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Review Article

Role of Bioactive Compounds in Human Health

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Abstract

Bioactive compounds are defined as components of food that have an impact on physiological or cellular activities in the humans or animals that consume such compounds. They include flavonoids, anthocyanins, tannins, betalains, carotenoids, plant sterols, and glucosinolates. They are mainly found in fruits and vegetables; have antioxidant, anti-inflammatory, and anti-carcinogenic effects; and can be protective against various diseases and metabolic disorders. Such beneficial effects make them good candidates for development of new functional food with potential protective and preservative properties. Various fruits and vegetables provide a range of nutrients and different bioactive compounds including phytochemicals (phenolics, flavonoids, and carotenoids). Most importantly, flavonoids have antioxidant and anti-inflammatory health benefits, positive effects on cardiovascular health, and anti-cancer properties. Anthocyanins have positive cardiovascular health effects, though it is needy of further evaluation. Carotenoids exert protective effects against several kinds of cancers, in addition to benefits to vision and skin. Glucosinolates have protective roles against cancers and dementia. However, there is a great variation in the literature on the role of different bioactive compounds in human health, which calls for further research and better understanding in order to maximize potential health benefits.

Keywords: Anthocyanins; Betalains; Bioactive Compounds; Carotenoids; Flavonoids; Glucosinolates; Plant Sterols; Tannins

Abbreviations

AMD: Age-Related Macular Degeneration; CVD: Cardiovascular Disease; LDL: Low-Density Lipoprotein; UV: Ultraviolet.

Introduction

A bioactive compound is a compound having some biological activity. As the name suggests (Greek 'bios' means life and Latin 'activus' means dynamic or full of energy), a bioactive compound (or substance) has its direct physiological or cellular effects on a living organism. Such effects may be positive or negative depending on the nature of the substance, its dose, and its bioavailability. Accordingly, bioactive food components are components in foods or dietary supplements, other than those necessary to meet the basic nutritional needs, which can change the health status of the humans or animals that consume them. Several definitions attribute the term 'bioactive compound' directly to compounds derived from foods (products, or present in food, or part of the food chain) in such a way that it is presented as synonymous with 'bioactive food', and even more specifically, limited to plants or food crops [1].

In plants, nutrients are generally not included in the term "plant bioactive compound". Typically, bioactive compounds in plants are produced as secondary metabolites that are not necessary for the daily functioning of the plant (such as growth); however, they play an important role in the competition, defense, attraction, and signaling. These compounds can then be defined as secondary plant metabolites eliciting pharmacological or toxicological effects in humans and animals [2].

Types of bioactive compounds present in plants

Bioactive compounds are primarily found in fruits and vegetables, and include flavonoids, anthocyanins, tannins, betalains, carotenoids, plant sterols, and glucosinolates. Various fruits and vegetables provide a range of nutrients and different bioactive compounds including phytochemicals (phenolics, flavonoids, and carotenoids) which may exert their peculiar physiological and cellular effects.

Flavonoids

Flavonoids form the largest and a diverse group of bioactive compounds, known as phytonutrients or phytochemicals, which are the major constituents of polyphenols and can be considered more into flavanols, flavones, isoflavones, flavanones, anthocyanidins, flavanonols, and flavans (catechins and proanthocyanidins) [3]. Each subgroup and its type of flavonoids have a distinctive range of plant source, functions, and health benefits. This collection of plant bioactive compounds is known to possess benefits to human health due to their identified antioxidant and anti-inflammatory effects [4]. Flavonoids exist in every fruit and vegetable, and along with carotenoids, they are responsible for their unique colors. There are more than 6,000 different identified types of flavonoids which are beneficial in human diet.

- **Chemical structure:** Flavonoids are generally soluble in water and grow in cell vacuoles. Their basic molecular structure is two benzene rings bonded to a three-carbon chain that forms a closed pyran ring.
- **Sources:** Flavonoids are ample in a range of fruits and vegetables. Its major sources include berries, leeks, ginger, grapefruit, carrot, apple, onion, broccoli, cabbage, kale, tomato, lemon, parsley, buckwheat, and legumes. Coffee, tea, chocolate, a range of spices, herbs and red wine are also bursting with health-giving flavonoids.
- **Bountiful health benefits:** Many studies have revealed that a diet rich in phytonutrients is good for human health. Flavonoids are beneficial in this regard as they act as influential antioxidants; they also neutralize free radicals and limit damage to cells and other body tissues [5]. They also possess anti-inflammatory and anti-aging properties [6]. Various studies have shown that there is a relation between certain polyphenols and their preventive effects on such diseases that can bring 'oxidative stress' (for example, cancers, cardiovascular disease [CVD], and neurodegenerative diseases). Their ability to improve the quality of blood vessel walls has also been shown in various experimental studies. Flavonoids have a supportive effect on the nervous system. In addition, they can control the action of certain enzymes and cell receptors. Studies suggest that flavonoids can also help regulate blood flow in the brain, which may result in better cognitive function [4,7].

Anthocyanins

These compounds are present in cell sap and are soluble in water. They are responsible for the red, purple, and blue colours of fruits, vegetables, and flowers.

- **Chemical structure:** Structurally, an anthocyanin is a phenolic molecule with 15 carbon atoms and seen as two benzene rings joined together with a three-carbon chain. The presence of flavylium nucleus makes it highly reactive.
- **Sources:** Though anthocyanins can be found in many plants, they are mainly present in acai, blackcurrant, blueberry, bilberry, cherry, red grape, and purple corn.
- **Bountiful health benefits:** Even though anthocyanins are important antioxidants in vitro, their real biological activity is generally low because of their low stability and poor absorption. Various studies have shown health benefits of anthocyanins, which mainly focus on their positive effects on cardiovascular health, anti-cancer activity and anti-inflammatory properties [8].

Tannins

Tannins are a class of astringent, polyphenolic biomolecules that bind to and precipitate proteins and various other organic compounds and macromolecules.

- **Chemical structure:** Tannins are complex mixtures of polymeric polyphenols, with the gallic acid as base unit (so, also called as gallo-tannic acid). Gallnuts of oak trees contain 50-70% tannin. Tannins are divided into two groups: condensed tannins and hydrolysable tannins; the former group comprises of compounds in which the nuclei are held together by carbon- carbon or ether linkages whereas the latter group comprises of ester-like compounds that are the polymers of gallic acid and ellagic acid. The color of tannins ranges from colorless to yellow or brown. It leads to astringency of foods and enzymatic browning reactions.
- **Sources:** Key sources of tannins are teas, coffee, pomegranates, persimmons, most berries (cranberries, strawberries, blueberries), grapes, red wine, chocolate (with cocoa content 70% and higher), and spices (cinnamon, vanilla, cloves, thyme) [9].

- **Bountiful health benefits:** In experimental animals, tannins have been described to decrease feed intake, growth rate, feed efficiency, net metabolize energy, and protein digestibility. So, foods rich in tannins are of low nutritional value. However, recent studies have specified that their major effects may be because of a decreased effectiveness in translating the absorbed nutrients to new body substances rather than due to an inhibition on food consumption or digestion [10]. Of late, there is considerable interest in considering various tannins as bioactive substances because of their capability of producing beneficial effects in the body if they are ingested in the diet for long periods of time. This is particularly because of their antioxidant properties that protect the tissues from the action of free radicals due to the cellular aging and other physiological processes [11]. Tannins have also been shown to have other positive effects on health including acceleration of blood clotting, reduction in blood pressure, decrease in serum lipid levels, and modulation of immune responses; the dosage and the kind of tannins are critical to these effects [12].

Betalains

These pigments are red and yellow; and they resemble the anthocyanins and flavonoids in appearance. However, unlike them, the betalains contains nitrogen.

- **Chemical structure:** Betalains are indole-derived pigments which can be divided into the red-violet betacyanins and the yellow betaxanthins, with their colours ascribed by the betalain structures resonating double bonds. They are soluble in water and thus can get integrated into aqueous food system [13,14].
- **Sources:** The edible sources of betalains are red and yellow beetroot, coloured swiss chard, leafy or grainy amaranth, prickly pear, red pitahaya, and several cacti.
- **Bountiful health benefits:** Owing to their antioxidant, anti-cancer, anti-lipidemic and antimicrobial activities, betalains have progressive health effects. In diet, they are nontoxic and thus have potential application as functional foods and a promising alternative to supplement therapies in oxidative stress-, inflammation-, and dyslipidemia-related diseases such as stenosis of the arteries, atherosclerosis, hypertension, and cancer, among others [13]. Due to their toxicological safety, accessibility, low price, biodegradability, and potentially advantageous biological effects on health, the incorporation of betalains in food manufacturing and related industries could pave the way to overcome current concerns over the health risks of artificial colours [15]. Nevertheless, larger, longitudinal studies are needed to ascertain the exact mechanism of these bioactive compounds and their practical application in human health.

Carotenoids

Carotenoids – also known as carotenes – belong to the group of lipid-soluble hydrocarbons; and their oxygenated derivatives are called xanthophylls. The name 'carotenes" is derived from the red colour of carrots; but they are commonly distributed in various other plants also as they are found in green leaves, in most yellow and red fruits, and many roots. The colour of egg-yolk and some fish is also due to carotenoids.

- **Chemical structure:** A carotenoid consists of eight isoprenoid units jointed in such a manner that the arrangement of isoprene units is reversed in the center of the molecule. Carotenoids absorb wavelengths ranging 400–550 nanometers (violet to green light), which is directly linked to their structure and causes the compounds to be deeply colored yellow, orange, or red.
- **Sources:** Some of the rich sources of carotenoids are carrots, plums, apricots, mangoes, cantaloupes, sweet potatoes, kale, spinach, cilantro (coriander), collard greens, fresh thyme, turnip greens, and winter squash.
- **Bountiful health benefits:** Carotenoids exert protective effects against several kinds of cancers, in addition to benefits to vision and skin. Importantly, the β-carotene is a precursor of vitamin A which is needed for robust immune system, healthy skin and mucous membranes, and good eye health and vision.
- Several studies have shown that carotenoids are associated with a diminished risk for different kinds of cancer such as lung cancer, prostate cancer, breast cancer, and head and neck cancers [16-19]. Consequently, it has been demonstrated that there is a relation between serum β-carotene levels and a diminished cancer risk (e.g. for lung cancer). However, most intervention trials with β-carotene as a component of a supplement did not show any effects regarding the risk for cancer; interactions of β-carotene with other compounds, either carotenoids or other dietary constituents, might play a role. It has been suggested that among the biological conditions related to the risk, the prooxidant effects of β-carotene are implicated in the development of lung cancer.

- As regards the carotenoids' protective effects on vision, the current carotenoid research supports the possible role of this group of compounds in the protection against age-related macular degeneration (AMD). AMD is a major cause for irreversible blindness among the elderly worldwide, affecting about 20% of the population above the age of 65. The macula lutea is an important part of the retina, and the area of maximal visual acuity; the coloration of this tissue is due to the carotenoid pigments lutein and zeaxanthin (other carotenoids such as lycopene, α-carotene or β-carotene are not found here). Lutein and zeaxanthin also dominate the carotenoid pattern of the entire retina but their concentration in the macula lutea is considerably higher than in the rest of the retina [20]. Moreover, a high-carotenoid diet has also been shown to reduce symptoms of eyestrain (dry eye, headaches, and blurred vision) and improve night vision [21]. However, further research is needed to ascertain the exact role and mechanism of such protective effects of carotenoids.
- High-carotenoid diets have been shown to exert positive effects skin's texture, clarity, color, strength, and elasticity [22]. Commercial β-carotene supplements are used as oral sunscreens as their antioxidant properties have protective effects on the skin from the sun and harmful ultraviolet (UV) radiation. Photo-oxidative damage due to UV-irradiation of skin affects cellular lipids, proteins, and DNA; such pathophysiological processes may lead to erythema formation, premature aging of the skin, development of photo dermatoses, and even skin cancer. Several studies in humans have shown that carotenoid levels in plasma and skin decrease upon UV-irradiation [23].

Plant sterols

The naturally-occurring parts of all plants are called plant sterols or phytosterols. Several such compounds have been considered to have bioactive food properties.

- **Chemical structure:** Plant sterols include phytosterols, phytostanols, and their fatty acid esters. Chemically, they are cholesterol-like substances; this property can be used in an analogous role to affect cholesterol absorption and metabolism in animal and humans.
- **Sources**: The main sources are vegetable oils and they are also present in lesser amounts in nuts, legumes, grains, cereals, wood pulp and leaves. In several countries, some food products such as margarine, milk, yoghurt, breakfast cereals, soybean oil, and tall (pine) oil are fortified with plant sterols to increase their sterol content [9].
- Bountiful health benefits: The cholesterol-like property of the plant sterols can affect the cholesterol absorption in the gut. When consumed in diet or as dietary supplement, there occurs a preferential absorption of the plant sterols over the low-density lipoprotein (LDL) cholesterol (the 'bad cholesterol'), which can naturally reduce the level of the LDL cholesterol in blood. Studies have shown that when consumed in recommended amounts (e.g. 1.5-3 grams per day), plant sterols can reduce the level of LDL cholesterol in blood by 7.5-12% [24].

Glucosinolates

Glucosinolates are natural components of certain pungent plants (such as mustard, cabbage, and horseradish) and their secondary metabolites, which contain sulfur and nitrogen. When such a plant material is chewed, cut, or otherwise damaged, its glucosinolates produce mustard oils which give the peculiar pungency to these plants and products.

- **Chemical structure:** Glucosinolates contain sulfur and nitrogen, and are derived from glucose and an amino acid. Every glucosinolate contains a central carbon atom, which is bound via a sulfur atom to the thioglucose group and via a nitrogen atom to a sulfate group (making a sulfated aldoxime). In addition, the central carbon is bound to a side group; different glucosinolates have different side groups, and it is variation in the side group that is responsible for the variation in the biological activities of these plant compounds [25].
- **Sources:** The main rich sources of glucosinolate are cruciferous vegetables, such as wasabi (Wasabia japonica), broccoli, cabbage, kale, watercress, and garden cress. Isothiocyanates form the key biologically active breakdown products of glucosinolates; the cruciferous vegetables hold a variety of glucosinolates, each of which makes a different isothiocyanate with its associated physiological or cellular properties.
- **Bountiful health benefits:** Studies have shown that several glucosinolates and their biologically active metabolites, particularly the isothiocyanates, have protective roles against cancer and dementia [26-29]. These unique biochemical substances which are not found in any other vegetable have known to be very effective at killing various cancer cells without damaging normal cells. They lower the risk of dementia and slow down the rate of cognitive decline in elderly.

Effects of bioactive compounds on chronic diseases

Various bioactive compounds have unique effects on different chronic diseases such as cancers, diabetes mellitus, CVD, certain neurological conditions etc. Key physiological and cellular actions of these bioactive compounds in select such diseases are discussed here.

- **Cancer:** Cancer is one of the most important and major causes of death worldwide. It has been estimated that the global cancer burden has risen to 18.1 million new cases and 9.6 million cancer deaths in 2018 [30]. One in 5 men and one in 6 women worldwide develop cancer during their lifetime, and one in 8 men and one in 11 women die from the disease. It has further been foreseen that the deaths due to increase in cancer cases will continue over the next decade too. Hence, it is highly required that suitable steps are taken to control the risk of cancer development. Certainly, one of the easiest ways to prevent and control the risk of cancer is to consume enough fruits and vegetables which are high in biologically activity. Several studies have shown that there is positive relation between consumption of carotenoids-rich fruits and vegetables and decreased risk of cancer, particularly lung cancer, prostate cancer, breast cancer, and head and neck cancers [16-19,23].
- **Lung cancer:** In the backdrop of risk assessment and control of lung cancer, many studies have shown a fall in morbidity due to β-carotene supplementation in subjects who were non-smoking adults [16]. Moreover, the studies which were done recently on diet of lung cancer patients who did not smoke confirmed an inverse relation between the carotene-rich diet (for example, α-carotene, lutein, lycopene, β-cryptoxanthin, and β-carotene) and the risk of lung cancer. Results of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial showed higher incidence of lung cancer involving heavy cigarette smoking men, which indicated a significantly and total mortality in comparison to individuals obtaining the placebo, possibly due to a pro-oxidant effect of high-dose β-carotene supplementation [31]. These results were confirmed by the Beta-Carotene and Retinol Efficacy Trial, as well as some others, in which a combination of β-carotene and vitamin A supplementation was tested among men and women at a high risk of developing lung cancer (asbestos workers and smokers) and in subjects who consumed larger amounts of alcohol [32]. However, in the course of the latest detailed analysis, it turns out that the unexpected "cancerogenic" (pro-oxidant) effects of carotene supplementation can be explained in terms of their strong interference with unhealthy lifestyle of the individuals.
- **Prostate cancer:** Another important collection of data comes from the studies on prostate cancer. Many epidemiological studies support the idea that several carotenes, as well as their rich sources, could help in reducing the risk of prostate cancer [17]. Among various carotenoids, lycopene is regarded as the most effective against the risk of this type of cancer. The studies propose several ways of lycopene action, showing its importance in the enhancement of the oxidation stress defense system. Additional, evidence supporting this conclusion has been given by the recent meta-analysis of the observational studies on the role of tomato products and lycopene in the prevention of prostate cancer. Moreover, recent human intervention and clinical trials provided additional support to this research [23].
- **Other cancers:** In several research studies, β-carotene has been shown to play an important role in preventing against cancers of breast, head, mouth, pharynx, and larynx [18,19,23]. These studies have further suggested that consumption of high fruits and vegetables in diet could reduce the risk of head and neck cancers by as much as 50%. Similarly, observational research data have also shown correlations between the consumption of fruits and vegetables and the incidence of esophageal, colon, and other gut cancers, as well as an inverse relation between serum concentration of carotene and such cancer risk [23].

Diabetes mellitus

Owing to their antioxidant, anti-inflammatory, and immunoprotective effects, the bioactive compounds found in fruits and vegetables can potentially defend against several diseases and metabolic disorders. Their positive health effects make them good candidates for development of new functional foods, including those with potential protective and preventive properties for Type 1 and Type 2 diabetes mellitus also [1].

- **Effects of flavonoids on beta cells of pancreas:** Flavonoids and isoflavonoids are polyphenolic compounds commonly found in fruits and plants; and because of their abundance, they make up a significant proportion of the human diet. They are antioxidants and have anti-inflammatory and protective effects on metabolic diseases. Results from several cohort studies and randomized trials suggest that flavonoids may lower the risk of type 2 diabetes and CVD; moreover, meta-analyses of randomized trials indicate that the strongest evidences exist for their beneficial effects on LDL-cholesterol, endothelial function, and insulin sensitivity [1,33,34].

- **Genistein:** Genistein is the most considered isoflavone with respect to diabetes. Some of its good plant sources include lupine, fava beans, soybeans, and soybean products. Genistein is viewed as a promising candidate for alternative or complementary approach to prevent and treat diabetes as various cell-culture and animal-based studies have demonstrated its positive effects on β-cell function. A human study conducted among postmenopausal women demonstrated that genistein given in a dose of 54 mg/day could help reduce the fasting glucose and increase the glucose tolerance and the insulin sensitivity [35,36].
- **Lycopene:** Lycopene is one of the powerful antioxidant carotenoid compounds. It is naturally present in tomatoes and pink grapefruit, and is well-known in promoting health through prevention of such chronic diseases as cancer and CVD. While there are rare studies on its effect on diabetes (β-cells of pancreas). In an animal study, exogenous administration of individual gradual doses of lycopene to hyperglycaemic rats caused a dose-dependent decrease in glucose level, increase in insulin concentration, improvement in serum lipid profile, and an increased total antioxidant status with increased antioxidant enzyme activities; this study has suggested that lycopene acts as an antidiabetic agent, primarily through lowering the free radical [37]. However, in humans, various studies investigating the effects of high consumption of lycopene on reducing the risk of developing type 2 diabetes have yielded equivocal results; therefore, further studies are needed in this regard.
- **Anthocyanins and anthocyanidins:** These compounds are well known for imparting colours to fruits, vegetables, and flowers, many of which are used in the human diets. Various in vitro studies have shown that anthocyanins and anthocyanidins stimulate insulin secretion and have pro¬tective effects on β-cells of pancreas. In an animal study, the administration of bayberry fruit extract rich in cyanidin-3-glucoside (an anthocyanin) reduced blood glucose levels and improved impaired glucose tolerance in streptozotocin-induced diabetic mice [38]. In a large study by Wedick., et al, a total 3,645,585 women and men, who were free from diabetes, CVD, and cancer at the beginning of the study, were followed; and subsequently 12,611 cases of type 2 diabetes were found out; the consumption of anthocyanin-rich foods, particularly blueber¬ries and apples or pears, was associated with a lower risk of type 2 diabetes in the study [34]. In another study, diabetic patients who consumed pomegranate juice (384 mg/dL anthocyanins) exhibited anti-oxidative effects such as a significant reduction in their serum lipid peroxides and the oxidative state of their monocytes/macrophages by 56% and 28%, respectively [39]. These observations show a significant effect of anthocyanins on diabetic patients, which further suggests that it will be helpful if any functional food is made out of such anthocyanin extracts [1].

Cardiovascular disease

Oxidative stress and inflammation have a key role in the progression of atherosclerosis and CVD. Anti-oxidative, anti-inflammatory, and metabolic properties of various bioactive compounds may be associated with their protective roles against atherosclerosis and CVD.

- **Berries (Anthocyanins):** Berries are good sources of polyphenols, especially anthocyanins, micronutrients, and fiber. In several studies, it has been shown that berries are associated with improving heart health. Some of the intervention studies were done using chokeberries, cranberries, blueberries, and strawberries (either fresh, or as juice, or freeze-dried), or purified anthocyanin extracts, which demonstrated significant improvements in LDL oxidation, lipid peroxidation, total plasma antioxidant capacity, dyslipidemia, and glucose metabolism. Essential mechanisms for these kinds of beneficial effects were supposed to include upregulation of endothelial nitric oxide synthase, decreased activities of carbohydrate digestive enzymes, decreased oxidative stress, and inhibition of inflammatory gene expression and foam cell formation. Although inadequately, this data supports the recommendation of berries as one of the essential fruit group in a heart-healthy diet [40].
- **Flavonoids:** Several cohort studies and randomized trials have suggested that flavonoids may lower the risk of CVD, particularly by exerting their beneficial effects on LDL-cholesterol, endothelial function, and insulin sensitivity [33]. A systematic review with meta-analyses of several prospective cohort studies has also suggested that dietary intakes of six classes of flavonoids, namely flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones and flavan-3-ols, significantly decrease the risk of CVD [41]. In this regard, the content of flavonoid subclasses may be more important than that of total flavonoids in foods. Moreover, the inverse relationship between the flavonoid intake and the risk of CVD is more evident among women than men.
- However, there is a great variation in the literature due to the heterogeneous nature of the randomized controlled trials

conducted in different regions. It calls for further research and understanding within this area in order to maximize potential health benefits [42].

Conclusion

Various bioactive compounds have been described and evaluated for their protective effects in human health. They have unique antioxidant, anti-inflammatory, and anti-carcinogenic properties, with associated physiological and cellular effects that can be protective against various chronic diseases and metabolic disorders such as diabetes, CVD, cancer etc. They are mainly found in fruits and vegetables; and their consumption in diets with pertinent beneficial health effects make them good candidates for development of new functional food with potential protective and preservative properties. Although further research is needed to understand the exact mechanisms of their biological actions, it is beyond doubt that consumers should eat more of fruits and vegetables so that they get these bioactive compounds and benefit from their positive health effects.

Conflict of Interest

None. There is no direct or indirect real or perceived financial interests or conflicts; and this work of the authors is without any prejudice to their professional association with HCL Healthcare India.

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