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Review

Plant-food-derived bioactives: Key health benefits and current nanosystems as a strategy to enhance their bioavailability

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Abstract: Natural products interest is gradually increasing worldwide. Plant-food-derived bioactives have a long history of use as a good source of ingredients for valuable medical usages. Plant-based foods consist of micro and macronutrients, and bioactive components, with health-promoting benefits. The handling of complex mixtures of plants has been methodically switched by therapies using a single isolated substance. The delivery of bioactive molecules in nanosystems is enhancing their bioavailability, it is much safer and cost-effective. However, there are many challenges in combining bioactive substances in nanocarrier materials. A discussion related with nanocarriers will be done in this review.

Key words: Plant-food bioactives; Nutrients; Nanocarrier systems; Bioavailability; Drug delivery.

Introduction

Nature-derived products, such as fruits, vegetables, wild plants and nuts can be processed into derived products (1). In these complex matrices, multiple micro and macronutrients (phytonutrients) and bioactive components (2) are present, and are briefly divided in primary and secondary metabolites (3, 4).

Fibers (e.g. cellulose, hemicellulose, pectins and starch) are found in high amount in all intact parts of plants, being indigestible for humans, but offering protection of the gastrointestinal, cardiovascular, and immune systems. In fact, plant-based foods differentiate from animal-based foods as well because of their fiber fraction. Phytonutrients (e.g. glucosinolates, carotenoids and flavonoids) work synergistically to decrease inflammation and oxidation processes providing protection from disease initiation and progression (1, 5). It is reported by Hever (6) that there is significant interest in understanding the potential effects of plant-based diets, regarding properties associated with nutrition and health. For that reason, bioavailability of micronutrients with food synergies effects has been a highly explored topic for years. It has also been consecutively demonstrated that plant-based diets result in lower heart disease mortality, support a sustainable weight management, reduction of medication needs, lower risk for most chronic diseases, and decrease high-risk diseases incidence and severity. Actually, people facing to chronic diseases have a high demand for healthier foods, which poses a challenging step to food industry (7).

Additionally, humankind has always had a close interest with plants as a great source of potential drugs to treat both spiritual and physical ailments. Over the centuries, we have testified the progress in the use of complex plant extracts mixtures, methodically converted in therapies using a single isolated substance (8). A high quantity of plant extracts has been assessed for their chemopreventive and chemotherapeutic abilities. The advent of innovative chromatography systems allowed the isolation of important quantities of ingredients, from complex mixtures. Moreover, with the development of chemical synthesis procedures, numerous isolated synthetic metabolites/chemicals and phytochemicals have been pre-clinically tested. In fact, numerous compounds identified as promising mediators have been effectively converted into marketable drugs (9). On one hand, since cancer prevention research has advanced, several researchers have started to be interested in plants, as a source of new effective agents. On the other hand, there has been a tendency to use naturally-occurring bioactive components ("phytochemicals") as functional foods, for the significant benefits on the human physiology and metabolic functions, treating or preventing certain illnesses, increasing the mental or physical performance, and as a good source for supplements and pharmaceutical products (10, 11). Nonetheless, several researchers have also exposed concerns regarding human health claims related to phytochemicals use and their true efficiency (12, 13). In point of fact, unlike drugs taken in a certain dose and under well-controlled situations, phytochemicals are usually taken at low and changeable levels, as part of a complex diet at irregular intervals over extended periods of time (14). Thus, it is hard to determine whether any change in health status can be related with an exact phytochemical intake. Furthermore, phytochemicals may be physically or chemically changed during storage, processing and ingestion, which can impress their bioactivity and bioavailability (15, 16). As so, phytochemicals efficacy can be strongly impressed by the structure, composition, quantity, and of foods taken with it (15, 17). The purpose of this study is to look for the variety of plant chemicals and their efficacy and bioavailability, according to the published literature.

Micronutrients

Micronutrients include minerals, vitamins and trace elements (18). Some minerals are easily absorbed as salts (ionic form) and some foods are fortified with minerals to enhance uptake (19). Regarding vitamins, the most relevant are fat-soluble vitamins (A, D, E and K) and water soluble vitamins (C, B1, B2, B3, B6, B9 and B12) (20). As a matter of fact, "hidden hunger" or "micronutrient deficiencies" is known serious disorder related to the lack of iron, vitamin A, zinc, iodine and all dietary antioxidants, both in developed and developing countries (21).

Secondary metabolites are produced by plants, bacteria, fungi and many marine organisms (22). It is estimated that total number of secondary metabolites in plant can exceed 500,000 (23, 24). Apart from main and most abundant molecules found in plants, secondary metabolites are generally produced in the phase of growth, have low molecular mass and low abundance (22). Tough they play a role in many survival functions in plant, they are not involved plant growth and development (23). Guerriero and *et al.* (25) and Wianowska and *et al.* (26) indicated that biotic stress and physiological tasks are responsible for the huge variety of secondary metabolites with complex chemical composition.

Previously defined as waste products, secondary metabolites are nowadays considered to be fundamental elements for plant life (23). Many of them can actually support the immune system, exhibit antioxidant, anti-inflammatory, antibacterial, antifungal and antiviral activities (26).

Macronutrients

Macronutrients are known as primary metabolites. They are the chemical molecules responsible for plant growth and plant development. The main examples are carbohydrates, proteins, lipids and amino acids (7, 27). Amino acids and lipids are also called 'structural materials', since they provide energy (27). Generally, primary metabolites are fundamental for basic biochemical reactions and are formed by reduction, oxidation or hydrolysis processes (28).

Oligosaccharides and Biological Effects

Orzecowski *et al.* reported that oligosaccharides are widespread class of structurally diverse macromolecules (29). Functional oligosaccharides are a group of carbohydrates, composed of 2 to 10 monosaccharides units linked with glycosidic bonds. Examples of functional oligosaccharides are: fructo-oligosaccharides, galactooligosaccharides, lactosucrose, maltooligosaccharides, isomalto-oligosaccharides, trehalose, cyclodextrins, xylooligosaccharides, and soyoligosaccharides (30). Functional oligosaccharides are non-digestible by human gut enzymes and they are reported as fibers and prebiotics (30), (31) (32), fermented by anaerobic bacteria in human colon. These molecules are responsible for growth of intestinal *Lactobacillus* and *Bifidobacteria*, and recognized as beneficial microorganisms to human health, regulating the structure of intestinal microbiota.

Produced by primary and secondary fermentation pathways in the colon, fiber supports digestive health in different ways. Dietary fibers assist the growth of both beneficial and harmful bacteria and have no selectivity against bacteria, so it cannot be called as a prebiotic product. On other side, prebiotics are specific for microorganism and microbiota-shaping compounds (31, 32). The classification of a fiber as a prebiotic ingredient requires scientific proof of the following properties: gastric acidity resistance, mammalian enzymes hydrolysis, upper gastrointestinal tract absorption, intestinal microflora fermentation, and selective stimulation of the growth or activity of intestinal bacteria. All these feature will contribute to human health and well-being (32).

According to some animal studies fructooligosaccharides rise butyrate stimulation, sodium absorption and regulation of intestinal motility, as well as calcium, magnesium and iron absorption (30) (31) . In addition, immunomodulation and anti-cancer effects of fructooligosaccharides were also shown (31).

Polyunsaturated Fatty Acids (PUFA) and Biological Effects

Fatty acids (FA) have a variable length carbon chain with a methyl terminus and a carboxylic acid head group. These molecules can be divided into two groups - saturated and unsaturated fatty acids – according to the degree of carbon chains saturation. Saturated FA have the maximal number of hydrogen atoms, and monounsaturated and polyunsaturated FA (PUFAs) have one or two or more double bonds, respectively (33).

Polyunsaturated fatty acids have two main compounds: linoleic acid (LA) and α-linolenic acid (α-LA). LA is a fatty acid of the w-6 family with 18 carbon atoms and two double bonds (18:2n6), whereas α-linolenic acid is a fatty acid of the w-3 family with 18 carbon atoms and three double bonds (18:3n3). LA can be expanded to arachidonic acid (AA) with two intermediary metabolites that are g-linolenic acid (GLA) and dihomo-g-linolenic acid (DHLA). α-LA can be elongated to either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) (34).

LA and linolenic acid are both only produced by plants in large amount, but they are not synthesized by humans and other mammals, hence their relevance (33). **Table 1** presents 20 wild plants including with their total lipid content studied by Abedi *et al*. (34). Importantly, EPA and DHA are responsible for normal brain development, normal vision, have anti-inflammatory and cardioprotective effects including anti-arrhythmic, antithrombotic outcomes, decreasing risk of cardiovascular diseases. They also reduce blood pressure, improve the endothelial function and diminish the growth of atherosclerotic plaque (33, 34). Anti-depressive, antiaging and anti-arthritic effects have also been discussed (35). Long chain n-3 PUFA has showed anticancer effect (inhibition of tumor cell proliferation) in colon and breast cancer, via alteration of prostaglandins synthesis. It was also emphasized that n-6/n-3 PUFA ratio is very important to treat diseases (36).

Bioactive Peptides and Biological Effects

Bioactive peptides generally possess between 20 amino acid residues, and is its location in the sequence of amino acids that determine its bioactive effects (37). These compounds are produced in different ways (38), such as enzymatic proteolysis (e.g. gastrointestinal digestion), *in vitro* hydrolysis (e.g. proteolytic enzymes), and some food processing methods (e.g. cooking, fermentation, ripening) (39).

Bioactive peptides can be found in dairy fermented products, legumes, cereals, meat as well as fish-derived products. Bioactive peptides are detected during hydrolyzation or fermentation processes, in wheat, maize, soy, rice, mushrooms, pumpkin and sorghum products (40). Approximately 20,000 bioactive peptides whose protein sources are meat, fish, cereal, pseudocereals and legume grains have been investigated up to date (40).

Bioactive peptides have activities on cardiovascular, digestive, endocrine, immune, and nervous systems. According to most researches, these molecules have hypotensive, antimicrobial, immunomodulatory, anticancer, antithrombotic, opioid, and antioxidant effects. In addition, hypocholesterolemic or anti-diabetic, hypocholesterolemic, and anti-inflammatory effects are also provided by bioactive peptides (37, 40, 41).

Bioactive Secondary Molecules

There is a rising interest for medicinal and aromatic plants-derived bioactive molecules. Fruits, vegetables and whole grains are also sources of these secondary metabolites. This group of compounds include a heterogeneous class of molecules with different chemical structures and hydrophilic or lipophilic units (29). Basic and important functions of this type of foods are to collect and inactivate free radical-containing metabolites (2), as well as to stimulate the immune system and to regulate antibacterial and antiviral effects (42, 43). There are two different ways to obtain phytochemicals: from plants naturally containing phytochemicals and production with gene expression.

Table 1. Fatty acid contents in edible wild plants (%).

Spices	18:3 ALA	18:4 SDA	18:3 GLA	20:5 EPA	20:4 AA	22:5 DPA	22:6 DHA
Amaranthus viridis L. (amaranth)	22.34	0.00	0.25	0.93	0.00	0.00	0.00
Beta maritima L. (wild beet)	22.44	0.50	0.17	0.54	0.52	0.49	0.65
Cakile maritima Scopoli (sea rocket)	23.84	0.38	0.00	0.09	0.00	0.00	0.00
Cardaria draba L. (hoary cress)	30.56	0.62	0.60	2.16	0.56	0.00	0.00
Chenopodium album L. (goosefoot)	44.82	0.17	0.00	0.36	1.30	0.00	0.00
Chenopodium murale L. (goosefoot)	36.04	0.14	0.00	0.41	1.01	0.00	0.00
Chenopodium opulifolium Schrader (goosefoot)	33.02	0.00	0.57	3.06	0.00	0.74	2.30
Crithmum maritimum L. (rock samphire)	9.98	0.42	0.25	0.76	0.00	0.76	0.00
Malva sylvestris L. (common mallow)	42.22	0.29	0.50	0.00	5.30	0.00	0.00
Parietaria diffusa Mert. (pelitory-of-the-wall)	21.18	3.64	1.99	0.00	0.00	0.00	0.00
Pichris echioides L. (ox-tongue)	43.20	0.20	0.42	0.00	0.00	0.15	0.00
Plantago major L. (plantain)	33.32	2.02	0.00	1.27	1.02	0.00	1.47
Portulaca oleracea L. (purslane)	32.60	0.00	0.27	0.00	0.00	0.00	0.00
Rumex crispus L. (curly dock)	41.21	1.73	0.00	0.12	0.00	0.00	0.00
Salicornia europaea L. (glasswort)	28.03	0.44	0.55	0.39	0.00	0.00	0.00
Sisymbrium irio L. (hedge mustard)	31.04	0.19	0.00	0.55	0.32	0.21	0.83
Sonchus oleraceus L. (sow-thistle)	43.58	0.09	0.34	0.35	0.00	0.25	0.00
Sonchus tenerrimus L. (sow-thistle-of-the-wall)	30.33	0.11	0.35	0.00	1.83	0.38	0.00
Stellaria media Villars (chickweed)	22.75	4.68	2.40	0.42	0.41	0.00	0.00
Verbena offieinalis L. (vervain)	54.99	0.00	0.25	0.60	0.62	0.00	0.00

AA, arachidonic acid; ALA, Alpha-Lipoic Acid; DHA, Docosahexaenoic acid; DPA, Docosapentaenoic Acid; EPA, eicopentaenoic acid; GLA, gamma-Linolenic acid; SDA, Stearidonic acid.

They are generally divided into three main categories: terpenes and terpenoids, alkaloids and phenolic compounds, consisting of 25,000, 12,000 and 8,000 types, respectively (44). Thirumurugan and *et al.* also indicated that around 2,140,000 bioactive molecules are known, and they are generally categorized based on their vast diversity in structure, function, and biosynthesis (22). Five main classes of secondary metabolites are defined: terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, non-ribosomal polypeptides and enzyme cofactors. The synthesis of bioactive compounds can be performed by shikimic, malonic and mevalonic acids and non-mevalonate (MEP) pathways (45).

They are especially important in pharmaceutical industries, used in drugs, dyes, fragrances, flavors and dietary supplements formulation. In food sector, they are employed as coloring-agents, flavoring or texturizing agents. Particularly, metabolites with antioxidant properties find any role in many applications as preservatives or anti-browning agents (44). Owing to their huge usage area, both the scientific and industrial interests for plant bioactive metabolites have been growing (23).

Terpenoids contain numerous molecules, such as iridoids, monoterpenoids, sesquiterpene lactones, sesquiterpenoids, diterpenoids, steroid saponins, triterpenoid saponins, phytosterols, cardenolides and nortriterpenoids, cucurbitacins, bufadienolides, other triterpenoids and carotenoids (46). The alkaloids comprehend indole, amaryllidaceae, betalain, isoquinoline, diterpenoid, lycopodium, sesquiterpene, monoterpene, pyrrolizidine, peptide, pyrrolidine and piperidine, quinolizidine, quinoline, steroidal, and tropane compounds. The phenolic substances include anthochlors, anthocyanins, chromones, minor flavonoids, benzofurans, coumarins, isoflavonoids, flavonones and flavonols, phenolic ketones, stilbenoids, lignans, phenols and phenolic acids, quinonoids, phenylpropanoids, tannins and xanthones. Finally, other nitrogen-containing components include cyanogenic glycosides, amines, nonprotein amino acids, glucosinolates, purines and pyrimidines (47) (Figure 1).

Terpenes and Terpenoids and Biological Effects

Essential oils are natural, volatile and complex liquids, with a characteristic smell and flavor that varies depending on the type of molecules present in the oil. Aromatic plants synthesize essential oils as secondary metabolites and they are generally exerted as flavoring agents or for further isolation of flavoring substances (48).

Essential oil components are low molecular weight molecules, grouped into two classes, based on different biosynthetic origin. Terpenes, including monoterpenes and sesquiterpenes and terpenoids, consisting of monoterpenoids, (48, 49). Terpenoids the are largest group of natural bioactive compounds and represent most abundant and huge class of natural compounds among plant bioactive molecules. They are a large component of volatile floral and fruit scents. Terpenoids are divided into several classes: monoterpenes, diterpenes, triterpenes and tetraterpenes, according to the number of building blocks (49). They derive from either acetyl-CoA or pyruvate/glyceraldehyde-3-phosphate molecules (50). Approximately 25,000 terpenoids derive from the five-carbon precursor isopentenyl diphosphate (IPP) (22). It has been demonstrated that terpenes are responsible for human health owing to their anti-inflammatory, anticarcinogenic and neuroprotective effects, as well. According to in vivo and in vitro experiments, it has been shown that terpenes are responsible for anti-tumorigenic effects against such processes and they can be used as chemotherapeutic agents for treating tumors (51). Furthermore, terpenoids are used for some diseases and disorders, as they have antimicrobial, antifungal, antiparasitic, antiviral, hypoglycemic, anti-inflammatory and immunomodulatory effects (49).

Several terpenoids are used as drugs. Artemisinin is used as antimalarial, paclitaxel (also known as taxol) is an effective anti-cancer agent and avicins and parthenolide reduce tumor cells growth. Therefore, they are usable to produce disease-related drugs (50).

Terpenoids antimicrobial activity is related to their functional groups. Specifically, in phenolic terpenoids, hydroxyl groups and delocalized electrons determine functions against microorganisms. These compounds can easily interact with bacterial wall interfering with the biosynthesis of its components owing to their lipophilic character. They penetrate the bacterial cell and break protein synthesis, DNA replication and repair mechanisms. Carvacrol (a monoterpenoid phenol) is one of the most active components to inhibit microorganisms (52, 53).

Apart from health effects, terpenoids have extensive applications in pharmaceutical, cosmetic and food industries, besides to present good colouring, disinfectant, flavoring and agrichemicals potentialities (50). In addition, terpenes have also been employed as preservatives, plant hormones and insect attractants (26).

Alkaloids and Biological Effects

Alkaloids are a structurally wide class of nitrogen containing groups within heterocyclic rings. They comprehend one or more nitrogen atoms and are produced by three aromatic amino acids or by glutamate, aspartate or glycine molecules. To date, around 12,000 alkaloids have been identified (22, 45). Furthermore, alkaloids are biosynthetic precursors, which can be divided into various categories which contain indole, piperidine, tropane, purine, pyrrolizidine, imidazole, quinolozidine, isoquinoline and pyrrolidine molecules (54, 55). A broad range of biological effects on human health were deter-

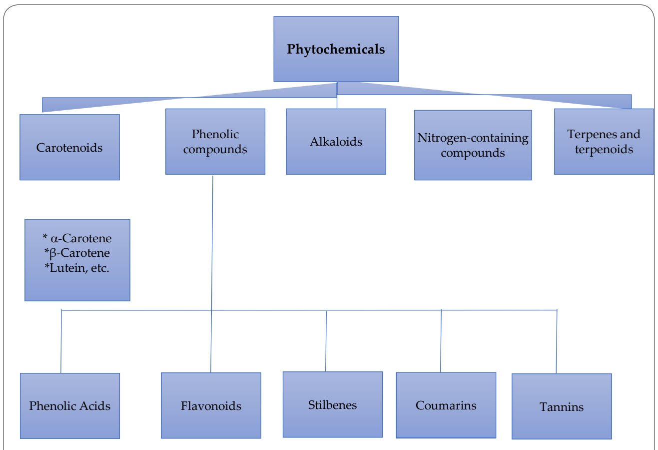

Figure 1. Classification of phytochemicals.

mined: anti-cholinergic, antitumor, diuretic, sympathomimetic, antiviral, antihypertensive, hypno-analgesic, antidepressant, mio-relaxant, anti-tussive, antimicrobial and anti-inflammatory outcomes (56). Some alkaloids also exhibit antiproliferative, antibacterial, antiviral, insecticidal and anti-metastatic effects on various types of cancers, according to pre-clinical studies (57, 58). Besides, vinblastine, vincristine, camptothecin are used to treat cancer; and reserpine, ajmalicine and quinine alkaloids are also applied to prevent hypertension and malaria, respectively (59). At molecular level, alkaloids can affect membrane permeability, membrane proteins with ion channels and receptors, enzymes and other proteins ,such as DNA, RNA and corresponding proteins, electron chain, and the cytoskeleton (60). According to Shi *et at.* the isoquinoline (from barberry) is one of the most studied issues. Berberine affects the AMP-activated protein kinase (AMPK) which regulates tumor progression and metastasis. The effect mechanisms of this molecule are diverse, such as regulation of blood cholesterol and triglyceride, lowering blood glucose, enhancing the insulin resistant state, and influencing the function of the pancreatic β-cells. It has also anticancer activity (61).

A wide range of alkaloids have influence on nervous system. It was shown antidepressant like effect mediated through serotonergic, noradrenergic, and dopaminergic intervention (62). For example, β-carboline alkaloids which are harmane, norharmane and harmine behave as antidepressants interfering with MAO-A and several cell-surface receptors including serotonin receptor. Akuammidine, rhaziminine, and tetrahydrosecamine alkaloids cause a biphasic effect on the MAOA inhibitory component of tribulin. Mitagynine reduces release of corticosterone, meaning that an antidepressant-like effect can appear (62). Furthermore, alkaloids stimulate α- and β-receptor and enhance the activity of prefrontal cortex, thalamus and visual system (62).

Phenolic Compounds and Biological Effects

Plant phenols are secondary metabolites, described by having one (monophenolic) or more (polyphenolic) aromatic rings attached one or more hydroxyl groups, and synthesized from aromatic amino acids (63). The main dietary sources are fruits and plant-derived beverages, such as fruit juices, tea, coffee and red wine, besides to be also found in vegetables, cereals, chocolate, and dry leguminous (64).

Phenolic compounds (PC) can be divided into different classes based on their basic chemical structure, wide substitution patron and numbers and variations in C ring (65). Therefore, they are categorized according to two major units, flavonoids and non-flavonoids. Besides, they have a different class, eight of which depend on the number of phenol rings and on the some structural elements linking these rings (66). Polyphenols can be grouped as phenolic acids (e.g. gallic acid), flavonoids, stilbenes, lignans, coumarins, and tannin polymers (67). As a matter of fact, the flavonoid group shares a common structural feature that have two aromatic rings bounded together by three carbon atoms that form an oxygenated heterocycle (68). According to their abundance in food, two major flavonoid classes can be defined. First group includes flavones, isoflavones, flavanones, flavandiols, anthocyanins, proantho-cyanidins and cathechins. The second involve flavan-3-ols, anthocyanidins, chalcones and other biosynthetic intermediates of the flavonoid biosynthesis (i.e. aurones, bioflavonoids and dihydrochalcones) (65). The non-flavonoids group consist of phenolic acids (PA), stilbenes and lignans molecules. PA are abundantly found in foods, being divided into two classes: hydroxybenzoic and hydroxycinnamic acids (66, 68). Each group vary with their number and arrangement of the hydroxyl groups and in their extent of alkylation or glycosylation process (68).

PC are usually used as antioxidants (69), and the structural properties of polyphenols determine their biological potential. In addition, PC also have neuroprotective, fungicidal, bactericidal, anti-atherosclerotic and anticancer effects (66).

Pance and *et al.* (70) indicated that quercetin is one of the most studied antioxidant, that has several mechanisms related with ROS removal, preventing lipid peroxidation and metal ion chelation. In addition to quercetin, myricetin, quercitrin and rutin molecules also help to inhibit the production of superoxide radicals. Besides, quercetin prevents inflammation onset and strength the immune system. On the other side, quercetin, naringin, hesperetin and catechin possess a variable degree of antiviral activity, by affecting the RNA and DNA viruses replication and infectivity (70).

In addition, many plant-based substances, such as terpenes, aromatic isothiocyanates, organosulfur compounds, protease inhibitors, dithiolthiones and indoles are shown as “chemopreventive" (71). Flavonoids have the ability to interrupt different stages of carcinogenesis, not only with antioxidant activity, but also with other anticancer mechanisms. For instance, tea polyphenols (green tea), gingerol (gingers), resveratrol (grapes), curcumin (turmeric), genistein (soybean), rosmarinic acid (rosemary), apigenin (parsley) and silymarin (milk thistle) have been used in chemotherapy and radiation therapy (72). As so, catechins (mostly epigallocatechin 3-gallate, from green and, black tea)(73), diallyl sulphides and allicin (garlic and onions), sulforaphanes and indole-3-carbanols (*Brassica* vegetables), genistein (soya), delphinidine and ellagic acid (soft fruits and various nuts), anthocyanins (berries, grapes, cherries, etc.) have also demonstrated to prevent cancer. Likewise, genistein, resveratrol and catechins have shown potent inhibitory activity on a wide number of cancer cells, binding growth factor and signaling pathways implicated in cancer growth and progression (63). Also, the autophagy-inducing capacity of curcumin, allows it to be used in cellular protection against oxidative stress-related cell death in human umbilical vein endothelial cells of cancer. Similarly, quercetin induces cytoprotective autophagy, which is desirable process for cancer treatment in gastric cancer cells (67, 74, 75). Silymarin, daidzein, luteolin, kaempferol, apigenin have also been found to have inhibition effect on several cancer types (76) Finally, caffeic and ferulic acid also affect the stomach tumorigenesis in mice. Caffeic acid is also inhibits the formation of carcinogenic nitrosamine (67).

It has been suggested that natural antioxidants have ability to change the metabolism of certain carcinogens (77). Some reports indicate that they decreased microsomal metabolism to DNA-binding metabolites and epoxidation, enhanced the formation of readily conjugated and excreted metabolites and increased both the activity and level of GSH and glucuronide conjugating enzyme (76).

It is recognized that high levels of proteasome activity characterize cancer cells. PC affect the proteasomal protein degradation pathway directly or indirectly, with influence on proteasome structure and modulation of the intracellular protein degradation efficiency. Particularly, quercetin, apigenin, kaempferol and myromycin molecules in Jurkat T leukemic cells can inhibit proteasome metabolism (77).

PC are also relevant in other disorders. Polyphenols can improve cardiovascular health by means of inhibiting platelet aggregation, reducing vascular inflammation, modulating apoptotic processes, limiting LDL oxidation and improving lipid profile (72). Moreover, many studies have also suggested that the main flavonoids found in citrus fruits, cocoa-rich products and dark chocolate at high doses are also related to cardiovascular disease risk reduction (78, 79). Saponin, myrcelin, pectin and glucosides display antidiabetic activities (80). Green tea and their extracts have high level of flavan-3-ol molecules, epigallocatechin-3-gallate (EPCG), which are among the most important cardioprotective antioxidants. Similarly, black tea has a high antioxidant ability, but lower than green tea extract. They both help to decrease blood pressure, which can positively affect the cardiovascular risk profile (78). In addition, some studies proved that cocoa polyphenols have a potential effect on preventing cardiovascular disease risk, with regard to vascular elasticity, improving pulse wave velocity (PWV), arteriolar and microvascular vasodilator capacity, inflammatory markers (81). These effects are also observed by smokers, diabetic, overweight, hypertensive and elderly patients (78, 82).

Hypoglycemic plants can enhance insulin secretion, glucoses absorption by muscle and fat tissues, preventing glucose absorption from the intestine and glucose production from liver cell (83). It is reported that approximately half percent of drugs that are approved as anti-diabetic in the last 10 years are plant-based. In fact, plants that possess better antidiabetic effects, have 1,200 phyto-bioactive compounds richer than other plants. Furthermore, 400 of these extracts have showed type 2 anti-diabetic activities (79). Some *in vivo* pancreatic islet assays revealed that resveratrol can decrease insulin secretion and have protective effect on the endocrine pancreas cells. Besides, it has a high antioxidant effect, affecting β-cell failure that causes to form type-2 diabetes (77, 84). Moreover, according to Pandey *et al.* the development of all stages of lung, skin, breast, prostate, gastric and colorectal cancer types can be prevented by resveratrol (68).

Carotenoids and Biological Effects

Carotenoids are produced by plants, algae and some photosynthetic bacteria. They are observed within C_{40} tetraterpenoid group and locate conjugated double bond system that provide their special properties and functions. Carotenoid pigments confer the yellow, orange and red colors in fruits and vegetables and these pigments are responsible for multiple functions (22, 85, 86).

The key carotenoids comprise β-carotene, violaxanthin, neoxanthin, lutein, and loroxanthin (19-hydroxylutein). Lutein and β-carotene each are responsible for about 25% of total carotenoids, other three xanthophylls group share between 10% and 20% of total amount of carotenoids (85, 86). Yilmaz *et al.* separated carotenoids in two groups: provitamin A and non-provitamin A carotenoids (87). These compounds are mostly found in green leafy vegetables and tend to be most bioavailable when consumed with lipid based-foods, like yolks of eggs. Moreover, this bioavailability increases when food preparation processes, such as blending or heating are applied, because food processes break down the cell walls of the plant (88). Generally, β-carotene, α-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin are the most commonly found carotenoids in food (89).

Carotenoids are valuable liposoluble molecules. They demonstrate pro-vitamin A activity and have antioxidant potential. They decrease the likelihood of several chronic diseases, such as cancer or cardiovascular diseases, macular degeneration and age-associated biological transformations. Lycopene is considered as potentially helpful against the risk of prostate cancer. In addition to lycopene, β-carotene is also responsible for considerable biological properties preventing oral, pharynx and larynx cancers. It is also main precursor of vitamin A. Vitamin A is one of the most powerful antioxidants, which stimulate the growth and development of night vision at same time that maintains the epithelial tissue and exerts immunological functions. Likewise, β-cryptoxanthin associates with vitamin A activity and plays significant role in eye vision. Lutein and zeaxanthin have several effects on eye health, as well. Lutein is found in wheat and durum, and is responsible for the reduction of cataracts incidence, age-related macular degeneration, as well as cancer and cardiovascular disease symptoms (90-92).

Heterologous Phytochemicals Manufacturing in Plant Structures

Phytochemicals are important substances that have impulse in the development and discovery of agricultural and pharmaceutical components, including medicines and pesticides. Nevertheless, these components are generally scarce in nature, and biosynthetic pathways for most of them are still not entirely clear (93).

Heterologous manufacturing of phytochemicals in bacteria, plant and yeast hosts has been followed as a key tactic to explain sourcing subjects related with lots of valuable phytochemicals, and has been recently used as a way to help in plant biosynthetic pathways clarification (93). Due to the structural difficulty of certain phytochemicals and related biosynthetic production pathways, reconstruction of plant pathways in heterologous hosts can face several challenges. Synthetic biology methods have been improved to overcome these difficulties in areas, such as precise control over improving functional expression of heterologous enzymes, heterologous gene expression, and modification of central metabolism to increase the supply of pathway precursor components. These methods have also improved plant pathway reconstruction and phytochemical manufacturing in a wide variety of heterologous hosts (93).

Choosing a Heterologous Plant Host to Produce Phytochemicals

Many plant hosts are naturally intractable or lack well-enhanced molecular biology means for heterologous gene transfer. Therefore, a small number of model plants is often employed for heterologous phytochemical manufacturing. The primary model organism for the study of plant biology, *Arabidopsis thaliana*, was the first to have its genome sequenced and a set of genetic modification attitudes were improved for genetic modification, containing nuclear transformation. These approaches were applied to the heterologous transfer of TPS10 maize terpene synthase into *A. thaliana,* producing a transgenic plant made with high levels of sesquiterpene yields, similar to those made by maize. The TPS10 heterologous gene transportation in *A. thaliana* also allowed the investigation of TPS10 products ecological functions, showing that the components formed by this enzyme were suitable to help females of the parasitoid *Cotesia marginiventris* locate their lepidopteran hosts (93).

Likewise, tobacco plant types of the genus *Nicotiana* are well-known organisms for heterologous reconstruction of plant biosynthetic production pathways. The BY-2 cell tobacco line, derived from *Nicotiana tabacum* seedlings*,* has generally been used in cell suspension culture, and as an organism model to examine plant molecular biology and physiology. *Nicotiana benthamiana* can be effectively infected by many plant viruses and has, therefore, been employed as an organism model to look for plant-pathogen relations. A great deal of biosynthetic production pathways have been reconstructed in *N. tabacum* and *N. benthamiana* to produce different components, containing mono, di and sesquiterpenes, lignans, glucosinolates, and flavonoids, with reconstituted pathways comprising up to ten heterologous enzymes (93).

Phytochemical Properties and Some Challenges to Distribution of Phytochemicals

Overall, multiple phytochemicals can be combined with supplements, foods and pharmaceuticals owing to their health promoter properties (94). These compounds alter in their molecular weights, functional groups, polarities and charges, causing changes in their partitioning, solubilities, chemical stabilities and physical states. As bioactive phytochemicals application in foods and supplements is commonly limited due to their poor stability, solubility and bioavailability, there is need to develop new system to utilize the health promoter properties of phytochemicals (95). Understanding the specific physicochemical and molecular characteristics of the phytochemical to be encapsulated is also crucial to design appropriate phytochemical delivery systems (96). On the one hand, the successful delivery of bioactive phytochemicals faces a lot of barriers during human digestion system.

Biocompatible and Biodegradable Nanosystems for Enhancing Phytochemicals Bioavailability

Nanotechnology designs in nano size range (10^{-9} m), allowing the instant release of a plant extract in the free form under dilution in biological liquids (97). So far, plant extracts have been designed for nanoemulsions, liposomes and nanoparticles, but several factors, including the presence of organic solvent, polarity of active ingredient, solubility, and volatility should be considered. For essential oils, as they are rich in terms of lipophilic substances and highly volatile molecules, lipid-based nano systems formulated at low temperatures and without solvent vaporization, like nano emulsion or liposome, are preferable. Regardless of the kind of nano system or preparation method, there are some plain classifications. Average size, surface charge and association efficacy are considered the basic physicochemical parameters (97). When looking at the colloidal structures size determination, this can be done by several methods like transmission laser diffraction, small angle and X-ray electron microscopy. Beyond that, dynamic light scattering provides different benefits, like a comprehensive range of simplicity, measurement, and reliability, besides to be a non-destructive method requiring a low quantity of diluted sample (98).

Protein Nanocarrier Systems

Protein matrix encapsulation is viewed as the most useful nutritional system. In spite of the popularity of protein-derived transporters for delivering other food bioactive compounds like vitamins, β-carotene flavonoids, protein carriers applied for bioactive core encapsulation is still restricted. Indeed, the encapsulation of bioactive core substance with a chemically alike material is challenging due to structural resemblance; thus, encapsulation shell is estimated to face variability issues similar to the encapsulated bioactive compound. Among the protein sources, milk proteins are mostly used to encapsulate non-peptide bio-active components, besides having a history of use in the encapsulation process of small hydrophobic ingredients (99).

Polysaccharide Nanocarrier Systems

Polysaccharides are usually ideal type of coating material due to their structural stability, plenteous in nature and inexpensiveness. On the other hand, the polysaccharide coating material is slightly sensitive, stablishing with bioactive core and forming complex products under extreme conditions, like high temperature or pressure (i.e. Maillard reaction products), being not only potentially toxic but may also trigger bioactive substances depletion (99). These polysaccharide materials are classified into polyelectrolytes containing anionic, cationic and neutral subtypes, and non-polyelectrolytes, that despite are biocompatible, have also been applied on polysaccharide nanoparticles development, interacting with specific receptors in cells and tissues, thus ensuring a site-specific controlled targeting for components carried in polysaccharide-based nanoparticles (100).

Lipid Nanocarrier Systems

Lipid-derived systems have been used to encapsulate bioactive substances, with liposphere and liposome being the most common, although liposome is more commonly used than liposphere, being less applied for food application systems due to its very high level of

Table 2. Appropriate techniques for nanoparticles design as transporters for bioactive compounds along with separate benefits and difficulties of each method (101).

Methods	Advantages	Disadvantages	References
Simple emulsion (w/o)	Simple, does not require organic solvent,	Two-step process	(102)
Double emulsion (w/o/w)	Suitable for hydrophilic molecules	Low reproducibility	(103)
High pressure homogenization	Simple, organic solvent free, robust method	Hard to scale-up	(104)
Coacervation	Good efficacy, easy to scale up	May cause proteins denaturation if organic solvent used	(105)
		Outflow of carried molecule to external water	(106)

saturated fatty acids, and the restricted option for substances selection. Nonetheless, liposome is compatible with many bioactive substances. The aqueous core seems appropriate for hydrophilic bioactive cores and other ingredients, while the bilayer internal is coherent with hydrophobic ones (99). **Figure 2** summarize the encapsulation materials for phytochemicals. **Table 2**. summarize the appropriate techniques for design of nanoparticles as transporters for bioactive compounds along with separate benefits and difficulties of each method.

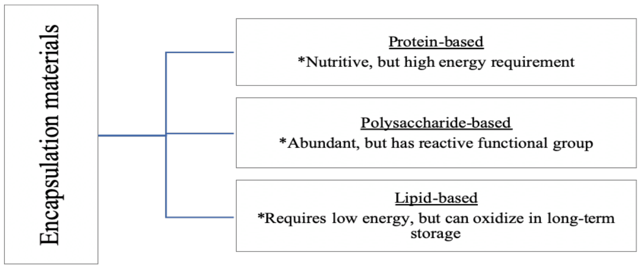

Figure 1. Encapsulation materials for phytochemicals.

Nanoemulsions

Nanoemulsion precipitations to transfer bioactive compounds in a controlled manner has been recently used in Food Science and Technology; so, there is still a long way to go. Nanoemulsions have been mostly used on functional foods production, as this technology permits to regulate both bioactive nutrients and non-nutrients release. On nanoemulsions formulation, liquid solutions of lipid droplets (size of droplets around 100 nm) are formed by using a lot of different strategies. The most common production technology is High Pressure Homogenization (HPH), avoiding the particle aggregation and components separation by gravitation when compared with normal emulsions. Actually, in nanoemulsions systems, functional components are only used to interact with food matrix, thus ensuring organoleptic properties preservation, while increase bioactive components bioavailability, favored by passive transport. Later, over human digestion, the nano encapsulation system enhances the solubility of bioactive compounds and others, in addition to their presence suiting absorption at the gastric and intestinal phases. In addition, the use of nanoemulsions offers benefits, among them reduced metabolism, increased protection, and lower the efflux transporters activity. At present, phytochemical components encapsulation using nanoemulsions systems have been target of extreme importance, thus ensuring to reserve these bioactive components from human digestion. Actually, the literature published as a result of *in vitro* and *in vivo* characterizations, led to marked improvements namely on human wellbeing and improved bioavailability of the bioactive phytochemicals in the target tissue (100).

Future Prospects and Conclusion

Presently, it is a current trend of global consumers to be nourished with healthy or natural food. However, it is not clear what the definition of healthy or natural food is. According to current studies, plant-based diets have more benefits for humans, reducing the incidence of several diseases.

The decision on the definition of healthy food still demands a lot of research, collaboration, and interaction. Long-term effects of plant-based molecules require more investigation. Particularly, the clarification of intracellular signaling pathways, bioavailability, or consumption of combinational foods and synergistic efficacy of bioactive compounds need to be fully understood, in order to be able to be clinically used. From this point, new tools and experimental designs should be developed.

In the future, with 3D printing technology, therapeutic personalization may be a short-period reality, as it does not need the use of organic solvents or high temperatures; so, combining bioactive substances in nanocarrier materials or other carriage systems, will becomes safer and much more cost-effective. In addition, as it allows to create carriage systems layer-by-layer, it will be possible to produce different reservoirs for several-drug transporting systems (107).

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Conflicts of Interest

The authors declare no conflict of interest.

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