levels serves as the foundation of the dietary approaches to stop hypertension (DASH) diet. The key components include a high intake of fruits and vegetables, a consumption of low-fat dairy, and a reduction in cholesterol, saturated and total fat. The beginning of coronary artery disease, stroke, heart failure, metabolic syndrome, and diabetes, as well as other cardiovascular risk factors, have been demonstrated to be decreased by the DASH diet. The Mediterranean-DASH diet intervention for neurodegenerative Delay (MIND) diet, which attempts to enhance cognitive health in old age, may be described as a hybrid of the MIND and DASH diets. Increased consumption of fruit, vegetables, legumes, whole grains, fish, chicken, olive oil, and wine in moderation are the cornerstones of the MIND diet [20].

Also, there is a strict restriction on foods that are thought to be bad for the brain, such as red meat, butter/margarine, cheese, pastries, sweets, and fried or fast food. It's interesting to note that following the MIND diet lowered the chance of Alzheimer's disease development by 35%. The Mediterranean diet, NASH, and MIND all have distinct ideas about what constitutes a good or harmful food, and in order to properly appreciate these variances, we must expand our understanding of these dietary patterns. The Korean diet is one of the traditional Asian diets that emphasizes the consumption of rice and other whole grains, fermented foods, locally grown land and sea vegetables, primarily legume and fish proteins as opposed to red meat, and medicinal herbs (such as garlic, green onions, and ginger). It also includes sesame and perilla seeds oils [21,22]. The Korean diet, in contrast to western diets, is based on modest quantities, seasonal food sources, and a lack of fried foods. According to epidemiological research, this diet is relevant since it lowers the risk of metabolic syndrome, diabetes, obesity, and hypertriglyceridemia. Last but not least, a variety of foods, including rice, fish, soups, pickles, algae, fruits, vegetables, and mushrooms, are often served in tiny

quantities in the traditional Japanese diet. A decreased prevalence of hypertension and positive effects on blood pressure have been linked to adherence to a traditional Japanese eating paradigm. Apart from the variations in the diets discussed, the consistent high intake of fruit and vegetables, which ensures a delayed beginning of cancer, appears to be the common factor [23-25]. It is currently understood that a number of naturally occurring bioactive substances have anticancer effects. It is crucial to emphasize that more than 100 naturally occurring plant-based substances are now being tested in clinical settings as anticancer medications. Natural substances with cancer-fighting abilities can eliminate altered or malignant cells without toxicating healthy cells. The majority of bioactive molecules found in fruits and vegetables taken with meals are from the polyphenol family, a class of naturally occurring substances found in large quantities throughout the plant kingdom; to far, more than 8000 phenolic structures have been identified [26].

Natural substances that have anticancer properties are increasingly used because of their low toxicity and little side effects, which allow for their use in adjuvant therapy or treatment of cancer. Apoptosis is a form of controlled cell death that is tightly regulated at the gene level and effectively rids the body of damaged cells. In precancerous lesions, inducing apoptosis is essential because it eliminates dangerous cells by halting unchecked cell growth and the spread of cancer. Transformed cells are able to avoid this process, despite the fact that the underlying processes are not well understood. Deregulation of apoptosis is one of the features of cancer growth. Because of this, therapeutic methods designed to increase the susceptibility of cancer cells to apoptosis are being investigated more and more. Fruits like citrus serve as important sources of flavonoids. Since flavonoids can interfere with the three major phases of carcinogenicity: the development, promotion, and advancement of cancer, several experimental investigations have conclusively shown that bergamot and its preparations can have antitumor effects [25,27].

Many *in vitro* studies have sufficiently emphasized BEO's anticancer properties. The cell cycle's cessation in phase G0-G1 in particular led to a decrease in cell proliferation. Cellular DNA damage and strong pro-oxidant activities have also been found. A very comprehensive work conducted in vitro on human cancerous cells of the nervous system (SH-SY5Y, PC12), prostate (PC3), and breast (MDA MB-231) showed that treatment with BJ at different concentrations (1–5%) arrested cancer progression. In addition, BJ demonstrated its ability to reduce the growth rate of various cancer cell lines with mechanisms dependent on the type of cancer [28].

The inhibition of mitogen-activated protein kinase (MAPK)-dependent pathways, cell cycle arrest, and altered apoptosis have all been demonstrated in human colon cancer cells when BJ is present in low concentrations, whereas DNA damage is caused by oxidative stress when BJ is present in high concentrations. BPF has drawn interest from scientists because of its unusual make-up and high concentration of flavonoids such naringin, hesperidin, and neo eriocitrin. Several publications indirectly involving BPF are known, despite the fact that there is few research on the relationship between BPF and cancer. In actuality, cancer mortality and incidence can be decreased by cholesterol-lowering medications [29].

Moreover, it has been demonstrated that quercetin can suppress proliferation, angiogenesis, and metastasis while encouraging apoptosis. Models of breast, pancreatic, prostate, and lung cancer showed these effects; the dose of quercetin was 50 mg/kg. In the past ten years, it has

been demonstrated that quercetin can strengthen its anticancer effects when combined with other medicines. One more effective treatment, for instance, was vincristine and quercetin co-encapsulated in liposomes. With a distinctive yellow hue, curcumin is the most representative polyphenol derived from the rhizomes of Curcuma longa. Curcumin is well-known for its application in food, drink, cosmetics, and nutritional supplements. Curcumin has so far demonstrated a wide range of therapeutic advantages against oxidative stress, inflammation, obesity, metabolic syndrome, neurological illnesses, and various malignancies [30-32].

The chemical makeup of curcumin also supports all these advantageous qualities. As an example, in the human colon cancer cell line HCT-116, curcumin decreased cell proliferation through cell cycle arrest at the G2/M phase and/or in a modest amount in the G1 phase. It has also been observed that curcumin inhibits cell growth, blocks the cell cycle, and stimulates apoptotic death. Early preclinical research on people was done to determine the tolerable dose, but more research has to be done. The information presented in this section demonstrates that the four polyphenolic substances under consideration—bergamot, ole europein, quercetin, and curcumin—have the potential to lessen cancer cell viability. Natural substances can halt the cell cycle from continuing, cause apoptosis, and enhance the expression of the tumour transcription factor p53 to accomplish this as shown in table 1 [29, 31, 32].

Molecular Targets of Nutraceuticals in Cancer Care

Early in vitro research revealed that phytochemicals may counteract the tumorigenic effects of carcinogens by inhibiting their ability to mutate cells and promoting cell division. Chemoprevention is the practice of using natural or manmade chemicals to stop, slow down, or prevent the development of cancer. Intraepithelial neoplasia or carcinoma *in situ*, which correlate to the promotion and advancement stages, are typically discovered as solid malignancies in the early stages. "Anti-promotion" and "anti-progression" drugs may therefore be of special therapeutic importance. Food bioactive compounds may significantly affect the control of gene expression, even at extremely low quantities. A greater understanding of the preventive mechanisms of illnesses including obesity, diabetes, atherosclerosis, hypertension, and cancer through dietary alterations should result from ongoing research on the impact of nutraceuticals on gene expression. Moreover, it was shown that phytochemicals control innate and inflammatory responses as well as act as a defence against lipid peroxidation [33,34].

Table 1: Examples of nutraceutical sources with their biological activity

Target Cancer	Compounds	Source	Biological Activity
	Fucoxanthin	Marine Carotenoid	Anti-proliferative
	Punicalagin	Pomegranate juice	Apoptosis
	Resveratrol	Grape skin and seeds	Apoptosis
	Epigallocatechin-3-	Green tea polyphenols	Anti-angiogenic

Breast	gallate Sulforaphane Genistein All-trans-retinoic-acid Parthenolide Soy Garlic Curcumin Thinone 6-Shogaol Dallyl disulfide. Dialiyl sulfide, Diallyl trisulfide, S—allyl mercaptocysteine Crocetin Piperine Capsaicin Supercritical fluid rosemary extract Eugenol Ethyl acetate extract	Cruciferous vegetables Soy Vitamin A *Tanacetum parthenium* Vegetarian food *Allium sativum* *Curcuma Longa* *Oenanthe aquatica* Flueggea suffruticosa, Zingiber zerumbet *Allium sativum* *Crocus sativus* *Piper nigrum* *Capsicum annuum* *Rosemarinus officinalis* *Syzygium aromaticum* *Nitraria Retusa*	Apoptosis Phytoestrogen Apoptosis Apoptosis Anti-angiogenic Apoptosis Anti-angiogenic Apoptosis/ Anti-proliferative Anti-angiogenic Apoptosis Anti-invasive Apoptosis Inhibiting Invasion Apoptosis Apoptosis Apoptosis
	Apigenin Lupeol Saponin	Flavonoids Guttiferae Soapwort plant	Anti-proliferative Anti-proliferative Apoptosis

Lung	Genistein	Soy	Apoptosis
	Luteolin	Fruits and vegetables	Apoptosis
	Taxol	*Taxus brevifolia*	Apoptosis
	Gallic acid	Grape seeds, rose flowers, sumac, oak, and witch hazel	Apoptosis
	Caffeic acid Phenetyl ester	Propolis	Anti-proliferative
	Gingerol	*Zingiber officinalis*	Apoptosis
	Curcumin	*Curcuma longa*	Apoptosis/ Anti-proliferative
	Seed extract and seed Oil; Thymoquinone	*Nigella Sativa*	Anti-proliferative Antiangiogenic
	Thiacremonone	*Thiamine*	Apoptosis/ Anti-proliferative
	Ethanolic extract, aqueous extract	*Vernonia amygdalina*	Apoptosis
	Capsaicin	*Capsicum annuum*	Apoptosis
Pancreatic	Genistein	Soy	Anti-proliferative
	Garcinol	*Garcinia indica*	Anti-proliferative
	Limonoids	*Cipadessa baccifera*	Anti-proliferative
	Crocin	*Crocus sativus*	Apoptosis
	Fisetin	Strawberry, apple, onion, and cucumber	Apoptosis
	Urolithin A	Pomegranate	Anti-proliferative
	Methyl protodioscin	Fruits	Anti-proliferative

	Blueberries	Flavonoids	Anti-proliferative
	Procyanidin	Flavonoids	Apoptosis
Colorectal	Carotenoids	Fruits and Vegetables	Anti-proliferative
	Beta-sitosterol	Prunus Africana	Apoptosis
	Saponin	Soapwort plant	Apoptosis
	Genistein	Soy	Anti-proliferative
	Ellagic acid	Medicinal plants	Apoptosis
	Ferulic acid	Whole grains, spinach, parsley, Grapes, rhubarb, wheat, oats, rye, and barley	Apoptosis
	Curcumin	Turmeric	Apoptosis
	Thymoquinone	*Nigella Sativa*	Apoptosis/Anti-angiogenic
	Ginger root/ leaf extract, 6-gingerol, shogaols	*Zingiber officinale*	Apoptosis/Anti-proliferative
	Se-Methyl-L-selenocysteine garlic extract	*Allium sativum*	Apoptosis/Anti-proliferative
	Se-M ethyl-L-selenocysteine	Enzymes	Apoptosis
	scallion extract	*Allium cepa*	Anti-carcinogenic
	Crocin	*Crocus sativus*	Apoptosis
	Piperine	*Piper nigrum*	Apoptosis
	Capsaicin	*Capsicum annuum*	Apoptosis/Anti-proliferative
	Rosemary extract,camosic acid, diterpenes	*Rosemarinus officinalis*	Apoptosis
		Eugenia aromatica	

	Clove extract	*Alpinia officinarum*	
	Galangin	*Cinnamomum ceylanicum*	Apoptosis
	Cinnamaldehyde		Antiangiogenic
			Antiangiogenic
Prostate	Gallic acid	Secondary metabolite in plants	Anti-proliferative
	Neobavaisoflavone	*Psoralea corylifolia*	Apoptosis
	Rhodioflavonoside	*Rhodiola rosea*	Apoptosis
	Luteolin	Fruits and vegetables	Anti-proliferative
	Berberine	Hydrastis canadensis, berberis aristate, coptis chinense, Coptis japonica, Phellondendron chinense Schneid, and *Phellondendron amurense*	Anti-proliferative
	Curcumin	*Curcuma Longa*	Anti-proliferative
	Ginger extract, 6-shogaol, 6-gingerol and 6-paradol	*Zingiber officinale*	Anti-proliferative
	Saffron extract	*Crocus sativus*	Anti-proliferative/Anti-carcinogenic
	Piperine	*Piper nigrum*	Anti-carcinogenic
	Rosemary extract	*Rosemarinus officinalis*	
Ovarian	Corilagin	Ellagitannin in a wild of plants	Anti-proliferative
	Gallic acid	Secondary metabolite in plants	Apoptosis
	Ellagic acid	Medicinal plants	Anti-proliferative

	Epigallocatechin-3-gallate	Green Tea polyphenols	Apoptosis
	Berberine	Hydrastis canadensis, berberis aristate, coptis chinense, Coptis japonica, Phellondendron chinense Schneid, and Phellondendron amurense	Anti-proliferative/ Apoptosis
Blood	Rosavin	*Rhodiola rosea*	Apoptosis
	Oleanolic acid	Fruits and vegetables	Antiangiogenic
	Silibinin	Milk thistle seeds	Antiangiogenic
	Kaempferol	Flavonoid aglycone in fruits and vegetables	Antiangiogenic
	Resveratrol	Grape skin and seeds	Antiangiogenic
	Withaferin A	*Withania somnifera*	Antiangiogenic
Cervix	Curcumin	*Curcuma longa*	Apoptosis/ Anti-angiogenesis
	Thymoquinone, methanolic extract	*Nigella Sativa*	Apoptosis/ Anti-proliferative
	Eugenol	*Syzygium aromaticum*	Anticarcinogenic/Anti-inflammatory
Liver	Thymoquinone	*Nigella sativa*	Anti-proliferative
	Carnosic acid	*Rosmarinus officinalis*	Apoptosis
	Eugenol	*Syzygium aromaticum*	Anti-proliferative
	Galangin	*Alpinia officinarum*	Anti-proliferative

Stomach	Curcumin	*Curcuma longa*	Apoptosis/ Anti-proliferative
	Diallyl disulfide	*Allium sativum*	Apoptosis
	Crocin	*Crocus sativus*	Apoptosis/ Anti-proliferative
	Capsaicin	*Capsicum annuum*	Apoptosis/ Anti-proliferative

A few studies on the effects of certain nutraceuticals on activity have opened the door to future research into these compounds in great detail using a variety of genetically ill animal models. The development of food supplements as an adjunct therapy to improve the quality of life for cancer patients is urgently needed in addition to the active role that nutraceuticals and functional foods play in the management of cancer progression. In reality, some cancer patients exhibit cachexia, which is characterized by major changes in their metabolism of carbohydrates, proteins, and fats and leads to poor quality of life, a decreased response to treatment, and a shorter survival time. In order to reverse these metabolic changes in cancer patients, nutritional modification may be helpful. Dietary intervention can be an effective technique for managing cancer and lowering the toxicity brought on by chemotherapy and radiation treatment. Nutraceuticals can also considerably increase tumour necrosis factor (TNF) and natural killer cell (NK) function in patients with advanced cancer [35,36-39].

Oxidative Stress (OS)

The essential requirement of life is a proper balance between oxidation and antioxidants. "Oxidative stress" (OS), which may result in tissue damage, is caused by a breakdown in the pro-oxidant-antioxidant equilibrium. When the body experiences a rise in oxidant processes as a result of a deficiency in antioxidant defence, OS is a physiological process that is formed. As a result of this imbalance, certain cell pathways associated in the development of cancer can be activated; if OS increases excessively or persists permanently, a disease may result. The body's components can all be harmed by OS (proteins, lipids, fatty acids, DNA, etc.) [35]. Due to an excessive formation of reactive oxygen species (ROS) or a diminished scavenging contribution, pathologies including cancer, atherosclerosis, diabetes, neurological and endocrinological disorders, and cardiovascular illnesses have all been linked to overexpression of OS. A common mechanism for the beginning and development of many illnesses, including cancer, has been thought to include an unchecked rise in ROS. As it turns out, tumours frequently exhibit altered redox balance and dysregulated redox signalling, two characteristics that are highly associated with the development of cancer and treatment resistance [36-38].

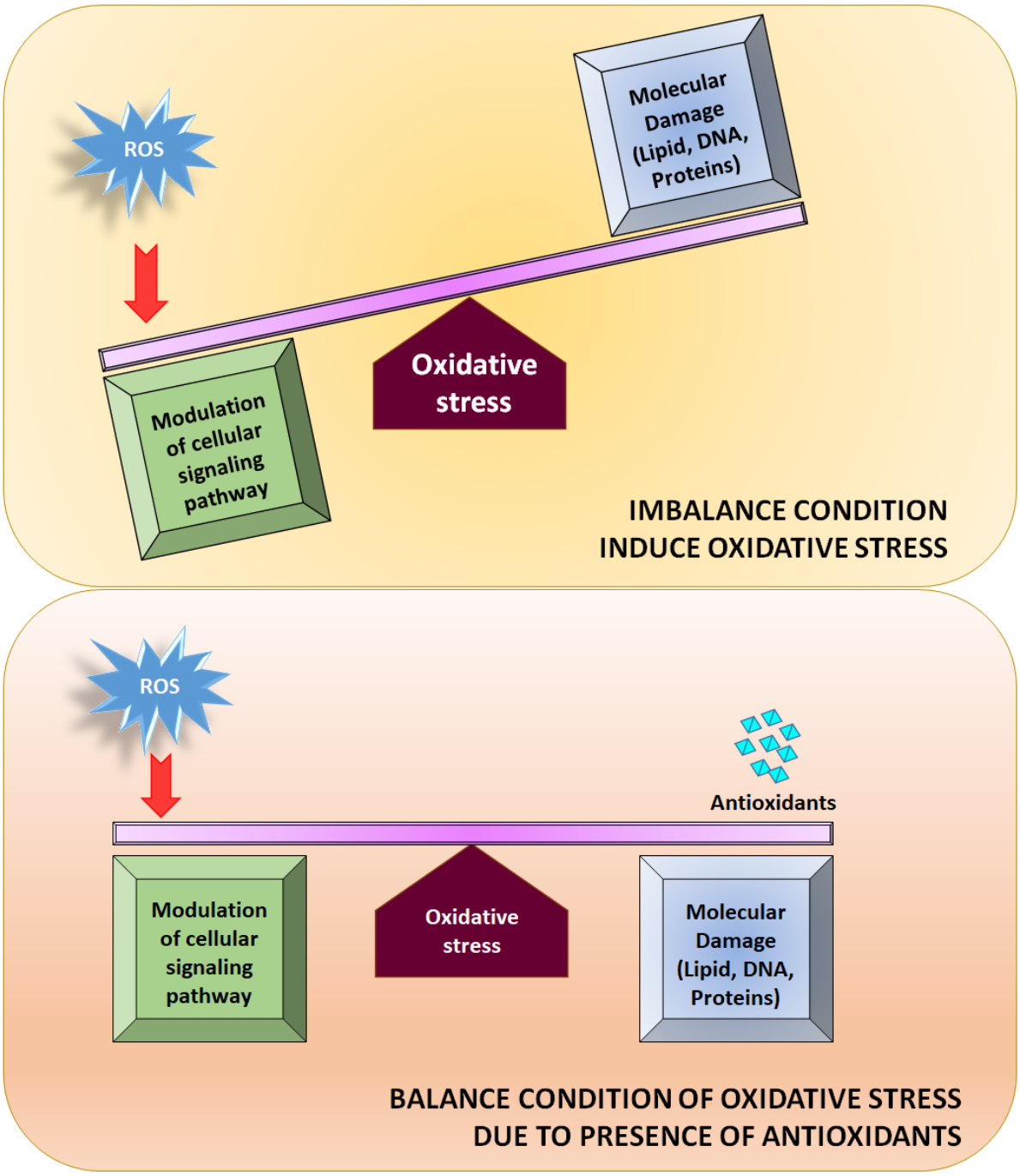

Figure 2: Relation between amount of antioxidant and ROS on oxidative stress

Reactive oxygen and nitrogen species, often known as free radicals or reactive species, are two types of reactive species (RONS). Further to reactive oxygen species (ROS), reactive nitrogen species (RNS) are produced by physiological processes to manufacture metabolites and energy as a defence against invading pathogens (Figure 2) [40]. Modest levels of ROS enhance mitogenic proliferation and serve as critical second messengers in a variety of redox-sensitive signalling cascades, which are necessary for the cell to operate normally physiologically. Modest levels of ROS are beneficial for wound healing, repair procedures, and defence against invasive infections. Tumor cells use their metabolic pathways and manage a variety of enzymes to maintain a suitable number of antioxidant systems. The

antioxidant capability of cells serves as a strong foundation to reduce OS damage. Cells develop a range of intricate systems for preserving redox equilibrium in order to combat the harmful effects of ROS. The physiological benefits of indirect antioxidants are longer-lasting because they increase cellular antioxidant capacity through increasing the expression of certain genes, notably NFE2L2, which codes for nuclear factor (erythroid-derived 2)-like 2. Direct antioxidants are those with redox activity and short half-lives that need to be supplemented or renewed during the process (Nrf2), known as a master regulator of the antioxidant response. Additionally, pro-oxidant effects, which have been an issue with the administration of high dosage vitamin E treatment, are unlikely to be elicited by indirect antioxidants [41,42].

Antioxidant Effect of Natural Compounds on Cancer

Reactive oxygenated/nitrogenated species are created and take part in a number of regulatory processes, such as gene expression, cell proliferation, and apoptosis. Oxidative reactions are also a crucial part of the metabolism of cells and are essential for their survival. The primary biological molecules, including DNA, proteins, lipids, carbohydrates, and enzymes, may oxidise and lose or change their activities when reactive species are produced in excess of the cellular antioxidant capacity. For instance, reactive oxygen species (ROS) have a significant interaction with nuclear DNA, leading to mutations and genomic instability; with proteins, leading to protein adducts; and with the lipids of cell membranes, changing their activities. Cancer cells and pathogenic states both exhibit this damage brought on by oxidative stress. Endogenous antioxidants exist in the body physiologically to combat reactive species. Exogenous antioxidants are those that are not produced by the body and are instead obtained via food, dietary supplements, and medications. The capacity of natural compounds to lessen cellular oxidative stress has been studied particularly recently [43,44].

The eukaryotic cells' mitochondria are significant organelles because they are crucial to the metabolism of energy. Cancer has been linked to mitochondrial malfunction. As byproducts of their regular metabolism, mitochondria can create free radicals such as the hydroxyl radical (OH•), superoxide anion (O2•), hydrogen peroxide (H2O2), hydroxyl ion (OH), and nitric oxide (NO•). Since they include one or more catechol groups, which are responsible for removing reactive oxygen species, most natural substances exhibit antioxidant activity. This prevents the development of free radicals and lipid peroxidation [39, 42].

Two hydroxyl groups are positioned in the ortho position on the benzene ring and the catechol, also known as 1,2 dihydroxybenzene, has a chemical formula of C6H6O2. The bergamot fruit's potent antioxidant function has been abundantly documented in scientific literature, and as a result, eating of the fruit is promoted as being healthy. A substantial antiradical property against superoxide and nitric oxide, O2• scavenging action, and prevention of lipid peroxidation, for instance, have all been demonstrated in vitro for BJ. Parallel in vivo experiments on individuals given BJ- or vehicle-fed hearts of mice for three months revealed statistically significant antioxidant responses [30,33].

One of the primary components of BPF is naringenin, a flavanone-class polyphenol that is found in large quantities in citrus fruits. In fact, it has been demonstrated that this substance can inhibit the growth of certain cancer cell types by inducing cytotoxic and apoptotic effects. However, because of its hydrophobic properties, brief half-life, and low absorption, its usefulness in vivo is limited. To increase its bioavailability, it was recommended that

nanoparticles be used. Oleuropein's antioxidant capabilities and capacity to stimulate the activity of ROS-detoxifying enzymes including glutathione S-transferase, catalase, superoxide dismutase, and glutathione S-reductase have been extensively studied in the scientific literature (GST). Oleuropein plays an antiox- Nutrients 2021, 13, 3834 11 of 27 idant function that is advantageous in certain malignant processes because it reduces lipid peroxidation [30]. In addition to lowering ROS, investigations have shown that oleuropein also inhibits the production of histone deacetylase, induces apoptosis, and delays cell migration and invasion in a dose-dependent way. Oleuropein also caused the genes for metalloproteinases to be downregulated, which may help prevent the metastasis of breast cancer. For differentiated thyroid carcinoma, an antioxidant and growth inhibitory effect was discovered [41].

Quercetin inhibits lipid oxidation and the generation of iron-catalyzed ROS by decreasing high-valent iron. In addition, it controls signal transduction pathways like NRkB, MAPK, and AMPK. It has been demonstrated that quercetin has a variety of inhibitory effects on different stages of carcinogenicity due to its low toxicity. Interest polyphenols have an antioxidant impact because of the catechol group's presence and the enhanced production of antioxidant enzymes [36-42].

Epigenetics, Cancer, and Involvement of Polyphenols

The potential modifications to DNA that might impact gene expression are deepened by epigenetics. These variants may be passed down from one cell to another and, once established, are rather permanent. Although these alterations take place during the early development of embryonic and primordial cells, it is now recognized that they can also happen later in life. The primary contributing factors may include drug use, poor dietary choices, or exposure to adverse environments. The numerous epigenetic processes cooperate and depend on one another to control gene expression. The three main epigenetic changes that have been examined are non-coding RNA modification, covalent histone modification, and DNA methylation [26-30]. Life-sustaining DNA methylation involves the straightforward addition of a methyl group (CH3) to position 5 on the pyrimidine ring of a cytosine residue in a cytosine-guanine pair (CG). Yet, this reaction on CpG dinucleotides contributes to a number of point mutations that cause genetic illnesses in humans and raise the risk of mutagenesis. DNA hypomethylation can cause DNA damage, genomic instability, and the stimulation of unchecked development in cancer. On the other hand, one of the most prevalent somatic abnormalities in cancer is gene silence, which is typically caused by DNA hypermethylation. Several cancer models have been used to assess the epigenetic effects of resveratrol. In cancer cells, resveratrol was able to cause the deregulation of many miRNA, but not in normal cells. The mobilization of intracellular copper and subsequent pro-oxidant activity are probable mechanisms underlying the anticancer and apoptosis-inducing effects of plant-derived dietary polyphenolic compounds [32,39]. Neoplastic and pre-neoplastic cells have been demonstrated to possess higher amounts of copper than normal cells [29] and may be more vulnerable to ROS generation through electron transfer with polyphenols. Regardless of the sort of malignancy, the course of the malignancy, or the genesis of the malignancy, it is noteworthy that all cancers have higher copper levels. As a result, normal cells may survive whereas pre-neoplastic and neoplastic cells are destroyed by DNA damage caused by polyphenols in the presence of Cu(II) (Figure 3).

Also, by controlling the transcriptional repression of several genes, including p53, this natural substance can guard against cancer. In a mouse model of skin cancer, it has been demonstrated that green tea polyphenols suppress the tumour, its invasion, and angiogenesis. Epigallocatechin gallate, a bioactive polyphenol found in green tea, has showed epigenetic effects in people by demethylating certain tumour suppressor gene promoters [36,38]. Intake of soybeans during infancy and adolescence has been shown to lower the incidence of breast cancer. Soybean isoflavones can affect the beginning of cancer. Menopausal women's methylation of five cancer-related genes was examined, and it was shown that doing so resulted in increased methylation in some of the genes linked to the development of breast cancer and lowered the probability of getting the illness. In addition to the above-mentioned examples, several more substances from the family of polyphenols have been shown to have epigenetic effects [40]. Among them are lycopene, curcumin, quercetin, isothiocyanates, genistein, and caffeic acid.

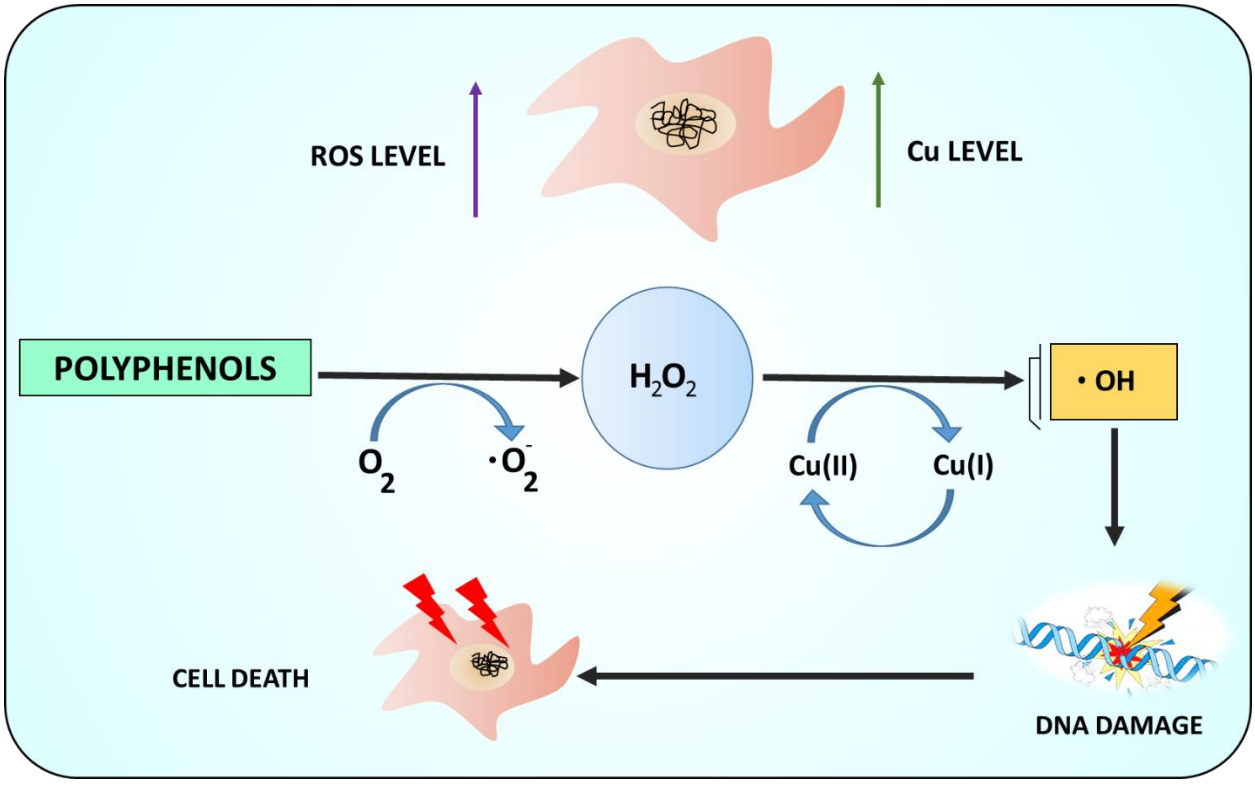

Figure 3: Mechanism for anticancer effects of polyphenolic compounds

Combination of Nutraceuticals and Antioxidant Substances

Depending on its dosage, the presence of additional antioxidants, and the concentration of endogenous antioxidants, an antioxidant molecule may have either hazardous or helpful effects. The additive and synergistic effects of phytochemical combinations have attracted attention recently. Many antioxidants interact through synergistic or "sparing" actions. It is advantageous to provide a variety of antioxidants because they may work in concert in different stages and may be more potent than large doses of a single antioxidant. It is recommended to use a mixture of antioxidants to control illnesses. For instance, polyphenols and vitamins work well together to prevent cancer, osteoporosis, cardiovascular disease, *diabetes mellitus*, and neurological disorders. In comparison to the biological effects obtained

by the individual phytochemicals alone, the combined action of phytochemicals demonstrates a greater biological effect [38, 40-44].

Fruit and vegetable phytochemical extracts have been shown to have potent anti-oxidant and anti-proliferative actions during the past 10 years. Furthermore, it has been proposed that the potent antioxidant and anti-cancer capabilities of fruits and vegetables are due to phytochemical combinations found in these diets [12,16,20].

Orange, apple, grape, and blueberry were combined in a way that increased their antioxidant activity. Fruits and vegetables are healthy when consumed in the recommended daily amounts (5–10 servings). The patient's quality of life is compromised as a result of secondary symptoms brought on by a rise in OS during chemotherapy. Antioxidant supplements have so been suggested as preventive agents in the prevention and treatment of cancer [23]. According to several studies, the anti-cancer effectiveness of polyphenols can be increased by combining them with chemicals that are either chemically related to or dissimilar from polyphenols. Piao et al. showed anti-cancer effects of curcumin, resveratrol, and epicatechin gallate on cell viability, apoptosis, clonogenic survival, and tumour development in HPV-positive head and neck squamous cell carcinoma in an in vivo and in vitro investigation. The phytochemicals known as polyphenols, and in particular resveratrol (RES), are the category of antioxidants that have been the subject of the greatest research. Black tea polyphenol and RES work together synergistically to limit the formation of skin tumours, resulting in a reduction in tumour size. Several phenolic substances may have both chemopreventive and anticancer effects because of their dual impact on cellular redox control. It appears that they exert a pro-oxidant action that encourages cell death in cancer cells and a pro-antioxidant effect that prevents carcinogenesis in normal cells [29-36].

Many research has examined the effects of various phytochemical or fruit and vegetable combinations on outcomes of disease prevention during the past ten years, but a concise review of the most recent scientific results is lacking. Although though natural antioxidants typically contain a variety of bioactive chemicals in varying quantities and ratios, it is frequently challenging to determine their safe doses because no such safety assessments have been documented. The FDA adopted the most recent Nutrition Facts Label for packaged goods in 2016 and mandated that customers should be better educated about dietary options based on scientific facts. The FDA papers only included vitamin C, vitamin E, and -carotene as antioxidants. Natural antioxidants have a wide range of applications and several health advantages, but their safety profile is not yet fully known. However, a maintenance dose of antioxidants, before or after the chemotherapy could be recommended [32,44].

Effects of Nutraceuticals on MicroRNAs

Cancer is prevented by bioactive phytochemicals' effects on a variety of physiological processes, including gene expression, cell cycle control, cell proliferation, cell migration, etc. They might alter non-coding RNAs (ncRNAs), up-regulate tumor-suppressive microRNAs (miRNAs), and down-regulate oncogenic miRNAs, which prevent the proliferation and self-renewal of cancer cells [27]. The expression of miRNAs can be altered by nutritional supplements, which may then have an impact on cellular responses in situations of health or illness, including cancer. It has been established that miRNAs play important functions in the control of gene expression. They are the most prevalent non-coding regulatory RNA molecules and may be found in a wide variety of organisms, from viruses to humans [31].

MiRNAs regulate a wide range of physiological activities, including growth, differentiation, neuronal asymmetry, metabolism, stem cell biology, proliferation, and programmed cell death (Figure 4). They may also promote, inhibit, or repress the development of cancer [42].

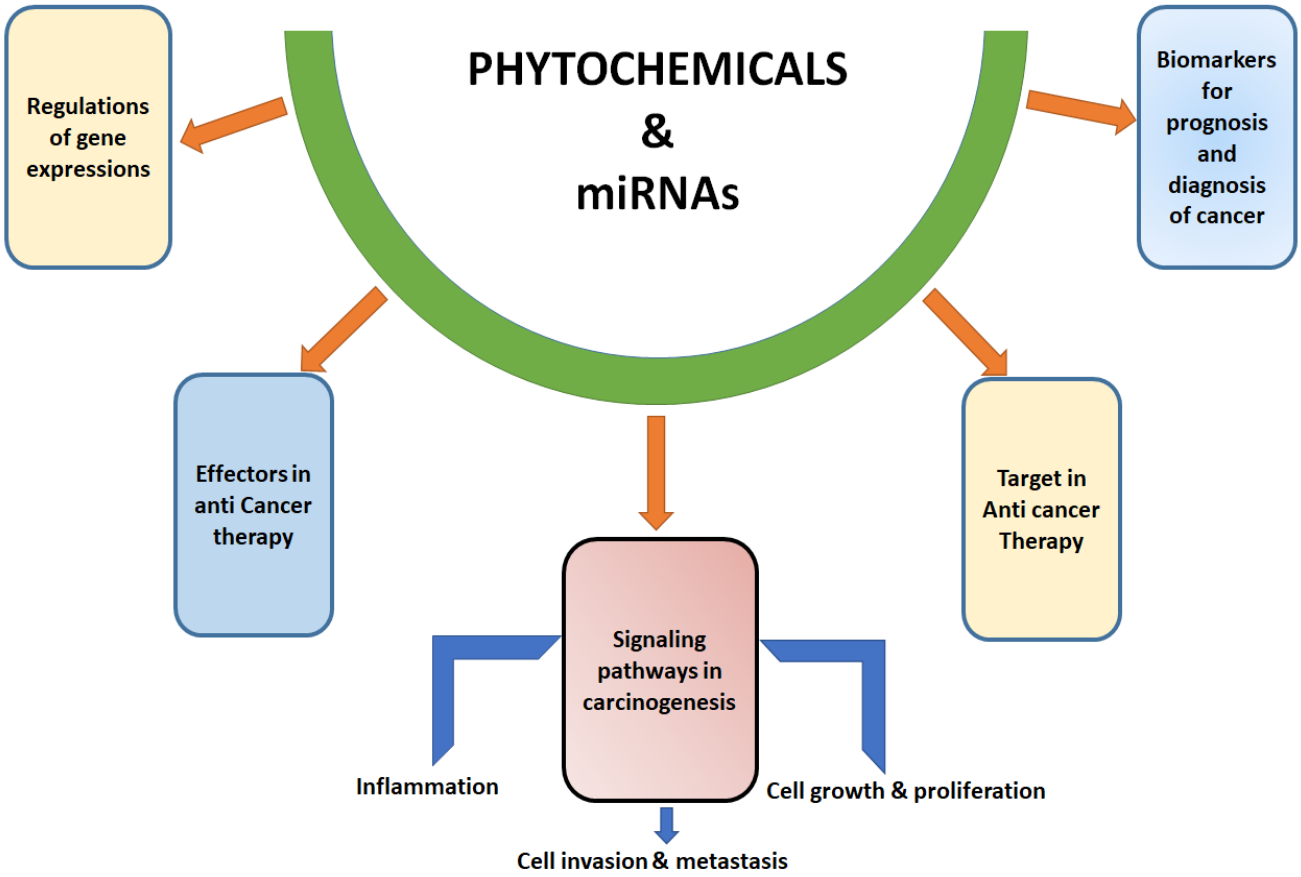

Figure 4: Phytochemicals and miRNAs involved in the carcinogenesis process.

The modulation of miRNA expression, which causes cell death or delays the onset of illnesses like diabetes, cardiovascular disease, and others, may be a major target of the impacts of natural products. Several research examining the diagnostic and prognostic value of dysregulated miRNA expression in thyroid carcinoma have been described.

Impact of nutraceuticals on Epigenetic Phenomena in Cancer

In the past ten years, research has concentrated on certain categories of botanical elements that have bioactive qualities that might affect epigenetic processes. The "epigenetic diet" refers to the combination of these bioactive substances that may be included in a person's diet [8]. Several human illnesses, including cancer, are thought to be prevented by some dietary elements having qualities that affect epigenetic processes. Numerous dietary and organic phytochemicals, including curcumin, genistein, quercetin, and resveratrol, among others, have been shown to have potent anti-tumor effects by reversing epigenetic changes brought on by the activation of oncogenes and the inactivation of tumour suppressor genes. They can also modulate the mammalian epigenome by controlling the mechanisms and proteins involved in chromatin remodelling. Epidemiological research on humans and animals has demonstrated that early ingestion of specific epigenetic diets may result in an epigenetic modification and might lower the risk of the onset of particular illnesses [26-29].

Phytochemicals, which are plant-derived substances that have a role in regulating epigenetic processes and reshaping the epigenome, have been shown in experimental experiments to alter the activity of proteins and ncRNAs, suggesting that they may soon play a significant role in pharmacogenomics [14]. Via influencing ncRNAs, particularly miRNAs and long ncRNAs, it has been demonstrated that they take part in DNA methylation, histone modifications, and post-transcriptional control of genes. If adequate dietary recommendations are followed, these food components can have an impact on the prevention of several human illnesses including cancer and diabetes. Numerous foods consumed by people contain epigenetic dietary elements, such as genistein, a naturally occurring isoflavone found in soybean products, sulforaphane, an isothiocyanate found in cabbage or broccoli sprouts, and EGCG, the main polyphenol in green tea, which has been linked to a lower risk of developing many common cancers [33]. At least three independent DNA methyltransferases (DNMTs), DNMT1, DNMT3a, and DNMT3b, maintain DNA methylation patterns and are necessary for cellular differentiation during early embryonic development. Accordingly, the right exposure to epigenetic modulators from the diet that target DNA methylation may result in early epigenetic reprogramming and disease prevention in later life [37]. Chemo-radiotherapeutic medicines, kinase inhibitors, individualised antibodies, and substances that activate the immune system are frequently used in the treatment of cancer. By undoing the abnormal epigenetic modifications formed during cancer, demethylating medicines and histone deacetylase inhibitors can change the way genes are expressed. Recent research has shown that phytochemicals may be an alternative therapeutic option for the treatment of cancer and that natural substances and dietary supplements may be able to restore the normal epigenetic marks that are changed during carcinogenesis [43]. The most researched phytochemicals in the fight against cancer include EGCG, quercetin, RES, curcumin, and sulforaphane, which halt tumour growth and spread by concentrating on important signalling pathways such the control of epigenetic machinery (regulation of DNMTs and HDACs activities). EGCG directly binds to the enzymatic substrates of DNMT3b and HDAC1, inhibiting their activity and reactivating tumour suppressor genes such retinoic acid receptor, cadherin1, and death-associated protein kinase-1 [44].

Nutraceuticals: Prevention, Cure and Chemotherapy

Modern cancer therapies have greatly increased patient survival rates in recent years. This improvement in the survival rate demonstrates advancements in the use of combination treatment and early-stage diagnosis. Natural antioxidants work in concert with some chemotherapy drugs, according to clinical research [31,36]. An improved response rate was seen in individuals receiving vitamin A supplements in conjunction to either doxorubicin or cyclophosphamide in a randomized experiment on 100 patients with a diagnosis of BC. Modest prospective research was carried out by Drisko et al. with two patients who had advanced ovarian epithelial cancer. Carboplatin and paclitaxel were given to both individuals. Prior to carboplatin, patient 1 had an oral antioxidant regimen (vitamins C, E, b-carotene, coenzyme Q-10, and a multivitamin/mineral), whereas patient 2 received the same chemotherapy regimen, the antioxidant regimen, and parenteral ascorbic acid but not consolidation paclitaxel. According to the findings, antioxidants and chemotherapy work together synergistically to induce remission in both individuals [5,18,32].

As compared to drug-alone therapy in HL60 and NB4, Zhao et al. showed that modest

dosages of Vitamin C and Decitabine have synergistic effects on proliferation, apoptosis, TET2 expression, and activity in both cell lines in vitro and in clinical studies. After one cycle of chemotherapy, safety analyses revealed that patients who got the Decitabine regimen (DCAG) in combination with intravenous vitamin C saw a greater rate of full remission. As compared to patients having the same treatment but not taking vitamin D supplements, Zeichner and colleagues discovered that women getting somewhat more than 10,000 IU/week (1500 IU/d) of vitamin D during chemotherapy for BC had a statistically significant enhanced disease-free survival [17]. Another dispute that still exists publicly relates to the nutraceuticals' precarious position in cancer therapy as well as their potential to prevent the development of cancer. Do dietary supplements shield cancer cells from chemotherapeutic effects? The stage at which cancer is progressing and their dual function as prooxidants or antioxidants confound the solution. The main causes of mortality and disability are chronic illnesses. Many research have linked nutraceutical phytochemicals to preventive effects against chronic illnesses, although other studies have shown significant discrepancies. The treatment of cancer may be impacted by several possible drug-nutrient interactions [19]. Due to their plentiful sources, low cytotoxicity, and safe ingestion, people have been paying special attention to the function of nutraceuticals in tumour prevention and cancer therapy during the past 10 years [20]. As practically all foods—including fruits, vegetables, beans, and nuts—contain antioxidants, vitamins, or other comparable compounds, this type of warning is difficult to understand. The regular use of high amounts of phytochemical extracts may not be safe or may have harmful consequences. The physiologic (nutritional) dose must be distinguished from the pharmacological dose. Instead, then treating localised lesions, chemotherapy is typically utilised to treat systemic illnesses. Antineoplastic drugs that disrupt cellular activity are used in chemotherapy to kill tumour cells (including replication). This medication therapy damages DNA fatally, which promotes more malignant cell death by apoptosis. Chemoprevention is the use of non-toxic chemicals to stop the growth of cancerous cells. Chemopreventive phytochemicals in plant-derived diets have the capacity to alter the NF-kB-mediated signal transduction pathways that promote the growth of cancer. NF-kB is a transcription factor that modifies the genes involved in cell proliferation, differentiation, adhesion, and survival, which aids in the development of cancer. Among the chemopreventive phytochemicals known to suppress carcinogenesis by blocking NF-kB activation process, there are curcumin (turmeric), catechins (tea), caffeic acid, capsaicin (red chilli), resveratrol (red grapes, peanuts and berries), lycopene (tomato), Beta-carotenes (carrots), 6-gingerol (ginger), ursolic acid (rosemary), ellagic acid (pomegranate), ajoene, allicin, diallyl sulphide (garlic), and many others. Dietary phytochemicals contain anti-inflammatory and anti-oxidative qualities that may aid in chemo preventive activity [33-38].

Free radicals are produced by several chemotherapy drugs to harm cells and kill cancerous cells, however these ROS frequently have adverse effects that last the whole course of treatment. By affecting cancer in its late stages and perhaps changing the trajectory of cancer's metastatic spread, nutritional supplements can work against cancer therapy. For instance, it is known that ginger and ginkgo supplements might interact with warfarin and that garlic has anticoagulant characteristics. The metabolism of the painkiller acetaminophen by cytochrome P4502E1 may be inhibited by the interaction between garlic and its organosulfides [41-44].

Doctors advise against using non-steroidal anti-inflammatory medicines before surgery for this reason. High quantities of OS are produced by chemotherapy medications to kill cancer cells, and this process may reduce the efficacy of the treatment [6, 19].

Despite the fact that cancer is one of the world's top causes of death, there is reason for optimism given the advancements in diagnostic and treatment methods. Early identification of the condition, in particular, can be addressed with better outcomes, and less intrusive therapies seek to improve patient tolerance in Nutrients 2021, 13, 3834 16 of 27 people. The ultimate objective is to lower cancer patient death rates by raising quality-of-life expectations. 90% of cancers can be prevented or reduced by modifying risk factors, such as poor food, environmental pollution, obesity, drinking alcohol or smoking, physical inactivity, and exposure to infectious diseases. Bad eating habits are thought to be the cause of 5–10% of all cancer incidences, making nutrition a crucial component of preserving health [20-24].

The Mediterranean diet, which emphasizes consuming large amounts of fruit, vegetables, dried fruits, legumes, grains, fish, and extra virgin olive oil, as well as a moderate amount of wine and little red meat, eggs, and dairy products, has been identified as the healthiest diet in a number of studies in the scientific literature. The Mediterranean diet has been demonstrated in several clinical and epidemiological studies to be protective against the development of various illnesses, including diabetes, obesity, cardiovascular disorders, and cancer. The majority of plant-based foods fall under the polyphenol class, which is the biggest category of phytochemicals and has been linked to a number of disorders including cancer, cardiovascular disease, diabetes, and degenerative neurological diseases [39,43].

In this review, the anticancer effects of bergamot, oleuropein, curcumin, and quercetin were investigated. The natural substances under consideration, according to the literature, offer a variety of protective actions and have a tendency to lessen changed physiological situations while still preserving cellular homeostasis. A chemical that can selectively discriminate between healthy and altered cells in order to be safe to the first and detrimental to the second is an effective anticancer medication. Since there isn't yet a molecule with these properties, researchers are looking at how natural substances work, which often has less adverse effects than traditional medications. Finding a molecule with antiproliferative effect as well as concurrent anti-inflammatory and antioxidant capabilities is required due to contemporaneous processes likely enhancing tumour transformation and development, such as the inflammatory process and oxidant activity [38,44].

Bergamot, oleuropein, curcumin, and quercetin, the substances taken into consideration and investigated in this study, have all shown this behaviour both *in vitro* and *in vivo*. Reduced cell growth in particular induced antiproliferative and/or death pathways. The molecular structure of these natural substances reflects their antioxidant and anti-inflammatory properties, which prevent the tumour from acquiring traits that might intensify it. These effects were also noticed at the same time. Furthermore, of interest was the fact that some of the processes by which these natural substances worked only affected cancer cells and not their healthy counterparts [19,28,42].

Conclusion

The preclinical evidence on the use of these drugs in anticancer therapy will be fascinating to expand in light of the findings given in this study. The absence of systemic side effects developed by polyphenols and their epigenetic involvement in cancer biology make them

particularly interesting and encourage scientific research to further the information available so that they can be considered a valid support in anticancer therapy. This is despite the fact that there is little information about the bioavailability of natural compounds *in vivo*. Nonetheless, it is crucial to stress that more high-quality research is required to substantiate the therapeutic effectiveness of plant extracts. Certain natural substances can help prevent cancer, either by itself or in combination with a healthy diet. The early phases of carcinogenesis, cancer spread, and metastasis have been suppressed by these natural substances, at least in animal experiments, although more in-depth research is still needed in this field. Including nutraceuticals with antioxidant activity into the diet may aid in cancer prevention by reducing the effectiveness of chemotherapy, whereas nutraceuticals with prooxidant activity may interfere with chemotherapy and increase its potency. This is one of the reasons patients should assess the advantages and disadvantages of using nutritional supplements during and after chemotherapy.

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