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Antioxidants as adjuvant in cancer therapy: A systematic review

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Abstract

While cancer therapies can effectively remove malignant cells from the body, their efficacy is mostly limited to a number of harmful side effects. Antioxidant treatment is therefore frequently necessary to lessen these negative effects by lowering reactive species levels and minimizing chronic oxidative damage. Antioxidants have a crucial role in inhibiting the production of reactive nitrogen and oxygen species as well as their activities. Reviewing the role of antioxidants in the development or prevention of cancer was the goal of this study. It is thought that antioxidants can both prevent and treat different kinds of cancer. As of right now, cancer prevention and treatment have primarily involved consuming natural antioxidant substances. These are unquestionably cell-type- and Reactive Oxygen Species (ROS)-specific, as evidenced by alterations in gene expression, cellular activities, and mechanisms of cell death. By decreasing hydrogen donors or quenching singlet oxygen and postponing oxidative reactions in cancer cells that are actively developing, natural antioxidants eliminate an overabundance of free radical intermediates. The primary topics covered in this study are antioxidant categorization, metabolic regulation, and antioxidant involvement in cancer treatment.

Keywords: Antioxidant; Chemotherapy; Endogenous; Reactive oxygen species; Phytochemicals

1. Introduction

In aerobic environments, oxygen is necessary for life and serves as the primary energy source for maintaining cell viability and metabolism. Owing to its paramagnetic properties, which promote the creation of partly oxidized highly reactive components known as reactive oxygen species (ROS), oxygen also poses a potential risk simultaneously [1]. ROS are byproducts of oxygen metabolism in living things, yet they have a big impact on redox homeostasis and cell signalling. Oxidative stress is a type of stress that occurs when a cell experiences an increase in reactive oxygen species (ROS) due to interaction with either endogenous or external causes. When this happens, the ROS level rises to a harmful point where it defeats the cell's antioxidant defences and avoids removal, staying within the cell [2]. By modifying cellular signalling pathways, causing genomic instability, or triggering immunosuppression, these ROS cause negative oxidative stress, which results in significant alterations in cellular function and metabolism and eventually leads to carcinogenesis [3]. Therapeutic medicines that cause excessive ROS production or reduce cells' ability to scavenge ROS are more likely to cause apoptosis in cancer cells [4].

Chemotherapy drugs can effectively remove rapidly growing cancerous tissues, but they can also affect the mucous membranes of different organs. As a result, cancer patients experience a number of side effects, including anaphylaxis, a different type of cytopenia, toxicity to the liver, heart, nephron, and ear, as well as nausea, vomiting, pain, diarrhoea, alopecia, anorexia, cachexia, inflammation in mucous membranes, and asthenia [5]. To offset these negative effects, antioxidant supplements are frequently prescribed; these supplements can help to mitigate side effects without compromising the effectiveness of treatment [6].

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Carotenoids, polyphenols, and vitamins are the antioxidants that are most frequently advised. Eating fruits and vegetables that are edible is a great way to store various antioxidant phytochemicals with varying capacities. It has been suggested that consuming more than 400g of fruits and vegetables per day can help prevent some cancer kinds [7]-[8]. Antioxidant chemicals have been investigated for their potential to protect several illnesses, including malignant tumours, and are frequently used as dietary supplements [9].

"Any substance that, present in low concentrations compared to oxidisable substrates (carbohydrates, lipids, proteins, or nucleic acids), significantly delays or inhibits the oxidation of the mentioned substrates" [10] is the original definition of an antioxidant given by Halliwell et al. in 1989. The word "antioxidant" refers to chemicals that function to counteract the effects of oxidants. Antioxidants are substances that slow down oxidative damage by inhibiting or squelching free radicals, which are produced naturally in the body during biological processes [11]-[12]. Endogenous antioxidants are those that our bodies naturally produce as a result of metabolic processes. Exogenous antioxidants are those that are introduced into the diet through meals and dietary supplements. Furthermore, a different class of synthetically manufactured antioxidants is also commonly utilised in the food sector [13].

2. Classification of Antioxidants

Based on their source, activity, size, solubility, and method of action, antioxidants can be categorized [14]-[15].

- **Based on Origin** (Natural , Synthetic)
- **Based on Activity** (Enzymatic{Primary and Secondary} , Non-enzymatic)
- **Based on mode of action** (Free radical scavenging, Chain breaking, metal chelating, Synergistic, Hydro peroxide decomposing and Singlet oxygen quenching)
- **Based on Size** (Small, Large)
- **Based on Solubility** (Water, Lipid)

2.1. Endogenous Antioxidants

Antioxidants can come from outside or internal sources. The endogenous antioxidants include both non-enzymatic antioxidants, which are further classified as metabolic and nutrient antioxidants, and enzymatic antioxidants such as catalase, glutathione (GSH) dependent enzymes such as glutathione peroxidases (GPx), glutathione reductases, glutathione S-transferases, superoxide dismutase (SOD), thioredoxin, etc. Bilirubin, coenzyme Q10, GSH, L-arginine, melatonin, uric acid, and other substances are examples of metabolic antioxidants. Lipopoic acid, carotenoids, flavonoids, polyphenols, and vitamins C and E are examples of nutrient antioxidants. Due to their ability to donate their own electrons and neutralize the electrical charge, all of these antioxidants have the special capacity to scavenge and mop up free radicals [16].

Antioxidants should ideally be easily synthesized, chelate redox metals, and remove free radicals to aid in the homeostasis of metabolically active cells. Endogenous antioxidants can have a preventative, scavenging, or often performing radical-induced damage repair effect on cellular free radicals. They are therefore further separated into the following groups [17].

- **First line of defense:** These include catalase, GPx, and SOD, which inhibit the production of free radicals and reactive oxygen species (ROS) by acting on hydrogen peroxides (H_2O_2), alkyl hydroperoxidases (ROOH), and superoxide ($\bullet O_2$) radicals, respectively[18].
- **Second line of defense:** As antioxidants, they scavenge active free radicals by contributing electrons to prevent the start and spread of chains. Later on, these free radicals from scavenging antioxidants transform into less powerful free radicals that are readily neutralized by the first-line antioxidants, such as vitamin E, glutathione, ubiquinol, ascorbic acid, and uric acid.
- **Third line defense:** These are de novo enzymes, such as nucleases, polymerases, peptidases, and lipases that restore cellular functioning by repairing damage produced by free radicals to cellular macromolecules including DNA, protein, and lipid [19].
- **Fourth line of defense:** These antioxidants use signals necessary for the generation of free radicals and are created as part of cellular adaptability [19].

2.2. Exogenous Antioxidants

Many of the exogenous antioxidants are found in nature and function as singlet oxygen ($^1O_2$) anion quenchers or hydrogen donors. They have the power to stop oxidative processes from happening or eliminate free radical

intermediates. Vitamins A, C, E, and diverse phytoingredients are natural antioxidants derived from diets that support cancer cell cycle arrest and death in different ways. It has been demonstrated that plant-based antioxidants, including carotenoids, flavonoids, phenols, and vitamins, inhibit both the early and late phases of carcinogenesis [20]. These reducing agents work against cancer through a variety of mechanisms, including as modifications to cell signalling, adjustments to the way the cell cycle progresses, and control over enzyme activity.

When creating and using new antioxidants in cancer treatment, it is essential to comprehend these antioxidants' methods of action [21]. Figure 1 illustrates oxidative stress and its connection to cancer [22]-[24].

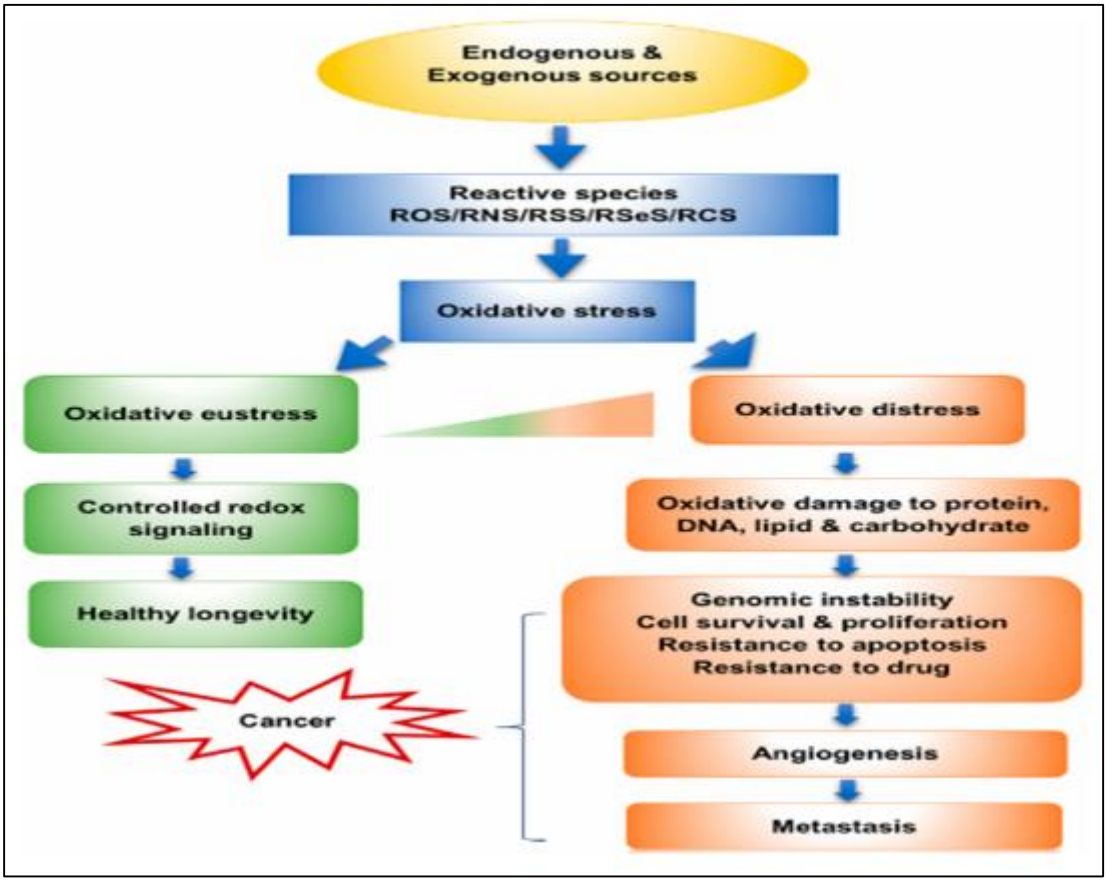

Figure 1 Oxidative stress and its relation to cancer

Table 1 Advantages and Disadvantages of Antioxidant therapies in Cancer

	Advantages	**Disadvantages**	**References**
Antioxidants	Disrupt too many free radicals in healthy cells.	Antioxidants may potentially be beneficial for cancers.	[25]-[26]
	Improvement of the host's resistance against cancer	It may be more effective to avoid cancer than to treat it.	[27]-[28]
	Accessible in an extensive range of fruits and veggies	Delivery to interior organs or tumour mass is difficult.	[29]-[30]
	Extremely quick and transient oxidising	It causes changes in DNA and increases the risk of cancer	[31]-[32]

3. Metabolic regulation of Antioxidants

Glycolysis is essential for highly proliferating cancer cells to fulfill their incredibly high energy needs. The inhibition of pyruvate dehydrogenase (PDH) brought about by the activation of hypoxia inducible factor-1 (Hif-1) opens up glucose transporters and increases glucose flow in the glycolytic cycle. The Warburg effect is the result of Hif-1 switching cell gene expression from Glycolysis to lactate synthesis and utilization under hypoxia [33]-[34]. Fumerate and succinate, two oncometabolites, may interact with Hif-1 to provide a "pseudohypoxic" reaction. Additionally, mutations in p53 reduce the inhibition of TP53-induced Glycolysis and Apoptosis Regulator (TIGAR), which in turn causes the activity of the enzyme glucose-6-phosphate dehydrogenase (G6PD) to be less inhibited. This results in an increase in the metabolic flux via the glycolytic and Pentose Phosphate Pathway (PPP). Two enantiomers of the metabolite 2-HG, D-2-hydroxyglutarate (D2HG) and L-2-hydroxyglutarate (L2HG), result from mutations in the enzyme Isocitrate Dehydrogenase 1/2/3 (IDH1/2/3). These alterations may eventually result in a changed metabolic flow, which would then be the cause of the development of tumours. Strong metabolite flow is shown by thick, solid lines, while weak flux is indicated by dotted lines [35]-[36]. Figure 2 shows how the Krebs cycle's metabolic control of antioxidants takes place [37].

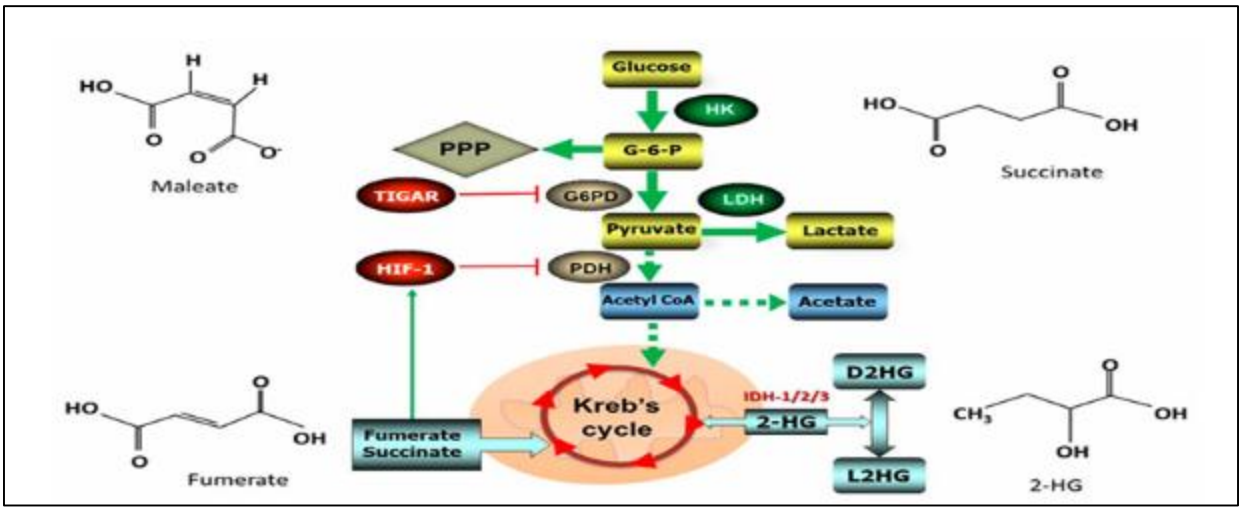

Figure 2 Metabolic regulation of antioxidants

4. Role of Antioxidant in Cancer

After they are created, free radicals have the power to alter the structure and metabolic route of cells, which might result in the production of additional free radicals. This may thus result in more severe tissue and cell damage. Unchecked generation of free radicals is thought to be a primary cause of many illnesses. Antioxidant therapy is a type of medical care that aims to prevent or lessen the negative effects caused by free radicals. Increasing the antioxidant capacity of cells or preventing the generation of ROS is one method of modifying oxidant-mediated cell damage. Antioxidants increase the efficacy of chemotherapy and have a chemo-preventive impact. The kind of antioxidant, its biological characteristics, its concentration at the location of action, and the type of oxidative stress all affect how effective exogenous antioxidants are at preventing oxidative stress in vivo [38]-[39]. A brief overview of alpha-lipoic acid (ALA) and ascorbic acid (AA) will be provided in the upcoming section. Because AA may control the cellular redox state, it induces apoptosis and inhibits cell growth [40]-[42]. It was shown that AA acted as an antioxidant at low concentrations. Low amounts of AA were shown to eliminate oxidative stress and lower ROS in earlier studies. This reduced the amount of free radicals that damaged cells and assisted in preserving the intracellular redox equilibrium. It also plays a part in regulating the production of Ki67, which lowers inflammation by lowering pro-inflammatory cytokines and C-reactive protein. Consequently, AA may be able to slow the growth of tumours in malignancies of the pancreas, breast, kidney, lung, and liver [43]-[45]. Because ALA may scavenge reactive oxygen species (ROS) and replenish endogenous antioxidants, its antioxidant activity is important for cellular proliferation. After being reduced from ALA, dihydrolipoic acid (DHLA) is produced. DHLA has the distinct ability to scavenge free radicals and alters several oxidative stress and inflammatory pathways [46]. The schematic depiction for antioxidant effects on reactive oxygen species (ROS) and/or mechanism of action in cancer cells is shown in Figure 3 (AA: ascorbic acid; ALA: alpha lipoic acid).

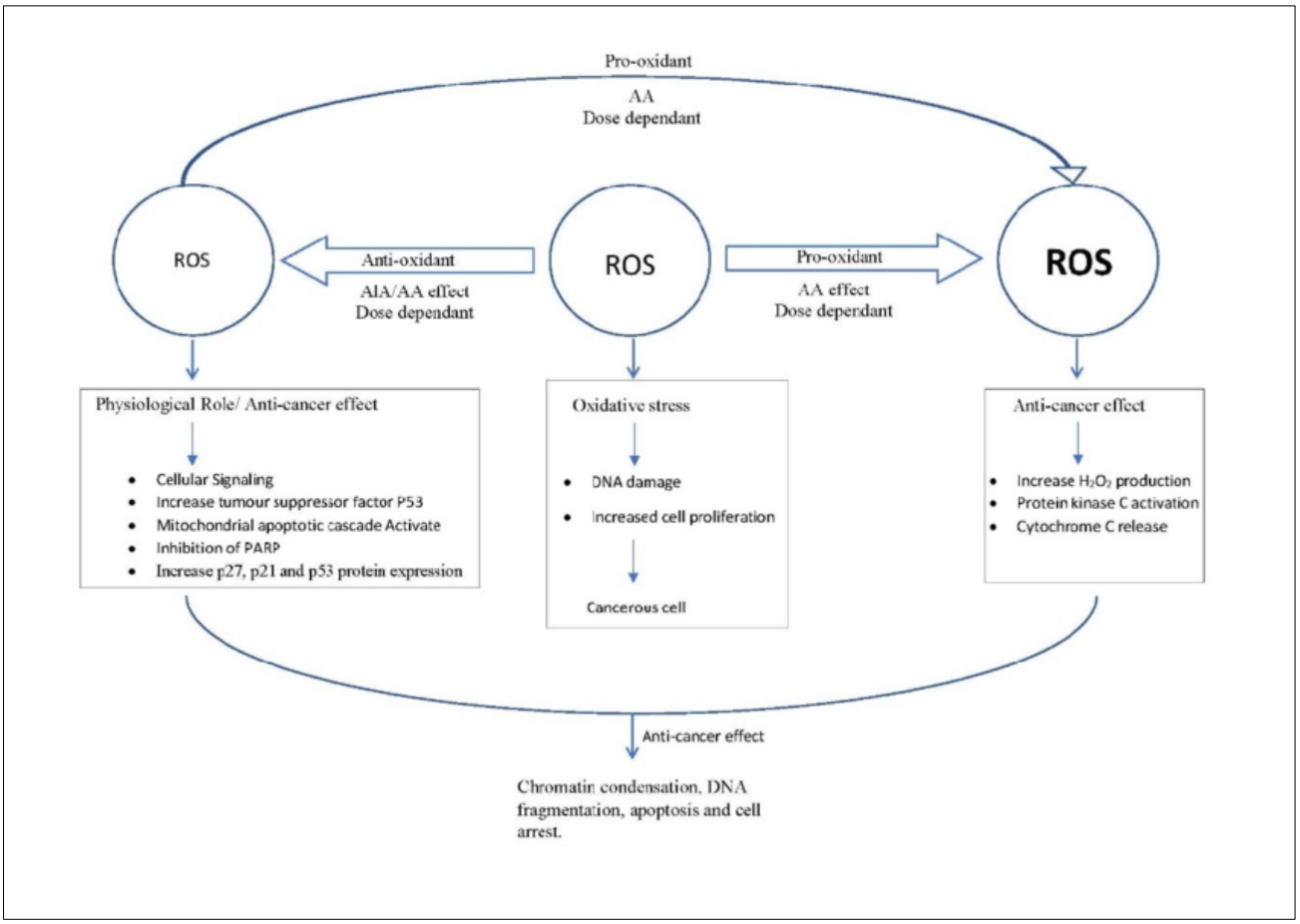

Figure 3 Schematic illustration for antioxidant (AA: ascorbic acid; ALA: alpha lipoic acid)

5. Photochemical Classification of Antioxidants: [47]

Based on their function in plant metabolism, a broad range of chemical substances are referred to as photochemicals and may be divided into primary and secondary metabolites. It has been established that secondary metabolites primarily account for medicinal plants' ability to treat a variety of illnesses [48]. Figure 4 represents the shematic representation of antioxidant classification.

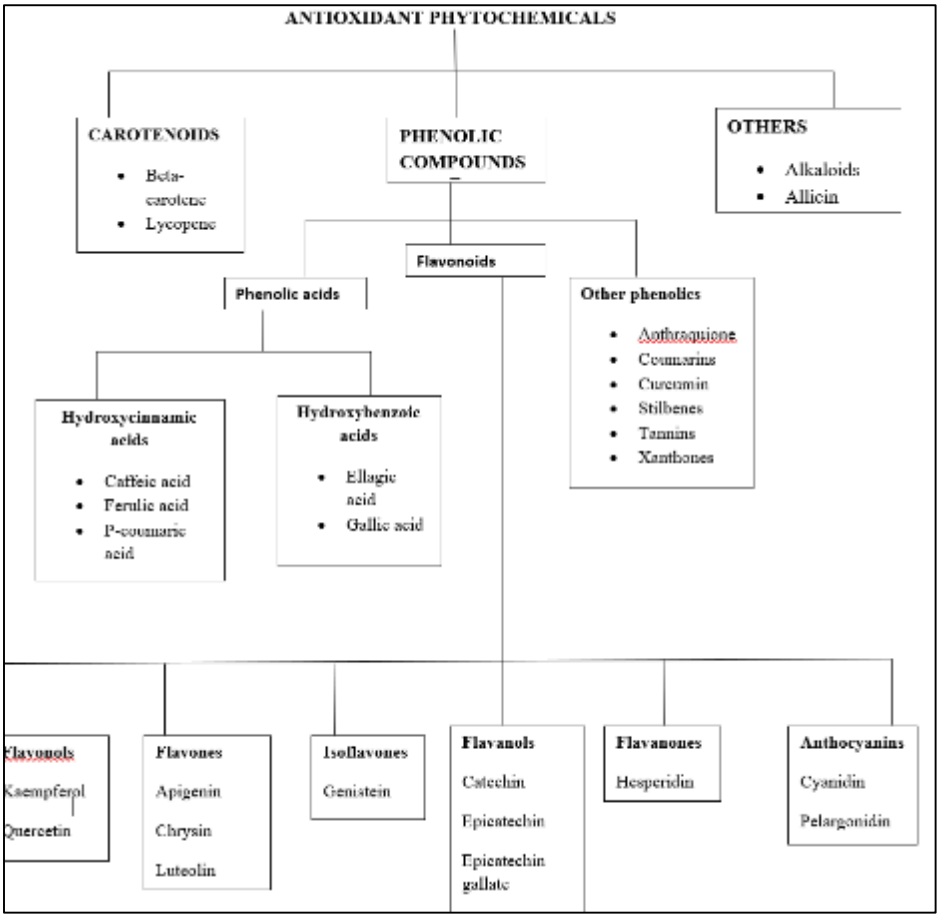

Figure 4 Schematic representation of antioxidants classification

Table 2 List of some Antioxidants showed antitumor activities

Antioxidant type	Cancer type	Mechanism	Reference
Beta-carotene	Human prostate cancer cell line(PC-3)	DNA fragmentation and mitochondrial malfunction are linked to apoptosis	[49]
Alpha-lipoic acid (ALA)	Gastric cancer	STAT3 has contributed to the inhibition of MUC4 caused by ALA. By inhibiting STAT3's interaction to the MUC4 gene's promoter region, ALA reduced the production of MUC4.	[50]
Carotenoids (mainly violaxanthin)	Human colon cancer cells (HCT116)	Apoptosis	[51]
N-acetyl cystein (NAC) and Vitamin E	Lung cancer	ROS-p53 pathway	[52]
Sterols	Human promyelocytic leukemia cell line(HL-60)	Apoptosis	[53]
Tocotrienol	Adenocarcinoma	Oct4, sox2 pathway	[54]
Astaxanthin	Human hepatomacancer cell line(HepG2)	DNA breakage, glutathione depletion, and cell cycle arrest at the G0/G1 phase	[55]
Curcumin	Breast cancer	Reduced development of the malignancy, linked to an increase in G1 arrest and the down	[56]

		regulation of the p38 mitogen-activated protein kinase (MAPK) pathway, which inhibits the activities of cyclins A, D1, E, and CDK2.	

- **Curcumin:** Differentipuloylmethane, or curcumin, is a chemical compound with the formula C21H20O6, a molecular weight of 368.38 g/mol, and a symmetrical molecular structure [57]. The National Cancer Institute [58] has categorized curcumin, a plant polyphenols found in the rhizome of turmeric, as a third generation cancer chemopreventive agent. Numerous investigations have documented curcumin's anticancer actions, which are mediated by the generation of increased ROS [59]-[60]. It has been observed that curcumin raises ROS levels and initiates oxidative stress in the cysteine asparaginase pathway in melanoma, leading to tumour cell death [61].
- **Violaxanthin:** The orange-hued carotenoid known as violaxanthin (VLX) is mostly found in fruits that have the same color as well as in leafy greens and microalgae. There is strong antioxidative action in VLX. It has been documented that the yellow-green microalgae Eustigmatos cf. polyphem produces VLX that demonstrates radical scavenging activity using DPPH and ABTS tests [62]. It has been shown that VLX extracted from Dunaliella tertiolecta and Chlorella ellipsoidea inhibits colon and breast cancer cells, respectively, and also induces apoptosis [63]- [64].
- **Alpha-lipoic acid (ALA):** Thioctic acid, or alpha-lipoic acid (ALA), is a naturally occurring short-chain fatty acid with sulphur in its structure. Because ALA may scavenge reactive oxygen species (ROS) and replenish endogenous antioxidants, its antioxidant activity is important for cellular proliferation. After being reduced from ALA, dihydrolipoic acid (DHLA) is produced. DHLA has the distinct ability to scavenge free radicals and alters several oxidative stress and inflammatory pathways [65]. Previous research has demonstrated that the intercellular redox balance is essential to carcinogenesis and is associated with cellular development. It was suggested that ALA would lessen the high levels of oxidative stress that malignant cells accumulated, which would cause apoptosis and impede cell growth [66]-[68].
- **Sterols:** Microalgae are thought to be a substitute source of several important commercial sterols with medicinal value, such as β-sitosterol, brassicasterol, ergosterol, stigmasterol, and campesterol [69]. Microalgal sterols have anticancer activity in addition to antioxidative action. Nannochloropsis oculate's sterol-containing fraction shown anticancer properties against human blood, lung, liver, and colon cancer cells [70]. Sterols can activate caspase-3, boost Bax/Bcl2, lower blood cholesterol, or inhibit tumour development, metastasis, angiogenesis, and cause apoptosis [71]. Consuming β-sitosterol can prevent tumour growth in human cancer cells, including those found in the colon, liver, prostate, and breast [72].

6. Conclusion

In order to comprehend the therapeutic applications and possible antioxidant qualities of several medicinal plants, the study assessed their primary biological characteristics. The biological characteristics of the plants as a whole, particularly their antioxidant capacities, have been thoroughly investigated. The availability of electrons to neutralise any free radicals is the foundation of the antioxidant activity concept. The availability of electrons to neutralize any free radicals is the foundation of the antioxidant activity concept. Often referred to as "scavengers of free radicals," antioxidants are molecules having the ability to interact with and neutralize free radicals in biological systems. While certain antioxidants have beneficial effects on the treatment of cancer, others have inducer effects on the development and spread of cancer. In order to develop more effective cancer treatments, this should be taken into account in both clinical and experimental antioxidant utilization. Because of their low bioavailability, easy breakdown, and poor penetration across cell membranes and internalization, the use of standard antioxidant-free therapy has been restricted in biomedical studies. A novel nanoantioxidant technology may offer viable ways to improve antioxidant efficacy and enable target delivery in order to get over these obstacles.

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