

Review

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Review

Antioxidants as Nutraceuticals of Phytochemical Nature (Plant Natural Foods) in Disease Prevention and Therapy

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Abstract: Oxidative stress and its relation on the onset of several chronic diseases has been increasingly studied and highlighted in recent years. This fact has been concurrent with increased reports on the antioxidant properties of various phytochemicals derived from fruits, vegetables, herbs, or seaweed, which can be accessible by intake or obtained following chemical extraction from these sources. These phytochemicals are majorly the result of each plant's secondary metabolism, out of which the main chemical groups include structural polysaccharides, unsaturated fatty acids (PUFAs), pigments (chlorophylls, carotenoids, anthocyanins) and chief among them, phenolic compounds. The structural features of each group allow them to act at different sites, levels, by different molecular mechanisms and display diverse effectiveness as chemo-preventive agents for various diseases. Beyond their antioxidant properties, these phytochemicals have been described to exert a plethora of chemo-preventive and therapeutic effects, including anti-inflammatory, antidiabetic, anti-obesity or neuroprotective, acting through various mechanisms and paths involved. This knowledge has led to the development of various nutraceuticals enriched in antioxidant phytochemicals to be used as functional ingredients in foods, or for their periodic separated intake, whether as enriched extracts, or isolated compounds of high efficacy. Overall, phytochemical antioxidants are attractive biomolecules to be used as nutraceuticals of relevant chemo-preventive and therapeutic properties on the onset of various diseases related to antioxidant stress.

Keywords: phytochemicals; natural antioxidants; chemo-preventive; nutraceuticals

1. Introduction

Phytochemicals are secondary metabolites synthesized by plants which comprise a diverse array of chemical groups. These include phenolic compounds, fatty acids, pigments, various polysaccharides, terpenoids, alkaloids, phytosterols or saponins, among others [1]. Phytochemicals have always been a matter of interest, as they serve as extremely relevant agents in medicine, agriculture, food, and various other fields, such as the textile and cosmetic industries. Thus, our world has a strong dependence on phytochemicals with various uses and purposes. However, in recent decades the interest in dietary phytochemicals has risen, as are thought to be of many health benefits such as cardio-protection, neuroprotection, anti-inflammatory effects and improved gut health, among others [2]. These effects are mainly attributed to the antioxidant properties of various

groups of phytochemicals, with phenolic compounds, unsaturated fatty acids (UFAs) or polysaccharides being chief among them [3]. Thus, diets which include more vegetables and fruits that may act as source of phytochemicals have attracted more interest from researchers, industry, and society, with focus on a more conscious and healthy diet. This has also prompted the surge of a nutraceutical industry based on producing purified or selected phytochemicals that have the potential to confer specific health benefits (e.g., phenolic compounds) [4]. These phytochemicals can thus be obtained from different sources. UFAs for example, can be feasibly obtained from oily crops, such as olive, sunflower, rapeseed, sesame, palm or peanut, among others [5]. Therefore, depending on the source, the composition and quantity of fatty acids will vary. These may be obtained from the mentioned fruits and seeds, but also from some less conventional sources like fruits seeds, such as pepper, grape or avocado [6,7]. Microalgae have also been increasingly highlighted as excellent sources of UFAs of interest in recent years [8]. Given their nature and metabolic function as reducing agents, plant pigments are used as colorants and antioxidants. Carotenoids can be distinguished between carotenes, which include carotene and lycopene, and xanthophylls, with some main examples being lutein, zeaxanthin or lycopene [9]. Moreover, they can be further distinguished between provitamin A carotenoids, which include carotenes and β -cryptoxanthin, and non-provitamin A carotenoids, including mainly xanthophylls [10]. Intuitively, carotenoids can be obtained from yellow, orange, and red-colored fruits and vegetables, with higher concentrations in the peels of these. Moreover, in recent years, both seaweeds and microalgae have become feasible and cost-effective sources of carotenoids, with some major examples being fucoxanthin from brown seaweeds and astaxanthin from red microalgae [11]. In this sense, carotenoids have been highlighted as relevant phytochemicals with various potential health benefits, ranging from their nutritional value as precursors of vitamin A to health-related properties such as antioxidant, metabolic modulation, anti-inflammatory or neuroprotective [12]. Polysaccharides with health-related properties tend to be structural polysaccharides. This means that polysaccharides serve as structural support to the plant organism. Among these, cellulose, hemicellulose or pectin are the major polysaccharides present in plants that constitute dietary fiber [13]. These polysaccharides may be found more abundantly in the "harder" parts of plants, such as seeds, leaves or peels, and are of high interest as promoters of healthy gut microbiota [14]. However, storage polysaccharides (that act as stored energy) include starches and other polysaccharides, such as fructans. These are more abundant in bulbs, tubers and pulps [15]. Beyond these, phenolic compounds are antioxidant phytochemicals of paramount importance that have been exhaustively studied in the last two decades and have a ubiquitous distribution in the plant kingdom. Phenolic compounds are phytochemicals with great antioxidant activity and are synthesized in response to biotic (predators, infections) or abiotic (drought, salinity) factors [16]. The diverse structural complexity and degree of polymerization of phenolic compounds also determine their bioavailability, activities, and occurrence. Some well-known examples of phenolic compounds and sources include tannins and catechins in grapes or tea, flavonoids in citrus or anthocyanins in berries [16]. Moreover, given their metabolic role in the plant, peels and leaves are usually the fractions of fruits and vegetables that contain the greatest concentration of them [17]. Altogether, there is a great interest in these phytochemicals, either by chemical or/and microbial synthesis, as these methods are more economically feasible and consistent [18]. Although these methods may be cost-effective, chemical extraction of phytochemicals from their natural sources is becoming increasingly extended, especially using fruit and vegetable agri-food waste as source of phytochemicals [19].

In this review, we discuss the role of antioxidants in plants, their significance in the mitigation of oxidative damage, and their implications for plant resilience and human overall health.

2. Chemical Classes of Antioxidant Phytochemicals: Structural Significance

2.1. Unsaturated Fatty Acids

Fatty acids are hydrophobic aliphatic carbon chains of variable length that contain a carboxyl (-COOH) group at the end of the chain [20]. The fatty acids with no double bonds present are called saturated fatty acids (MFAs), whereas those that present at some point of the chain a double bond are called UFAs. In addition, fatty acids can also be distinguished depending on their stereochemistry, presenting *cis* or *trans* isomers, with *cis* being more prevalent in plants, and *trans* in animal fats [21]. In the case of plant organisms, fatty acids may usually present a length in the range of 12 to 22 carbons, with 16 and 18 being generally the most abundant [22]. Among MFAs, plant organisms generally accumulate palmitic (C16:0) and stearic (C18:0) acids. Moreover, plants are the main source in nature and thus in the human diet of UFAs, with some major representatives being oleic acid (C18:1) and linoleic acid (C18:2) [5].

2.2. Carotenoids

Carotenoids represent a class of pigments naturally produced by plants, fungi, algae, and specific bacteria [23]. These compounds are responsible for the vibrant red, yellow, and orange colors seen in various fruits and vegetables [24]. Structurally, carotenoids are classified as tetraterpenoids, composed of a 40-carbon polyene chain, providing their antioxidant properties [25]. This antioxidant capacity arises from their ability to neutralize reactive oxygen species (ROS) and neutralize free radicals, providing protection against oxidative stress, which is linked to diseases such as cancer and cardiovascular conditions [26]. The conjugated double bond system present in the structure of carotenoids facilitates electron delocalization, thereby increasing their ability to neutralize free radicals and singlet oxygen [27]. Additionally, their antioxidant efficiency is modulated by the degree of unsaturation and the presence of functional groups, like hydroxyl (-OH) or keto (C=O) groups [28].

Based on their structure, carotenoids can be divided into two primary categories based on their chemical structure: carotenes, which are purely hydrocarbons, and xanthophylls, which contain oxygenated groups [29]. The functional groups in xanthophylls generally improve their solubility and interaction with cellular membranes, potentially influencing their antioxidant effectiveness [30]. In fact, the presence of additional oxygen-containing groups often makes xanthophylls more potent antioxidants compared to carotenes [31].

Plants, algae, and fungi can produce different isomers of carotenes, with α -carotene and β -carotene being the most prevalent in plants (Table 1). Other isomeric forms include γ -carotene, δ -carotene, ϵ -carotene, and ζ -carotene. Both α -carotene and β -carotene serve as precursors to vitamin A [32], although β -carotene exhibits greater antioxidant activity compared to α -carotene [33]. Among xanthophylls, key molecules include fucoxanthin, astaxanthin, lutein, zeaxanthin, and β -cryptoxanthin [29]. These compounds are recognized for their strong antioxidant properties, which play a role in their anticancer, anti-inflammatory, and neuroprotective effects, as well as their ability to enhance immune responses [29,34]. Owing to these attributes, carotenoids hold considerable potential for therapeutic use in managing OS-related diseases [35]. The variation in their efficacy stems from differences in their structural characteristics, such as terminal functional groups and chain length [29]. For instance, lutein and zeaxanthin, commonly found in leafy greens, are known to accumulate in the retina's macular region, where they filter harmful blue light and serve as powerful antioxidants [34].

Additionally, several studies support the inclusion of carotenoids in functional foods and dietary supplements, linking their intake to a reduced risk of chronic diseases, including cardiovascular disorders, specific cancers, and age-related macular degeneration [24]. Their role as precursors to vitamin A further enhances their significance in promoting visual health and supporting the immune system [36]. The numerous benefits of these compounds have favored the inclusion of these molecules as ingredients in the development of nutraceuticals aimed at improving health and preventing diseases.

2.3. Polysaccharides

Polysaccharides are complex polymers composed of monosaccharide units connected by glycosidic bonds, widely distributed in plants, fungi, algae, and certain bacteria [37]. These natural polymers have attracted significant attention due to their potential as nutraceuticals, particularly for their antioxidant, immunomodulatory, and anti-inflammatory activities [38,39]. As antioxidants (Table 1), polysaccharides protect biological systems by neutralizing ROS, limiting free radical damage, and shielding cellular components from OS [40]. Their protective effects are mediated through the regulation of antioxidant signaling pathways, enhancement of the body's antioxidant enzyme defenses, and reduction in ROS production. Additionally, polysaccharides prevent ROS-induced tissue damage through both free radical scavenging and modulation of the immune response [41,42]. However, under specific conditions, certain polysaccharides may also exhibit prooxidant behavior, adding complexity to their antioxidant profile [40,43].

Overall, the antioxidant capacity of polysaccharides is influenced by multiple factors rather than a single property [44]. Structural features such as monosaccharide composition, glycosidic linkages, molecular weight, and branching degree contribute to their antioxidant activity [45]. Moreover, polysaccharides with higher molecular weights, increased branching, or specific functional groups, such as sulfate or carboxyl groups, often demonstrate stronger antioxidant potential [46,47]. Moreover, the method of extraction plays a crucial role in determining their functional properties [48,49]. The ability of polysaccharides ability to donate electrons or protons, chelate metal ions, and scavenge free radicals forms the foundation of their antioxidant mechanism [44]. However, despite the established antioxidant potential of polysaccharides, there is limited research on highly purified forms, making it important to consider the possible influence of other bioactive components, such as proteins, peptides, or polyphenols, which may be present in combination with polysaccharides [44].

Polysaccharides are classified into different groups based on their structure, origin, and function. Structurally, they can be divided into heteropolysaccharides (e.g., hyaluronic acid, chondroitin sulfate, heparin) and homopolysaccharides (e.g., fructans, galactan, glycogen) [50]. Based on their source, they are categorized into several groups: plant-based (e.g., pectin, cellulose, starch), microbial-based (e.g., curdlan, dextran, bacterial cellulose), fungi-derived (e.g., β -glucans, chitin derivatives), animal-derived (e.g., chitosan, chitin, heparin), and marine-derived (e.g., agar, alginate, fucoidans) [51]. Polysaccharides like pectin, rich in galacturonic acid, exhibit significant antioxidant properties. This bioactivity is influenced by the uronic acid content and degree of polymerization [52]. Moreover, sulfated polysaccharides from marine algae are particularly effective in neutralizing free radicals and chelating metal ions, enhancing their antioxidant performance [53].

The growing recognition of polysaccharides' antioxidant properties underscores their potential in nutraceutical development, as they not only combat OS but also offer additional health benefits [49]. Therefore, the ability of polysaccharides to address OS, as well as other bioactivities, make these compounds valuable substances in the nutraceutical market for dietary supplements and functional foods. [54]. Ongoing research continues to shed light on the mechanisms by which these polysaccharides exert their health-promoting effects, opening new avenues for their use in preventive and therapeutic nutrition [55]. Moreover, beyond their role as prebiotics, polysaccharides are also widely utilized in industry for various functions, including as thickeners, emulsifiers, stabilizers, gelling agents, and controlled-release agents, broadening their applications [50].

2.4. Phenolic Compounds

Phenolic compounds, a diverse group of secondary metabolites, are produced by plants primarily in response to environmental stress factors such as drought, extreme temperatures, UV exposure, pollution, and pathogen attacks [56]. Their biosynthesis follows pathways like the pentose phosphate, shikimate, and phenylpropanoid routes [57]. Chemically, phenolics are defined by the presence of one or more hydroxyl groups attached to an aromatic ring, though their complexity varies across different subclasses. These compounds encompass a broad range of molecules, including phenolic acids, flavonoids, stilbenes, lignans, and related structures like chalcones, humulones, and alcohols [56,58].

These compounds are classified according to their structure, with more than 8,000 variations currently identified. The classification is typically based on the number of phenolic rings and the nature of the linkages between them. Major groups include phenolic acids, flavonoids, stilbenes, and lignans [59].

Phenolic acids are divided into two main categories: hydroxybenzoic acids (such as gallic acid) and hydroxycinnamic acids (including caffeic, ferulic, and coumaric acids) [59,60]. These acids are widely recognized for their ability to neutralize free radicals, reducing oxidative damage in cells. Flavonoids, another key category, have a C6–C3–C6 backbone and are further categorized into subgroups like flavonols, flavones, isoflavones, anthocyanins, flavanones, flavanols, and chalcones [60]. In plant cells, flavonoids are typically stored as glycosides, and their antioxidant potential is influenced by the degree of glycosylation. Aglycones like quercetin and myricetin are generally more potent antioxidants than their glycoside forms [61].

Tannins, another class of phenolics, are categorized into hydrolyzable tannins (e.g., gallotannins, ellagitannins) and condensed tannins (e.g., proanthocyanidins). These compounds are known for their protein-binding capabilities, contributing to the astringent taste of certain fruits and their antimicrobial activities [59,62].

Additionally, some phenolics like curcumin (diferuloylmethane) display a broad spectrum of biological functions, including antioxidant, anti-inflammatory, antimicrobial, antitumor, and liver-protective effects [63]. The structure of phenolic compounds is closely linked to their bioactivity, with different chemical arrangements providing specific biological functions [64,65].

Given their broad spectrum of bioactivities, phenolic compounds are increasingly being incorporated into nutraceuticals and functional foods aimed at improving human health and preventing chronic diseases [66]. Furthermore, these compounds contribute to the sensory qualities of many plant-based foods and beverages, particularly in terms of flavor and color [67]. In the context of human nutrition, phenolic compounds are known for their strong antioxidant properties (Figure 1) and represent a significant portion of the antioxidant content in plant-based foods [68]. In terms of dietary applications, phenolic acids are commonly found in functional foods due to their beneficial health effects, such as reducing inflammation, preventing allergic reactions, and offering cardiovascular protection [69]. As research continues to elucidate the specific mechanisms underlying their health benefits, phenolic compounds hold promise as key ingredients in the development of novel therapeutic agents and functional food products [69,70]. Additionally, phenolic compounds have extensive applications in the food, cosmetic, and pharmaceutical industries, where they are used for their antioxidant and preservative properties, as well as their ability to improve the stability and shelf life of products [2].

Table 1. Concentration and antioxidant activity of antioxidant phytochemicals in principal sources: data from chemical assays.

Class	Compound	Main source	Concentration	Assay	AA	Ref.
UFAs*						
ω-3	ALA	Olive, sunflower, linseed, rapeseed, fruit and vegetable seeds, other oily seeds, other oily crops	5.5–61.5%	ROS	16.86 mM	[71–74]
	EPA	Seaweed, microalgae, fish oil	6.6–22.5%	ROS	150 μM	[75,76]
	DHA	Seaweed, microalgae, fish oil	1–6.6%	ROS	100 μM	[75,77,78]
ω-6	LA	Olive, sunflower, linseed, rapeseed, nuts, fruit and	16.5–62.5%	ROS	39.5 mM	[71,74,79–81]

			vegetable seeds, other oily crops				
ω-7	PA	Olive, nuts, macadamia nuts, microalgae	0.6-50.1	-	-	[82-86]	
ω-9	OA	Microalgae, linseed, rapeseed, nuts, fruit and vegetable seeds, other oily crops	1.4-79.6%	SOD	53.1 mM	[74,75,83,87- 89]	
Carotenoids							
Carotenes	α-carotene	Carrots, pumpkins	13.44-30.11 mg/kg fw	ROS	40.6 μmol TE/g dw	[90,91]	
	β-carotene	Carrots, red peppers, oranges, potatoes, green vegetables	41.60-71.2 mg/kg fw	ROS	7.2 μmol TE/g dw	[90,91]	
Xanthophylls	Fucoxanthin	Brown algae	0.02-18.60 mg/g dw	ROS	201 μg/mL	[29,92]	
	Astaxanthin	<i>Haematococcus pluvialis</i>	3.8 %	ROS	1.33 mM	[93]	
	Lutein	Microalgae, algae, vegetables (i.e., kale, spinach)	0.7-5% dw	ROS	1.8-22 μg/mL	[94]	
	Zeaxanthin	Red and brown seaweed, red/orange vegetables/fruits	0.49-1230 μg/g dw	ROS	2.2 μg/mL	[29,95]	
	β- cryptoxanthin	Algae, red/orange vegetables/fruits	409-1103 μg/g dw	ROS	38.30 μg/mL	[96,97]	
Polysaccharides							
HE	Hyaluronic acid	<i>Streptococcus</i> spp., <i>Tremella fuciformis</i>	1300 μg/mL	ROS	69.2- 78.4%	[98,99]	
	Chondroitin sulfate	Bacteria and cartilage	-	Metal cations chelation	3.33 mg/mL	[100,101]	
	Heparin	Marine organism, Asteraceae	-	Enzymatic antioxidants	2.20 mg/mL	[102,103]	
HO	Fructan	Prokaryotes, lower and higher plants	0.9-1.8 g/100 g in different wheat cultivars	antioxidants, metal cations chelation	0.12 mg/mL	[15,104]	
	Galactan	Seaweeds, seeds of some plants	-	SOD and GSH-Px	9 μM	[105]	
Plant	Pectin	Cell walls of terrestrial plants	Citrus peels 30% fw, oranges 0.5- 3.5 % fw, carrots 1.4 % fw	ROS	161.94 ppm	[106,107]	
	Cellulose	Cell walls of terrestrial plants	40-50% fw	ROS	80.9 ppm	[108,109]	
	Starch	Cereals, pseudocereals, umes	60-75 % fw	ROS	97 μg/mL	[110,111]	

Microbial	Curdlan	<i>Agrobacterium</i> sp., <i>Rhizobium</i> sp.	34.04 mg/g	ROS	82 % DPPH, 72% ABTS	[112,113]
	Dextran	Lactic acid bacteria	580 mg/100 mL dw	ROS	97 µg/mL	[114,115]
	Cellulose	<i>Acetobacter</i> spp., <i>Sarcina</i> spp., <i>Agrobacterium</i> spp.	60.7 % dw	ROS	80.9 ppm	[108,116]
Fungi	β-glucans	Mycetes' cell walls	31% dw	ROS, antioxidant enzyme	161-4019 µg/mL	[117,118]
	Chitosan	Cell wall of filamentous fungi	20-45% dw	ROS	0.022 mg/mL	[119,120]
Marine	Fucoidan	Brown seaweed	20% dw	ROS	0.058 mg/mL	[121,122]
	Alginate	Brown seaweed	20-60 % dw	ROS	121.4- 346.3 mol/g	[123,124]
	Cellulose	Green algae	1.5-34 %dw	ROS	0.15- 0.39 mg/mL	[116,125,126]

Phenolic compounds						
Total PC	-	<i>Phoenix dactylifera</i> var Bunarinja	34.90 mg/ 100g fw	ROS	0.875 µg/mL	[127]
Phenolic acids	Caffeic acid	Green coffee	6.56 µg/mL	ROS	6.31 µg/mL	[128]
	Cichoric acid	<i>Echinacea purpurea</i>	56.03 mg/g dw	ROS	15 µg/mL	[129]
	Ferulic acid	Rice bran	8.71 mg/g	ROS	9.9 µg/mL	[130,131]
Flavonoids	Quercetin	Onion skin	2, 122 mg/g	ROS	62.27 µg/mL	[132]
	Myricetin	Green tea	0.40-0.79 mg/g	ROS	4.68 µg/mL	[133]
	Apigenin	<i>Gentiana veitchiorum</i>	37.50 mg/L	ROS	8.26 mg/mL	[134]
Total tannin	-	Ginger	35.08 mg/g	ROS	1 mg/mL	[135]
	-	Garlic	7.44 mg/g	ROS	3.7 mg/mL	[135]
	-	<i>Myristica fragrans</i>	14.03 % w/w	ROS	89.98 µg/mL	[136]

Abbreviations: UFAs: unsaturated fatty acids, EFAs: essential fatty acids, OA: oleic acid, DHA: docosohexanoic acid, EPA: eicosapentaenoic acid, HE: heteropolysaccharides, HO: homopolysaccharides, PC: phenolic compounds; dw: dry weight; fw: fresh weight; ROS: reactive oxygen species; AA: antioxidant activity (IC₅₀).

*UFAs concentrations are presented as % of total fatty acids. ns: not specified.

3. Chemopreventive and Therapeutic Properties of Antioxidant Phytochemicals

Many studies have explored the link between dietary intake and cancer mortality, predominantly focusing on pre-diagnosis intake and overall cancer mortality. However, evidence remains inconclusive, with mixed results on the impact of fruits, vegetables, nuts, legumes, and olive

oil on cancer outcomes (Figure 1) [137]. Despite this, diets rich in plant-based foods are generally associated with reduced cancer risk. This suggests that dietary phytochemicals from various plant species hold potential for cancer chemoprevention [138]. This section will explore *in vivo* and *in vitro* studies on the biological properties of phytochemicals, highlighting their effects and mechanisms (Table 2). Their activities, e.g., antioxidant, neuroprotective and anti-inflammatory, will be classified and related to specific compounds.

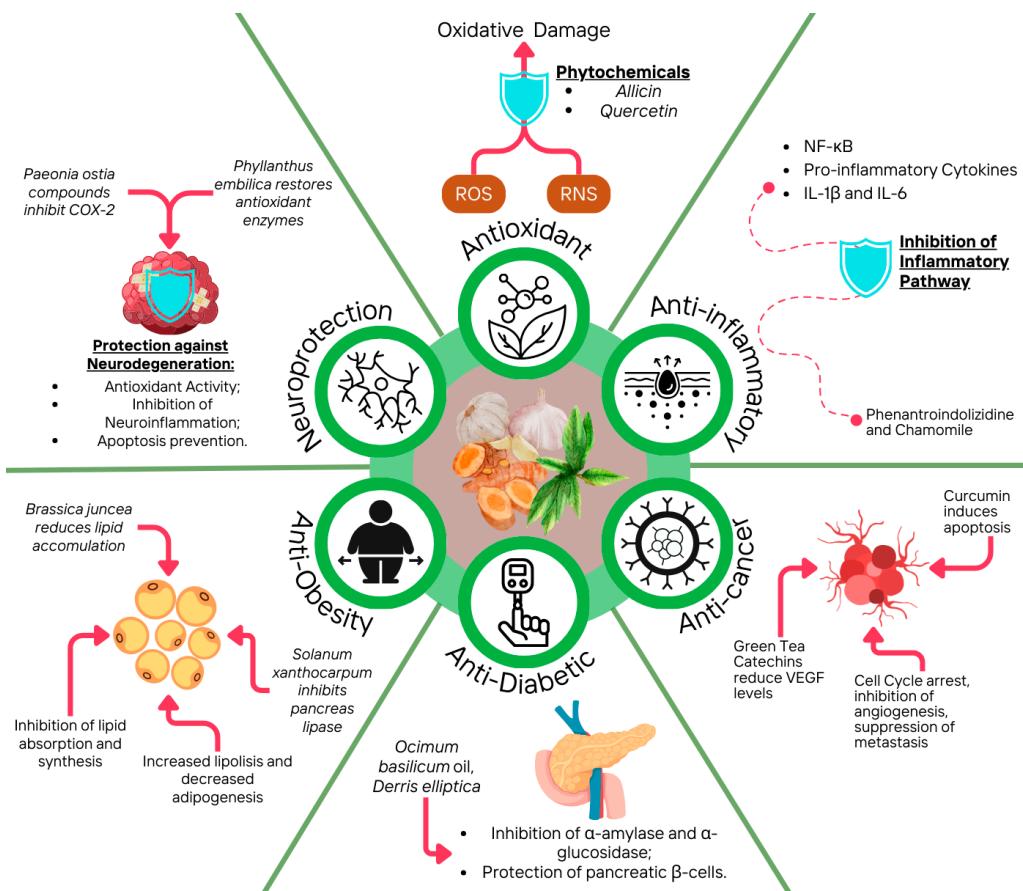


Figure 1. Overall view of the therapeutic properties of antioxidant phytochemicals.

3.1. Antioxidant

Antioxidants and phytochemicals act through two main mechanisms: chain breaking by donating electrons to free radicals, and removal of ROS/reactive nitrogen species (RNS) by quenching their catalysts. These processes are critical in the prevention and treatment of cancer [139]. In a recent study, authors examined the antioxidant properties of allicin, a phytochemical from garlic, in *in vitro* and *in vivo* models of cholangiocarcinoma (CCA). Allicin was found to reduce OS and inhibit the signal transducer and activator of transcription 3 (STAT3) signaling pathway, which promotes tumor growth. The study demonstrated that allicin suppressed CCA cell proliferation, migration, and invasion, while inducing apoptosis. Its dual action as an antioxidant and inhibitor of tumor-promoting signals suggests allicin could be a promising therapeutic option for CCA [140].

In a study of HS-1793, a plant-derived resveratrol analog demonstrated its ability to enhance the efficacy of radiation therapy. HS-1793 improved lymphocyte proliferation, reduced DNA damage in irradiated mice, and decreased interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β) levels. It also decreased regulatory T cells (Tregs) and inhibited CD206 $^{+}$ tumor-associated macrophages (TAMs), highlighting its potential as an antioxidant and immunomodulatory agent in cancer treatment [141]. An *in vivo* study evaluated the phytochemicals green tea (*Camellia sinensis*) catechins and curcumin (*Curcuma longa*) for chemopreventive effects in a hamster buccal pouch

carcinoma model. Green tea polyphenols reduced vascular endothelial growth factor (VEGF) levels and inhibited angiogenesis, while curcumin induced apoptosis through cytochrome c release and caspase activation. Both agents reduced cell proliferative and angiogenic activity, and when combined, they were more effective at inducing apoptosis and cell cycle arrest [138]. In one study, dicoumarol (DC), a coumarin-like compound, exhibited anti-proliferative potential by disrupting key cellular processes, including cell proliferation and survival. It effectively reduces cell viability and induces apoptosis in several cell tumor lines. Additionally, DC increases OS by disrupting antioxidant defenses. Importantly, it does not harm mouse ovarian tissue or developing oocytes, suggesting its promise as a chemopreventive agent without adverse effects on fertility [142]. The aqueous extract of *Fagonia cretica* was tested for its effects on breast cancer cell lines. The results proved that the extract induced cell cycle arrest and apoptosis through both p53-dependent and independent mechanisms. Specifically, it led to a significant increase in Tumor Protein p53 and Forkhead Box O3 (FOXO3a) expression [143]. On the other hand, plant-derived quercetin exhibited chemopreventive effects in HepG2 (human liver cancer) cells by reducing ROS, downregulating phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC), and cyclooxygenase-2 (COX-2), while increasing pro-apoptotic p53 and BAX expression, highlighting its antioxidant and anticarcinogenic action [144]. One *in silic* and *in vitro* study attributed *Markhamia lutea*'s strong antioxidant properties primarily to its rich phytochemicals, including flavonoids and phenolic acids, which effectively scavenge free radicals and reduce OS by neutralizing ROS and chelating metal ions[145].

A study on *Elephantopus mollis* Kunth. highlighted 3,4-di-O-caffeyl quinic acid for its significant antioxidant activity and chemopreventive properties, including apoptosis induction in NCI-H23 (human lung adenocarcinoma) cells and β -glucosidase inhibition [146]. Finally, the leaf extract of *Onobrychis argyrea* has demonstrated significant antioxidant, anti-diabetic, anti-Alzheimer's disease and anti-cancer *in vitro* properties. It induced apoptosis in human colorectal adenocarcinoma (HT-29) cells by disrupting mitochondrial membranes and activating caspases, and showed high antioxidant activity, enzyme inhibitory activities and strong anti-cancer capacity [147].

3.2. Anti-Inflammatory

Anti-inflammatory phytochemicals may help prevent cancer by targeting inflammation-related mechanisms. They induce cell cycle arrest by inhibiting cell cycle regulators, leading to halted cancer cell proliferation [148]. Moreover, they promote apoptosis by upregulating pro-apoptotic proteins and caspases while downregulating anti-apoptotic factors, thus facilitating cancer cell death [149]. They also promote autophagy by upregulating autophagy-related proteins and inhibit mTOR signaling, leading to the elimination of damaged cells. These combined effects decrease inflammation and suppress tumor progression [150]. For instance, phytochemical phenanthroindolizidine alkaloids from *Tylophora ovata* exhibit anti-inflammatory and chemopreventive properties against triple-negative breast cancer (TNBC). O-methyltylophorinidine (1) and its synthetic form (1s) inhibit nuclear factor kappa B (NF κ B), arrest the cell cycle, reduce spheroid growth, and block invasion [151].

In one study, real-time PCR analysis showed that *Mangifera indica* polyphenols (mainly gallic acid, hydroxybenzoic acid hexoside, and hydro- lysable tannins such as monogalloyl-glucoside) reduced Nuclear Factor kappa B (NF- κ B) expression and phosphorylation in tumor necrosis factor-alpha (TNF- α)-treated MCF-12A cells, indicating anti-inflammatory effects. Mango identified phytochemicals also upregulated microRNA-126 and downregulated microRNA-21 and modulated the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) signaling pathway [152]. *Commiphora leptophloeos* extract, rich in phenolic acids and flavonoids, showed anti-inflammatory effects through downregulation of NF- κ B/COX-2 and reduction of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6). This suggests its potential in the treatment of inflammatory bowel disease (IBD) [153]. The anti-inflammatory activity of *Helicteres isora* fruit extracts has been focused on its effects on pro-inflammatory mediators such as Prostaglandin E2 (PGE-2), COX-2, and Tumor Necrosis Factor-alpha (TNF- α). In the investigation, Enzyme-Linked Immunosorbent Assay (ELISA) assays were used to measure the inhibition of the production of PGE-

2 in LPS-stimulated Human Monocyte Cell Line THP-1 (THP-1 cells). Compared to celecoxib, a known COX-2 inhibitor, the hexane extract showed the strongest inhibition of PGE-2 (69.68%), followed by ethanol extract (57.17%). All extracts were less effective than dexamethasone, a standard anti-inflammatory drug, but the hexane extract showed 51.61% inhibition of TNF- α [154]. The extract of *Euphorbia hirta* has been shown to have anti-inflammatory activity in vitro, which is relevant to its potential chemoprotective effects. By reducing nitric oxide (NO) production through inhibition of inducible NO synthase (iNOS), *E. hirta* can help to lower inflammation, a known contributor to cancer advancement. Chronic inflammation can facilitate tumor growth and spread, so the extract's ability to suppress NO and inflammatory cytokines may play a role in its anticancer properties. Besides, compounds such as 5-hydroxymethylfurfural (5-HMF) in the ethanol extract are known for their anti-inflammatory effects, supporting the extract's potential to moderate cancer risk by managing inflammation [155]. Chamomile phytochemicals, including β -amyrin, quercetin, and lupeol, act as NF- κ B inhibitors and induce G2/M cell cycle arrest. These compounds lower pro-inflammatory cytokines IL-1 β and IL-6 and also interact with microtubules, which supports their potential as anti-cancer modulators of inflammatory pathways [156].

3.3. Antidiabetic

Diabetes mellitus is a metabolic syndrome condition which increases the levels of glucose in the blood [158,159]. The main chronic complications of this disease are linked to the level of exposure of patients with hyperglycemia [158]. Despite the availability of chemical drugs acting as therapeutical agents, there is a will to find natural alternatives to control the complications derived from the disease and improve glycemic control and glucose intolerance [159]. In this sense, traditional medicine revealed several molecules present in plants with antidiabetic activity, as well as their mechanisms of action [158].

For instance, leaves extracts have been widely studied to determine their antidiabetic potential. An in vivo and in vitro study investigated the volatile and phenolic compounds present in *Ocimum basilicum* L. essential oil to determine its potential antidiabetic activity. Chemical agent streptozotocin (STZ) (50 mg/Kg of body weight) was used as a model to induce diabetes mellitus (DM) in Wistar Albino rats. After 28 days of feeding with basil essential oil (70 mg/Kg of body weight), rats showed a protection effect in pancreatic β -cells and a decrease in blood glucose levels. Regarding in vitro assays, both α -amylase and α -glucosidase inhibitory activity were studied, showing a strong inhibition potential. Authors linked the antidiabetic effect of basil essential oil to the phenolic and flavonoid compounds content. However, the mechanism of action was not elucidated [160]. In another in vivo study, *Derris elliptica* methanolic leaf extract phytochemical profile and antidiabetic potential was determined. STZ was used to induce DM in Sprague Dawley rats and after 14 days feeding with the plant's extract at 2 different concentrations (200 and 400 mg/Kg body weight), results showed hypoglycemic effect, and reduction of cholesterol levels in a dose dependent manner. Moreover, the highest dose increased serum insulin levels, and antihyperglycemic effect was shown. Although authors did not explained the mechanism of action, quercetin was the compounds linked to these antidiabetic properties [159]. *Eugenia sonderiana* leaves extracts were also studied to determine the antidiabetic potential and to develop a structure-activity correlation. Both in vivo and in vitro studies were assessed, showing great α -amylase and α -glucosidase inhibitory activity, reduction of glucose and pancreatic enzymes and triglycerides, while HDL cholesterol levels were maintained within normal ranges. To explain the antidiabetic ability of *Eugenia sonderiana* leaves extracts, authors suggested a synergistic effect between polyphenols by increasing glycogen synthesis and α -amylase, and saponins by a complex formation with the cholesterol [158].

3.4. Antiobesity

Obesity is becoming a significant health problem worldwide. This condition contributes to the increase of prevalence of chronic diseases, including T2D, hypertension, dyslipidemia, cardiovascular diseases and some types of cancer [161,162]. Common strategies to decrease the

incidence of obesity are physical activity, surgery, drugs, and diet modifications [162]. In this regard, natural compounds present in plants have been suggested as potential chemicals to be used for both prevention and treatment of obesity [162]. Several studies have assessed the anti-obesity potential of phytochemicals. For instance, green tea has been traditionally used as a medical plant, and scientific studies have revealed its potential used for obesity prevention. In vitro results regarding green tea leaves suggest the anti-obesity potential of this plant by inhibiting adipocyte differentiation and proliferation [163].

In a study, C57BL/6J mice fed a high-fat diet supplemented with 0.25% *Rosa centifolia* polyphenols for 35 days showed decreased body weight and adipose tissue, as well as reduced serum cholesterol and hepatic triglyceride levels. The treatment increased fecal triglycerides and increased lipolysis-related proteins while suppressing lipid synthesis enzymes. Ellagic acid, a key component of *R. centifolia*, is likely responsible for these anti-obesity effects, emphasizing its capability for treating obesity [161]. *Solanum xanthocarpum* exhibits anti-obesity properties mainly by inhibiting pancreatic lipase, an enzyme essential for digesting lipids. The active phytochemicals in the plant, including solasodine, carpesterol, β -sitosterol, and diosgenin, are responsible for this effect. Although pancreatic lipase inhibition shows some potential, the efficacy is modest compared to orlistat. In addition, the hypoglycemic and hepatoprotective properties of the plant, largely attributed to solasodine, support its overall metabolic benefits [164].

Brassica juncea attenuated lipid accumulation in 3T3-L1 adipocytes and lowered epididymal white adipose tissue (eWAT) mass in obese mice fed a high-fat diet [165]. One study tested five rhubarb hydroxyanthraquinones (HAQ's) for their obesity-related activity. Rhein and emodin showed the most success, significantly reducing triglycerides and body fat in 3T3-L1 cells and high-fat diet-induced obese rats. Rhein was particularly effective in reducing plasma cholesterol and attenuating obesity-associated changes, making it a potential obesity-reducing agent [166]. *Anthophytes longifolius* compounds delayed lipid and carbohydrate digestion by inhibiting α -amylase, α -glucosidase, and pancreatic lipase [167]. Finally, acetone fractions from *Rumex rothschildianus*, rich in flavonoids and phenolics, strongly inhibited lipase activity, comparable to orlistat, and also affected α -amylase and α -glucosidase [168].

3.5. Neuroprotective

In the past five decades, there has been a rise in the incidence of neurodegenerative disorders (NDs), which has been linked to the increase of longevity that has occurred. NDs encompass a wide range of conditions that affect the central nervous system, having alterations in the neuronal structure and cellular dysfunction that leads to progressive degeneration [169]. The most prevalent NDs are Alzheimer disease (AD), Parkinson disease (PD) and multiple sclerosis (MS). Despite the drugs available to ameliorate these conditions, their efficacy is limited. In the past years, it has been suggested natural compounds as potential alternatives with the ability to delay the disease onset, reduce its progression and regenerate the damage via their anti-amyloid, antioxidant, and anti-inflammatory properties [170].

Paeonia ostia has traditionally been used as medical and ornamental plant in China. The neuroprotective effect of the stamens of this plant has been studied by NO inhibition assay in lipopolysaccharides-induced BV-2 cells (LPS-induced BV-2) and molecular docking. LPS-induced BV-2 results showed (+)-3"-methoxy-oxylationflorin excellent inhibitory property in inhibiting NO production. Moreover, molecular docking results showed that the anti-inflammatory mechanism of this molecule was through a binding action with protein cyclooxygenase-2 (COX-2) [171]. In another study, *Phyllanthys emblica* fruits extract were tested in rats with sodium valproate-induced postnatal autism. After treatment with the fruit's extracts in 100mg/Kg of body weight, amelioration of social interaction, social affiliation, anxiety, and motor coordination was achieved. Moreover, results showed the restoring effect of the extract in glutathione-S-transferase (GST) and glutathione reductase (GR), which are oxidative enzymes, and reduction of malondialdehyde (MDA) and NO levels [172]. Another in vivo study determined the neuroprotective potential of *Tabebuia impetiginosa*

leaves by using a chemo brain model. Authors fed rats with 200 mg/Kg of body weight. Cyclophosphamide inducing cognitive impairment and treated the animals with 30 mg/kg of body weight of the extract for 14 days. Behavioral tests including locomotor, Y-maze, and passive avoidance tests were conducted and results showed pronounced antioxidant and anti-inflammatory potentials. Moreover, the restoration of normal hippocampal histological features and attenuated apoptotic caspase-3 expression was achieved, demonstrating the neuroprotective activity of the leaves' extracts [173].

Table 2. Chemopreventive activities of plant extracts and their phytochemicals: in silico, in vivo and in vitro examples.

Plant species	Plant part/ extract/ fraction	Extra phytochemical compound	Chemopreventive activity	Analysis Method	Trials type	Mechanism of action	Results	Ref.
Antioxidant activity								
<i>Garlic (Allium sativum L.)</i>	ns.	Allicin (purity >90%)	Anti-tumor (Cholangiocarcinoma)	CCK-8, colony formation, FC, WB	In vitro/ In vivo	STAT3 inhibition via SHP-1 upregulation	Suppressed proliferation, invasion, EMT, and tumor growth	[14]
	ns. HS-1793	Resveratrol analogue	Anti-tumor proliferation, DNA damage (Murine breast cancer)	LYM assessment, Treg and TAM analysis	In vivo	Inhibition of LYM damage and immune suppression by Tregs and TAMs	Enhanced LYM proliferation, reduced Tregs, and decreased IL-10/TGF- β	[14]
<i>Green tea—Curcuma longa L.</i>	ns.	Catechins and curcumin	Anti-tumor (OSCC)	Histology, Immunofluorescence, FC	In vivo	AP induction and anti-angiogenesis	Increase in AP and reduction in tumor growth	[13]
<i>Melilotus officinalis L.</i>	ns.	DC (coumarin derivative)	Anti-proliferative, gonad-safe	DC injection in BALB/c mice ovarian apoptosis, meiotic spindle	In vitro/ In vivo	Alteration of cell cycle dynamics without effect on microtubule stability	DC suppressed cell proliferation and increased AP in Vero and MCF-7 cells	[14]
<i>Polyalthia longifolia L.</i>	ME	Tetranorditerpene	Anti-cancer (prostate, leukemia cells)	Proteomic analysis	In vitro	Activates ER stress, induces apoptosis	Inhibits prostate cancer, leukemia cell growth	[17]
<i>Fagonia cretica L.</i>	AqE	ns.	Cytotoxic, induces cell cycle arrest	siRNA knockdown, MTT and FC, comet assay, WB, LC-MS/MS, DPPH, Iron Reduction, Enzyme Inhibition, XTT, FC	In vitro	Induction of DNA damage, and activation of p53 and FOXO3a	Induce cell cycle arrest and AP in two phenotypic breast cancer cell lines	[14]
<i>Onobrychis argyrea L.</i> (leaves)	ME	Quinic Acid, Isoquercitrin, Epicatechin, Routine	Antioxidant, antidiabetic, anticancer	DPPH, Iron Reduction, Enzyme Inhibition, XTT, FC	In vitro	ME induces apoptosis in HT-29 cells by disrupting mitochondrial membranes and activating caspases	High antioxidant, enzyme inhibition, strong anti-cancer capacity	[14]
<i>Elephantopus mollis Kunth.</i>	ME	3,4-di-O-caffeoylequinic acid	Cytotoxicity and -glucosidase inhibitory effects	DPPH, FRAP, Metal Chelating, β -Carotene, Cytotoxicity	In vitro	Induces cell death in NCI-H23 cells by triggering apoptosis	High antioxidant, induces apoptosis	[14]
<i>Thymus vulgaris L.</i>	MetE, EAE, ChE,	Polyphenols, tannins, flavonoids	Antioxidant	DPPH, ABTS, Ferrous Ion Chelation, CVT	In vitro	Radical scavenging, metal chelation, and metal chelation, and CVT	Strong antioxidant capacity correlated	[17]

	BolE, AqE, PEE	and sterols/triterp ènes		electrochemical reduction	with phenol and flavonoid content		
<i>Markhamia</i> <i>lutea</i> L.	Leaves extract	Flavonoids (O-glycosides)	Antioxidant, Anti-AChE, Anti-BChE, A β -amyloid- 42 inhibition	DPPH, ORAC, Iron Reduction, FRAP	In silico / in vitro	Induces antioxidant effects and inhibits AChE, BChE, and A β -amyloid 42	DPPH: 35.69 μ g/mL, ORAC: 16,694.4 μ M TE/mg, and iron chelation: 70.7 μ M EDTA eq/mg DPPH: 38.83
<i>Hertia</i> <i>cheirifolia</i> L.	Organic and ethyl acetate fraction	Total phenolics (100–250 mg GAE/g)	Antioxidant	DPPH, ABTS, FRAP, β -carotene	In vitro	Synergistic mechanisms between different biomolecules	μ g/ml, ABTS: 23.76 μ g/ml; FRAP: 2628.87 μ mol Fe $^{2+}$ Eq/mL; β -carotene: 58.91%
Anti-inflammatory activity							
<i>Tylophora</i> <i>ovata</i> L.	Natural PAs	O- methyltyloph oridine (1, synthetic orinidine (1, 1s)	Anti-tumor orinidine (1, against TNBC	NF κ B inhibition, 3D co-culture	In vitro	Stabilizes Ik κ B α , blocks NF κ B	Inhibits spheroid growth, surpasses paclitaxel [15 1]
<i>Mangifera</i> <i>indica</i> L.	ns.	Polyphenols	Anti- inflammatory, anticancer	Real-time PCR analysis and protein expression	In vitro	Modulated PI3K/AKT/mTOR, NF- κ B, PARP-1, Bcl-2	Reduced cancer cell growth by 90% [15 2]
<i>Helicteres</i> <i>isora</i> L.	DCM- E/HeE	Rosmarinic Acid	Anti- inflammatory, Antioxidant	ELISA assays	In vitro	Differentiation in cancer cells and showed no cytotoxic effect at high levels	Reduced TNF- α , PGE-2, and NO levels; highest COX- 2 inhibition [15 4]
<i>Waltheria</i> <i>indica</i> L.	Roots and aerial parts/ CH ₂ Cl ₂ extract	Flavonoids	Anti- inflammatory, Cancer chemoprevent ion	NF- κ B inhibition, luciferase reporter assay, QR inducing assay	In vitro	Induce Phase 2 enzyme activity via QR induction assay	Of 29 compounds in the study, 7 showed inhibitory activity on the NF- κ B pathway [17 8]
<i>Commiphora</i> <i>leptophloeos</i> L.	Hydroalco holic leaf extract	Phenolic acids and flavonoids	Anti- inflammatory	NO radical inhibition analysis, qPCR, physicochemical tests	In vitro/ In vivo	Downregulates NF- κ B, COX-2, reduces cytokines	Reduces inflammatory markers, promising for inflammatory bowel disease [15 3]
<i>Matricaria</i> <i>chamomilla</i> L.	ns.	β -Amyrin, β - Eudesmol, β - Sitosterol, Apigenin, Lupeol, Quercetin, Myricetin	Anti- inflammatory, anticancer	Proteome analysis, WB, Quantitative Real-Time RT- PCR, Thermophoresis	In silico / In vitro	Inhibition of NF- κ B pathway, reduction of IL-1 β , IL6 mRNA expression, and G2/M cell cycle arrest	NF- κ B inhibition, potential cancer prevention, reduced proinflammatory cytokine expression [15 6]
<i>Asparagusde</i> <i>nsiflorus</i> <i>meyeri</i> L.	Root and aerial parts/ DCM-E	Saponins, glycosides, sterols, triterpenes	Cytotoxic, anti- inflammatory	MTT assay, MCF- 7 cell stimulation using TNF- α , RT-PRC	In vitro	Reduces NO release and NF- κ B gene expression	Significant cytotoxicity (IC ₅₀ 26.13 μ g/ml) [17 9]

Anti-inflammatory activity

<i>Tylophora</i> <i>ovata</i> L.	Natural PAs	O- methyltyloph oridine (1, synthetic orinidine (1, 1s)	Anti-tumor orinidine (1, against TNBC	NF κ B inhibition, 3D co-culture	In vitro	Stabilizes Ik κ B α , blocks NF κ B	Inhibits spheroid growth, surpasses paclitaxel [15 1]
<i>Mangifera</i> <i>indica</i> L.	ns.	Polyphenols	Anti- inflammatory, anticancer	Real-time PCR analysis and protein expression	In vitro	Modulated PI3K/AKT/mTOR, NF- κ B, PARP-1, Bcl-2	Reduced cancer cell growth by 90% [15 2]
<i>Helicteres</i> <i>isora</i> L.	DCM- E/HeE	Rosmarinic Acid	Anti- inflammatory, Antioxidant	ELISA assays	In vitro	Differentiation in cancer cells and showed no cytotoxic effect at high levels	Reduced TNF- α , PGE-2, and NO levels; highest COX- 2 inhibition [15 4]
<i>Waltheria</i> <i>indica</i> L.	Roots and aerial parts/ CH ₂ Cl ₂ extract	Flavonoids	Anti- inflammatory, Cancer chemoprevent ion	NF- κ B inhibition, luciferase reporter assay, QR inducing assay	In vitro	Induce Phase 2 enzyme activity via QR induction assay	Of 29 compounds in the study, 7 showed inhibitory activity on the NF- κ B pathway [17 8]
<i>Commiphora</i> <i>leptophloeos</i> L.	Hydroalco holic leaf extract	Phenolic acids and flavonoids	Anti- inflammatory	NO radical inhibition analysis, qPCR, physicochemical tests	In vitro/ In vivo	Downregulates NF- κ B, COX-2, reduces cytokines	Reduces inflammatory markers, promising for inflammatory bowel disease [15 3]
<i>Matricaria</i> <i>chamomilla</i> L.	ns.	β -Amyrin, β - Eudesmol, β - Sitosterol, Apigenin, Lupeol, Quercetin, Myricetin	Anti- inflammatory, anticancer	Proteome analysis, WB, Quantitative Real-Time RT- PCR, Thermophoresis	In silico / In vitro	Inhibition of NF- κ B pathway, reduction of IL-1 β , IL6 mRNA expression, and G2/M cell cycle arrest	NF- κ B inhibition, potential cancer prevention, reduced proinflammatory cytokine expression [15 6]
<i>Asparagusde</i> <i>nsiflorus</i> <i>meyeri</i> L.	Root and aerial parts/ DCM-E	Saponins, glycosides, sterols, triterpenes	Cytotoxic, anti- inflammatory	MTT assay, MCF- 7 cell stimulation using TNF- α , RT-PRC	In vitro	Reduces NO release and NF- κ B gene expression	Significant cytotoxicity (IC ₅₀ 26.13 μ g/ml) [17 9]

<i>Capparis cartilaginea</i> L.	Ethanolic extract	Alkaloids, flavonoids, phenols, fatty acids, carotenes, Tannins, flavonoids, phenolics, terpenoids, Hydroethanolic leaf extract	Antioxidant, cytotoxic, anti-inflammatory	FBRC, FRAP, MTT assay, COX-1 inhibition	In vitro	Dose-dependent inhibition of thermally induced protein denaturation	Anti-inflammatory (IC ₅₀ 60.23 and 17.67 [18 µg/mL] better than 0)
<i>Corchorus olitorius</i> L.							Strong antioxidative potential due to its high tannin content.
<i>Amaranthus hybridus</i> L.							Reduction in tumor size and incidence
<i>Euphorbia hirta</i> L.	Whole extract	Phytol, fatty acids and 5-HMF	Anti-inflammatory	NO Production	In vitro	Suppression of PG generation	Inhibition of iNOS directly involved in inflammation [15 7]
Antidiabetic activity							
<i>Tradescantia pallida</i> L.	Leave extract	Syringic acid, Glycosylation p-coumaric acid, morin, and catechin	Glycosylation and hemoglobin activity	α -amylase assay	In vitro	Glycosylation inhibition non-enzymatically	Boosts insulin production, revitalizes β -cells, inhibits AGEs, stimulates glucose transporters and AMPK [18 2]
<i>Cissampelos capensis</i> L.	Leaf, stem, and rhizome	Glaziovine, Pronuciferine and, cissamanine	Antihyperglycemic	α -amylase assay	In vitro	Enzyme inhibition pathway	Reduction of glucose levels [18 3]
<i>Phyllanthus emblica</i> L.	ns.	Flavonoids	Antihyperglycemic	Molecular docking assay	In silico	Hypoglycemic action, reduction of relative risk of T2D, and PPAR inhibition of T2D	High binding affinity and selectivity for T2D therapeutic targets [18 4]
<i>Ocimum sanctum</i> L.	Leaves	Eugenol	Antihyperglycemic	ELISA, RIA, and Neutral Red assay	In vitro	Physiological pathway	Reductions in plasma glucose levels in T2D are associated with enhanced insulin secretion [18 5] from pancreatic islets, perfused pancreas
<i>Ocimum basilicum</i> L.	Leaves	TPC and FC	Antihyperglycemic	Enzyme inhibitory activity assay	In vitro	Enzymes inhibition pathway (α -glucosidase, α -amylase, DPP-IV, PTP1B, and SGLT2)	Inhibition of intestinal sucrase, maltase, and porcine pancreatic α -amylase [18 6]
<i>Derris elliptica</i> L.	Leaves	QUE and ceramide	Antihyperglycemic	Biochemical analysis and histopathology study	In vivo	Enzymes inhibition pathway	Increase insulin secretion, protect pancreatic β -cells [15 9] from oxidative stress

<i>Carica papaya</i> L.	Seeds	Hexadecanoic acid Methyl ester, 11-ODA Oleic acid	Antihyperglycemic	α -amylase and α -glucosidase inhibition assay	In vitro	Enzymes inhibition pathway	Reduction of glucose levels	[18] 7]
<i>Rhazya stricta</i> L.	Root	Hexadecanoic acid, Methyl ester	Antihyperlipidemic activity and hepatoprotective effect	DPP-IV, α -amylase, α -secretase inhibition assay, GLP-1 measurement	In vitro/ in vivo	Enzymes inhibition pathway	Reduce blood glucose and HbA1c, reduce cholesterol and triglyceride levels, reduce liver enzyme activity	[18] 8]
<i>Halooxylon stocksii</i> L.	Root and aerial parts	8-ODA Methyl ester	Antidiabetic	α -amylase and α -glucosidase assay	In vitro	Enzymes inhibition pathway	Reduction of glucose levels	[18] 9]

Antiobesity activity

<i>Rosa centifolia</i> L.	Petals	Ellagic acid (polyphenols)	Lipid metabolism improvement	PCR	In vivo	Suppression of lipid synthesis, Inhibition of intestinal absorption, Downregulation of <i>Scd1</i> and <i>Hmcgr</i> mRNAs in the liver	Reduced body weight and adipose tissue, increased fecal triglycerides, improved lipid, and cholesterol metabolism	[16] 1]
<i>Rheum rhabarbarum</i> L.	ns.	Emodin, rhein (anthraquinones)	Lipid lowering	ELISA assay and histological evaluation	In vitro/ in vivo	prevented through decreased PPAR γ and C/EBP α expression, leading to a reduction in lipid accumulation	Body weight and adipose tissue reduction	[16] 6]
<i>Brassica juncea</i> L.	ns.	Sinigrin (glucosinolate)	Anti-obesity	Cell Culture and XTT Assay, WB, Histological Analysis	In vitro/ in vivo	Reduce expression of adipogenic and lipid synthesis proteins	Inhibition of lipid accumulation in 3T3-L1 and decrease eWAT mass in obese mice fed a high-fat diet	[16] 5]
<i>Anthophycus longifolius</i> L.	ns.	Rhodomycinone, salsolinol, 5-HCO, 2-COS, demethylalanide	Anti-obesity and Anti-hyperglycemi	α -amylase, α -glucosidase, and pancreatic lipase assay	In vitro	Enzymes inhibition pathway	Delay lipid and CH digestion and absorption	[16] 7]
<i>Solanum xanthocarpum</i> L.	Fresh and dry leaves	Solasodine, Carpesterol, β -Sitosterol, Diosgenin	Hypoglycemic, hepatoprotective and MTT hypotensive	Pancreatic Lipase Inhibition Assay and MTT	In vitro	ns.	At 62.5 μ g/mL, the reduced cancer cell viability by 50%	[16] 4]
<i>Rumex rothschildianus</i> L.	Acetone fraction	Flavonoids, phenolics	Anti- α -amylase, anti- α -glucosidase, anti-lipase	Lipase inhibition activity	In vitro	Inhibits OS, α -amylase, α -glucosidase, and lipase	Strong lipase inhibition (acetone fraction IC ₅₀ 26.3 μ g/ml), close to orlistat (IC ₅₀ 12.3 μ g/ml)	[16] 8]

Neuroprotective activity

<i>Paeonia ostii</i>	Stamen	(+)-3''-methoxy-oxylactiflorin	Anti-inflammatory	Molecular docking and NO inhibition assay	In vitro/ in silico	Inhibition of NO production by binding with protein COX-2	NO production reduced to values of EC ₅₀ 3.02 μM	[17]
<i>Phyllanthus emblica</i>	Fruit extract	ns.	Anti-inflammatory	NO inhibition assay	In vivo	Reduction of pro-inflammatory markers IL-1β and TNF-α and up-regulation of expression of up-regulated 5-HT1D, 5-HT2A, and D2 receptor proteins	Amelioration of social interaction, social affiliation, anxiety, and motor coordination	[17]
<i>Tabebuia impetiginosa</i>	Leaves	Iridoids and organic acids	Anti-inflammatory	AChE inhibitory activity, LA detection, Y-maze test, PA assay	In vitro/ in vivo	Attenuation of cognitive impairment induced by CP supported by its effect on rats' performance in Y-maze and PA tests	Reduction of CP-induced chemo brain and restoration of normal hippocampal function	[17]

Abbreviations: CCK-8: Cell Counting Kit-8; STAT3: Signal Transducer and Activator of Transcription 3; WB: Western blotting ; FC: Flow cytometry ; SHP-1: Src Homology 2 Domain-Containing Phosphatase-1; EMT: Epithelial-Mesenchymal Transition; Treg: Regulatory T cell; TAM: Tumor-associated macrophage; LYM: lymphocyte; IL-10: Interleukin-10; TGF-β: Transforming growth factor-beta; ME: Methanol Extract; OSCC: oral squamous cell carcinoma; AP: Apoptosis; DC: Dicoumarol; BALB/c: Bagg Albino Laboratory strain/c; Vero: African green monkey kidney epithelial cells; MCF-7: Human breast cancer cells; siRNA: Small interfering RNA; MTT assay: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; p53: Tumor Protein p53; FOXO3a: Forkhead Box O3; QUE: Quercetin; ROS: Reactive Oxidative Species; OS: Oxidative Stress; PKC: Protein Kinase C; PI3K: Phosphatidylinositol 3-Kinase; COX-2: Cyclooxygenase-2; RT-PCR: Reverse Transcription Polymerase Chain Reaction; HepG2 cells: Human liver cancer cell line; AMPK: adenosine monophosphate-activated protein; AGES: advanced glycation end products; T2D: type 2 diabetes; PPAR: peroxisome proliferator activated receptor; NFκB: Nuclear Factor kappa B; IκBα: Inhibitor of Nuclear Factor kappa B alpha; HT-29 cells: Human colorectal Adenocarcinoma cell line; DPPH: 2,2-Diphenyl-1-picrylhydrazyl, FRAP: Ferric Reducing Antioxidant Power; NCI-H23 cells: Human Lung Adenocarcinoma cell line; ORAC: Oxygen Radical Absorbance Capacity; ER: Endoplasmic Reticulum; HeE: Hexane Extract; DCM-E: Dichloromethane Extract; MetE: Methanolic Extract; EAE: Ethyl Acetate Extract; ChE: Chloroform Extract; BoE: Butanol Extract; AqE: Aqueous Extract ; PEE: Petroleum Ether Extract; CVT: Cyclic Voltammetry Techniques; PI3K/AKT/mTOR: Phosphoinositide 3-Kinase/Protein Kinase B/Mechanistic Target of Rapamycin; -κB: Nuclear Factor kappa B; PARP-1: Poly (ADP-ribose) Polymerase 1; Bcl-2: B-cell Lymphoma 2; TNF-α: Tumor Necrosis Factor-alpha; THP-1 cells: Human Monocyte Cell Line THP-1: ELISA: Enzyme-Linked Immunosorbent Assay; QR: Quinone reductase ; NO: Nitric Oxide; 5-HMF: hydroxymethyl-2-furancarboxaldehyde; iNOS: Inducible NO synthase; PG: Prostaglandins; T2D: type 2 diabetes; RIA: radioimmune assay; TPC: total polyphenol compounds; FC: flavonoids content; 11-ODA: 11-octadecanoic acid; HbA1c: glycosylated hemoglobin; PCR: polymerase chain reaction; FAS: fatty acid synthase; ACC: acetyl-CoA carboxylase; 5-HCA: 5-hydroxyconiferyl; 2-COS: 2-caffeoyleisocitrate; DPP-IV:p ipeptidyl peptidase-IV; PTP1B: protein tyrosine phosphatase 1B; SGLT2: sodium-glucose co-transporter 2; qPCR: polymerase chain reaction; RT-PCR: Reverse Transcription-Polymerase Chain Reaction Assay; FBRC: Ferric-bipyridine reducing capacity of total antioxidant; ER-β; Strogen Receptor Beta; eWAT: Epididymal white adipose tissue; IL-1β: interleucina 1 β; TNF-α: tumor necrosis factor alpha; 5-HT1D:serotonin 1D receptor ; 5-HT2A: serotonin 2A receptor; D2: dopamine 2 receptor; AChE: acetylcholinesterase; LA: locomotor activity; PA: passive avoidance. ns: not specified.

4. Development of Phytochemicals as Nutraceuticals

4.1. Extraction, Purification and Encapsulation

Based on the above information, phytochemicals, which include a diverse range of compounds, have been recognized for their potential influence on health promotion and disease prevention. Due to their therapeutic effect, phytochemicals have become prime candidates in the development of nutraceuticals, which are food-derived products that offer additional health benefits beyond basic nutrition [190]. However, direct ingestion of phytochemicals within their native plant matrices presents several challenges [191]. The bioavailability of these compounds is often restricted by factors such as low concentrations, poor solubility, instability under gastrointestinal conditions, and rapid metabolic degradation and excretion [192]. These obstacles highlight the need for developing methods to concentrate, purify, and encapsulate phytochemicals, thereby enhancing their effectiveness as nutraceuticals (Figure 2) [193].

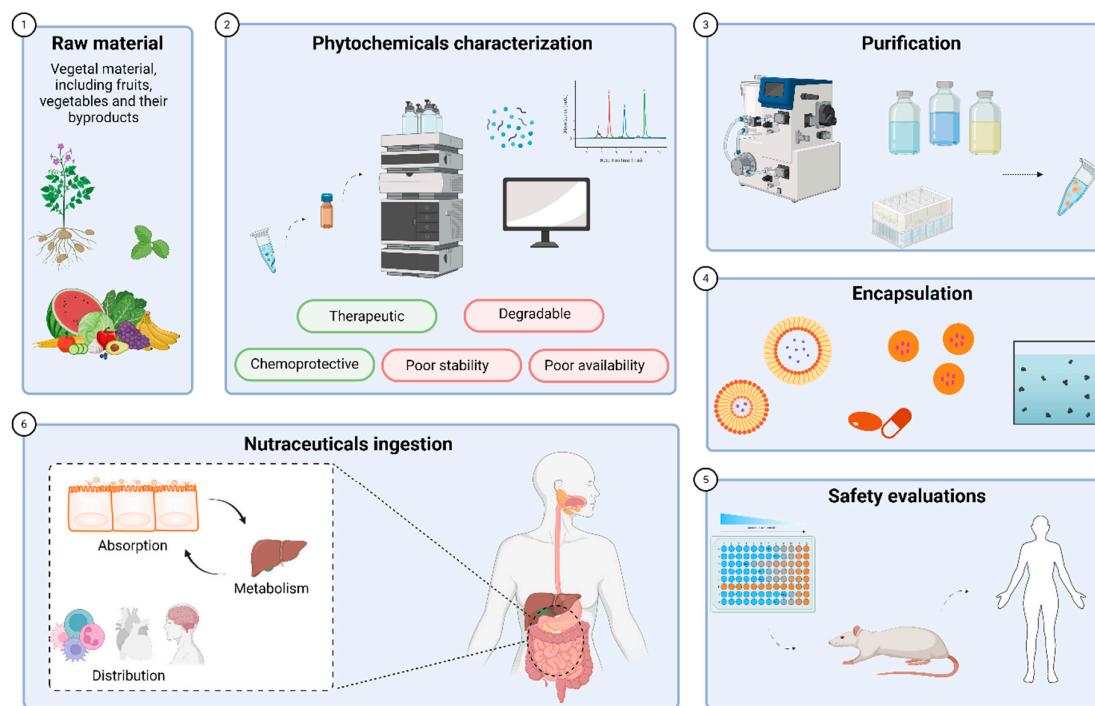


Figure 2. Process of development of phytochemicals as nutraceuticals.

The initial phase in the utilization of phytochemicals for nutraceutical purposes involves their extraction from plant sources [194]. This extraction process is complex and must be carefully optimized to preserve the structure and bioactivity of the target compounds [195]. Traditional extraction techniques, such as solvent extraction, have been improved by emerging methods like microwave-assisted extraction and ultrasound-assisted extraction, since they offer increased efficiency and selectivity [196]. A major challenge in phytochemical extraction and recovery is to incorporate environmental sustainability into the design and optimization of production processes, with the aim of developing more eco-friendly methodologies [197] and enhancing economic outcomes within the food industry [198]. The choice of appropriate extraction techniques is crucial, as it directly impacts the quality and characteristics of the final product [199]. Key factors influencing the efficacy of both conventional and emerging extraction techniques include the solid-to-solvent ratio, solvent concentration, particle size, and the mode of extraction (flow or batch) [200]. These parameters critically affect the efficiency of extraction and the phytochemical composition of the resultant extract [201].

Following extraction, the subsequent step involves the purification of the bioactive compounds from the crude extract. This is necessary because the initial phytochemical mixture typically contains

a combination of active and inactive substances, along with impurities that could affect the safety and efficacy of the final product [202].

Recent advancements in purification and isolation techniques for bioactive compounds from plant sources have addressed some of the challenges posed by the complexity and diversity of phytochemicals [203,204]. These advancements focus on optimizing methods to concentrate the desired compounds, thereby enhancing bioactivity—such as antioxidant, antibacterial, or cytotoxic effects—while maintaining simplicity, specificity, and efficiency in processing [205,206]. Techniques such as high-performance liquid chromatography (HPLC), solid-phase extraction (SPE), and preparative thin-layer chromatography (TLC) are commonly used for the isolation and purification of bioactive molecules due to their practicality, cost-effectiveness, and the availability of various stationary phases [199,205]. Notably, silica, alumina, cellulose, and polyamide have proven effective in separating phytochemicals [205]. To achieve the separation of complex mixtures, the use of multiple mobile phases with varying polarity is often required [199,205]. The degree of purification achieved is directly linked to the pharmacokinetic properties of the compounds, influencing their bioavailability, distribution, metabolism, and excretion [207].

Despite the successful purification of phytochemicals, the formulation of these compounds into nutraceuticals remains challenged by issues of stability, solubility, and bioavailability. Encapsulation technologies have emerged as vital strategies to overcome these challenges [208,209]. Additionally, encapsulation can improve the quality of food products by masking undesirable odors and flavors and extending shelf life [198]. This process involves enclosing phytochemicals within a protective matrix or carrier system, which shields them from environmental degradation, enhances their solubility in biological fluids, and facilitates controlled release in the gastrointestinal tract [210,211]. Various encapsulation methods have been developed, each offering unique advantages depending on the physicochemical properties of the phytochemicals and their intended application [212]. Microencapsulation, for instance, is widely used to protect sensitive compounds and improve their stability during processing and storage [213,214]. Conversely, nanoencapsulation provides enhanced bioavailability and targeted delivery due to the small particle size and large surface area [215,216], which improve interactions with biological membranes and allow for more precise control over release kinetics [217,218].

In conclusion, the effective application of phytochemicals as nutraceuticals is closely linked to advances in extraction, purification, and encapsulation techniques. These processes not only enhance the pharmacological potential of phytochemicals but also ensure their stability, bioavailability, and functional integration into various nutraceutical products.

4.2. Considerations of Bioavailability

Phytochemicals offer a wide range of health benefits, yet their effectiveness is often compromised by challenges related to bioavailability, including issues with water dispersibility, chemical stability, and gastrointestinal absorption [219]. For phytochemicals to be effective, they must be released from their food matrices, solubilized in gastrointestinal fluids, and absorbed by enterocytes in the gastrointestinal tract (GIT). However, these compounds may precipitate, interact with other dietary molecules, or be chemically altered by digestive enzymes, metabolic pathways, or gut microbiota, which can significantly reduce their bioactive forms by the time they enter systemic circulation [220].

Therefore, the bioavailability of phytochemicals is affected by various factors, including the complexity of the food matrix, the chemical form of the compound, and individual physiological differences such as gut microbiota composition, mucosal health, and metabolic activity. These factors contribute to considerable inter- and intra-individual variability in bioavailability, complicating the prediction of their efficacy [221]. Additionally, the impact of food processing on phytochemical stability and bioavailability is critical, as processing techniques can either enhance or diminish their bioactive potential [222].

To address these issues, in vitro digestion models and cellular uptake assays are employed to assess factors affecting both bioaccessibility and bioavailability. These models are essential for screening and optimization of formulations prior to more expensive in vivo studies. Despite the availability of various assessment methods, a universally accepted standard for bioaccessibility remains elusive, and current methods must account for the diverse structural characteristics of phytochemicals [207]. For lipophilic compounds such as carotenoids and fat-soluble vitamins, formulation techniques like encapsulation and emulsification have shown potential in enhancing bioaccessibility and protecting these compounds from degradation [207].

In silico modeling, commonly used in pharmaceutical research, offers an interesting approach as it allows to predict phytochemical bioavailability based on their physicochemical properties. However, these models are still developing for dietary phytochemicals, indicating a need for further research to establish effective predictive tools [223]. Moreover, technological processes such as thermal processing and biotechnological interventions, including enzymatic hydrolysis and fermentation, have demonstrated their influence in improving the bioavailability of phenolic compounds. However, while these strategies have shown promise in animal studies, further human trials are necessary to validate their effectiveness [224]. Thus, both research and innovation in processing and formulation techniques are essential for advancing nutraceuticals and optimizing the bioavailability of phytochemicals.

5. Current Applications of Nutraceuticals

Nutraceuticals, which combine nutritional and medicinal properties, are increasingly being incorporated into food products to promote health and prevent disease. These bioactive compounds, derived from a variety of matrices, offer a wide range of benefits, such as improving cardiovascular and immune system function, or managing chronic diseases. In addition, advances in encapsulation and nanotechnology have further improved their efficacy in food applications, expanding the potential of health-promoting foods [199].

5.1. Ingredients of Functional Foods

The incorporation of antioxidants in functional foods has been widely researched due to their health benefits and potential enhancement food quality and shelf life. This incorporation can be done in several ways, including through the addition of crude extracts, fibers, color additives or other food enrichment (**Figure 3**) [225].

Crude extracts are raw, unrefined substances obtained from plants, animals, or other natural sources that contain bioactive compounds. The most widely utilized are plant polyphenol extract, such as green tea extract, grape seed extract, rosemary extract, but also mushroom extracts, spice and herbs extracts (garlic extract, ginger extract, turmeric extract), vanilla extract and more recently, algae extract (spirulina, chlorella extracts). Plant polyphenols are often used to delay lipid oxidation, thereby enhancing the shelf-life of lipid-bearing foods [226]. These extracts also exhibit antimicrobial activity with green tea extract having major antimicrobial activity against major foodborne pathogens such as *Listeria monocytogenes*, *Salmonella Typhimurium*, *Escherichia coli* O157:H7, and *Campylobacter jejuni*, contributing to food safety [227,228]. Some crude extracts also contribute to flavoring such as mushroom extracts, garlic extracts, rosemary extracts and spices and herbs extracts in general. These can also provide distinctive aroma and color enhancing their sensory attributes. For example, spirulina extracts that are naturally greenish blue can modify the color of a food [229].

Fiber can be added to foods due to their functional and health benefits. They can be roughly divided into soluble and insoluble fibers. Soluble fibers include pectins and inulin while insoluble fibers include cellulose, psyllium and wheat bran. Functionally, adding fiber to foods can impact their sensory properties, such as appearance, texture, taste, and flavor [230]. Pectins can be found on fruit jams and jellies, acting as a gelling agent, giving jams and jellies their thick, spreadable consistency. Additionally, it allows for a lower sugar amount to be used while improving the product's shelf life and stability [231]. Inulin, usually extracted from chicory root is used as a fat replacer and provides

a creamy texture in low-fat or reduced-calorie foods [232]. It also serves as a prebiotic, promoting the growth of beneficial gut bacteria [233]. Cellulose and its derivatives, such as microcrystalline cellulose (MCC) and bacterial cellulose, are commonly used as stabilizers and thickeners in food products, including meat products, emulsions, beverages, dairy products, and bakery items [234]. Furthermore, MCC and other cellulose derivatives are used in functional and nutraceutical foods for their positive effects on gastrointestinal health and lipid metabolism [234]. Cellulose gels are also widely used in the food industry for their high-water absorption capacity and biocompatibility. They are applied in food packaging, functional foods, and food safety due to their structural flexibility and stimulus-responsive properties [235]. Other more unrefined fibers such as psyllium husk and wheat bran are also often used in the food industry. Unmodified wheat bran and psyllium husk are used as nutritional enhancements as they are a source of dietary fiber, minerals, vitamins, and bioactive compounds such as phenolic acids, which contribute to improved bowel health, prevention of diseases like colon cancer, and cardiovascular health [236]. These fibers, when modified through processes such as mechanical milling, enzymatic hydrolysis, and thermal treatments can be utilized as functional ingredients. For example, modified wheat bran can be incorporated into cereal foods, baked products, and fried snacks to reduce oil content and increase fiber content [236].

To specifically modify the color of a food, color additives can be used. The main natural color additives used in the food industry are anthocyanins, beta-carotene, betanin and curcumin. Unlike synthetic dyes, these are usually less resistant to degradation via sunlight or heat exposure, but do not carry risks like causing hyperactivity in children [237]. Anthocyanins are widely used as natural food colorants due to their vibrant colors, which range from red to blue depending on pH levels [238,239]. Often, these anthocyanins are chemically modified, such as acylation and glycosylation, which offers enhanced color stability, making them more suitable for industrial applications as natural colorants [240]. These also provide additional health benefits, improving carbohydrate metabolism and decreasing the risk factors of metabolic disorders [240]. Anthocyanins are used in beverages such as fruit juices, smoothies, teas, and energy drinks, dairy products such as flavored milk and ice creams, candies, jams and jellies, bakery products and many others [241]. Beta-carotene is also known as pro-vitamin A, contributing to the recommended intake of this essential nutrient on foods where it is added [36]. Beta-carotene is used to provide an orange hue to various food products such as margarine and butter substitutes, fruit juices and smoothies, dairy products such as cheese and yogurt, snack, baked goods, infant formula among many others [242]. Betanin, a red-violet pigment found in beetroots, is also widely used in the food industry. Betanin exhibits high antioxidant activity, which helps in scavenging reactive oxygen species and preventing lipid oxidation in foods, thereby preserving food quality [243]. It retains its antioxidant ability even after simulated digestion, making it effective in protecting against oxidative stress [244]. Betanin shows significant stability at low temperatures, which is beneficial for its use in frozen or refrigerated foods [244]. Encapsulation techniques, such as liposomal nanocarriers and microencapsulation, improve the stability and bioavailability of betanin [245,246]. Furthermore betanin can delay the retrogradation of starches, which is beneficial for maintaining the quality and texture of starchy foods like bread and pastries [247].

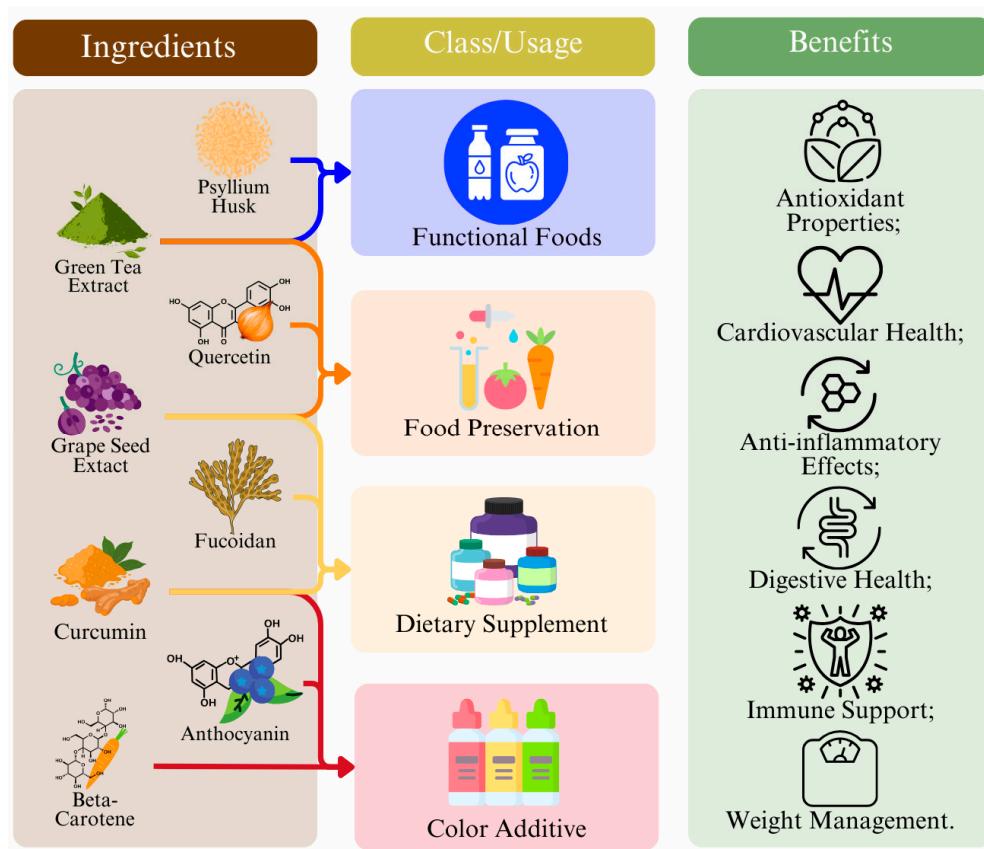


Figure 3. Ingredient types, uses and benefits in food applications.

Curcumin, whether as a turmeric extract or in its unprocessed form, is commonly used to impart a yellowish-orange hue to foods [248]. It has also demonstrated potential in the prevention and management of various health conditions, including cardiovascular diseases, diabetes, metabolic syndrome, arthritis, and mental disorders [249,250].

In conclusion, the incorporation of antioxidants, fibers, crude extracts, and natural color additives into functional foods has been shown to enhance not only the nutritional value but also the sensory qualities, shelf life, and safety of various products. Both soluble and insoluble fibers, such as pectin, inulin, cellulose, psyllium husk, and wheat bran, play crucial roles in improving texture and stability, while providing health benefits like enhanced digestive health and disease prevention. Crude extracts, including plant polyphenols, as well as mushroom and spice extracts, contribute to preserving food quality by delaying lipid oxidation, offering antimicrobial properties, and improving both flavor and color.

5.2. Isolated Phytochemicals as Nutraceuticals

Isolated phytochemicals, bioactive compounds derived from plants, have gained significant attention as nutraceuticals due to their potent health-promoting properties. These compounds, which include flavonoids, alkaloids, terpenoids, and polyphenols, are increasingly being isolated and studied for their potential to prevent and manage various chronic diseases, such as cancer, cardiovascular disorders, and neurodegenerative conditions (Table 3). Phytochemicals are often extracted from agricultural and food waste streams, promoting a circular economy by converting waste into value-added functional ingredients [251]. By concentrating the active ingredients, isolated phytochemicals offer more targeted therapeutic effects compared to whole plant extracts, making them valuable in the development of functional foods and dietary supplements [195].

Table 3. Nutraceutical Applications and Functionality.

Nutraceutica 1	Source	Applications	Functionality	Health Benefits	Ref.
Pectin	Fruits (Apple, citrus...)	Jams, jellies, dairy products	Gelling agent, thickener	Anti-cancer, immunomodulatory, anti-inflammatory, cholesterol-lowering (...)	[252]
Inulin	Chicory root	Low-fat foods, fiber supplements	Prebiotic, fat replacer	Gut-microbiota regulating, lipid metabolism regulating, mineral absorption enhancing, anti-inflammatory (...)	[253]
Cellulose	Several plants	Low-fat foods, plant-based meats, bakery products	Stabilizer, thickener	Gut-microbiota regulating, cholesterol reducing, blood glucose levels regulating, anti-inflammatory (...)	[234]
Wheat Bran	Wheat	Cereals, bread and bakery products	Texture enhancer, fiber source	Gut-microbiota regulating, cancer-risk reducing, cardioprotective (...)	[254]
Psyllium husk	Plantago ovata seeds	Fiber supplement, cereals	Fiber source, thickener	Anti-diabetic, reduces cholesterol levels, and aids in gastrointestinal health (...)	[255,256]
Green tea extract and catechins	Green tea leaves	Beverages, supplements, snacks	Antioxidant, antimicrobial	Antioxidant, anti-inflammatory, antiviral, antiobesity (...)	[257,258]
Grapeseed extract	Grape seeds	Beverages, supplements	Antioxidant, antimicrobial	Anti-inflammatory, antioxidant, cardioprotective, antimicrobial, anti-cancer (...)	[259]
β-carotene	Carrots, sweet potatoes	Supplements, snacks, beverages, candies	Natural colorant, antioxidant	Antioxidant, supports immune function (...)	[260]
Anthocyanins	Berries, red cabbage	Supplements, snacks, beverages, candies	Natural colorant, antioxidant	Antioxidant, anti-inflammatory, antidiabetic, anti-obesity (...)	[261]
Betanins	Beetroot	Supplements, snacks, beverages, candies	Natural colorant, antioxidant	Antioxidative, anti-inflammatory, antidiabetic, potential anticancer benefits (...)	[243]
Curcumin	Turmeric root	Supplements, snacks, beverages, candies	Natural colorant, antioxidant	Antioxidant, anti-inflammatory, anticancer, and immune-regulatory properties (...)	[262]
Resveratrol	Grapes, red wine	Beverages, supplements	Antioxidant, antimicrobial	Antioxidant, anti-inflammatory, anti-cancer, cardioprotective (...)	[263]
Fucoidans	Blown algae	Supplements, fortified foods	Gelling agents, thickeners	Antioxidant, anti-inflammatory, anticoagulant, antitumor, antiviral (...)	[264]
Agar	Red algae	Jellies, jams, candy, plant-based gelatin	Gelling agent, texture enhancer	Antioxidant, antiviral, antibacterial, prebiotic, anti-tumor (...)	[265]
Carrageenan	Red algae	Jellies, jams, candy, plant-based gelatin	Thickener, gelling agent	Cardioprotective, anticancer, antiviral, anticoagulant, antioxidant (...)	[266]
Quercetin	Onions, apple peels	Supplements, fortified foods	Antioxidant, preservative	Anti-inflammatory, antimicrobial, anticancer, cardioprotective (...)	[267,268]

Polyphenol extracts, concentrated from fruits, vegetables, herbs, and seeds, are well-known for their antioxidant properties. Green tea catechins, particularly epigallocatechin-3-gallate (EGCG), are

effective in delaying lipid oxidation and extending the shelf life of lipid-containing foods [226,249]. These polyphenols are also incorporated into convenient products such as chewing gum and gelatin gummies, enhancing consumer accessibility and palatability [269]. Furthermore, green tea extracts demonstrate antimicrobial properties against common foodborne pathogens, enhancing both food safety and quality [227]. Similarly, resveratrol, often sourced from grape industry waste, exhibits strong antioxidant and antibacterial activity, making it suitable for use in oil-in-water emulsions, bulk oils, ground meat, and as a potential natural preservative in food packaging and processing [270,271].

Omega-3 oils, particularly eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), are widely recognized for their roles in supporting brain development and cardiovascular health [272]. Sourced from marine species such as some microalgae like *Schizochytrium* and *Nannochloropsis*, these oils are extracted through solvent methods [273]. Due to growing consumer demand for plant-based omega-3s, microalgae supplements have become popular as they contain lower levels of heavy metals compared to traditional fish oils [274]. However, the high cost and instability of algae oils limit their use in food products, though nano-emulsification techniques have shown promise in stabilizing omega-3s for functional food applications [275]. Additionally, algae-derived omega-3s are used in livestock feed, enriching meat, milk, and eggs with bioactive compounds that benefit human health [276], including increasing omega-3 blood indices and reducing diastolic blood pressure [277].

Fucoidans, polysaccharides extracted from brown algae, have gained recognition for their multifunctional bioactive properties. These include anticoagulant, antiviral, antitumor, antibacterial, and immunomodulatory effects [278]. Fucoidans are also valuable as gelling and thickening agents in the food industry, offering both functional and health benefits [279]. Their solubility and ease of incorporation into food formulations make them suitable for various applications, including the development of UVB-protective cosmetics and functional foods [280,281].

Agar and carrageenans, two polysaccharides derived from red algae, are widely used as gelling, thickening, and stabilizing agents in food products. Agar's ability to form gels at low concentrations makes it ideal for candies, soups, snacks, and plant-based formulations [265,282]. Agar is also often used on plant-based and halal formulations of products that otherwise require animal gelatin [283]. Additionally, agar and its derivatives exhibit multiple bioactive functions such as antioxidant, antiviral, antibacterial, prebiotic, anti-tumor, anticoagulant, and antidiabetic activities. These bioactive properties make agar a valuable ingredient in functional foods and nutraceuticals [265,282]. Carrageenans are similarly utilized as thickening, gelling, and protein-suspending agents, enhancing texture and water retention in food products while also providing various health benefits [284]. In low-fat meat formulations, the incorporation of carrageenans promotes gel formation and water retention, thereby improving textural properties [284]. In parallel with agar, carrageenans exhibit anti-inflammatory, anticoagulant, antitumor, and antithrombotic effects [285].

Quercetin, a flavonoid present in a variety of plants, is predominantly extracted from onions and apple peels due to their commercial availability [286]. In food products like bread, quercetin demonstrates antioxidant and antiglycation effects in a dose-dependent manner. Furthermore, it inhibits the formation of advanced glycation end-products (AGEs), thereby enhancing the shelf life of these products [287]. Quercetin has also been shown to offer protective benefits against cardiovascular and neurodegenerative diseases, underscoring its potential as a valuable bioactive compound for the development of functional foods aimed at promoting health [288].

In summary, phytochemicals such as polyphenols, omega-3 oils, fucoidans, agar, carrageenan, and quercetin are increasingly recognized for their dual roles in improving both the quality and health benefits of food products. These compounds, sourced from plants and algae, contribute to enhanced shelf life, nutritional value, and functional properties, while offering a wide range of health benefits including antioxidant, antimicrobial, and cardiovascular protective effects.

6. Conclusions

This review uncovers the versatile functions of antioxidants in plant organisms and their involvement in protection to OS. Several antioxidant compounds, such as flavonoids, carotenoids,

and phenolic acids, promote plant resistance and are also beneficial for human health. A better understanding of these mechanisms may allow the optimization of agricultural practices and food supply. Further research should be directed towards more efficient use of plant antioxidants to improve their productive capacity and nutraceutical value.

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