

Review

Role of Phytochemicals in Health and Nutrition

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Introduction

Earth is dominated by plants. It is estimated that there are about 250,000 - 500,000 species of plants on the earth, and nearly 10% of these are used as food and medicine by humans and other living things. Different compounds extracted from these plants possess various properties that which have significant effects on the health and nutrition of humans [1]. These compounds are known as phytochemicals, “phyto” means “plant” in Greek, which are non-nutritive, naturally occurring biochemicals.

The phytochemicals are produced by plants to protect themselves against environmental hazards such as water changes and microorganisms and to give them their specific color, flavor, aroma and texture [2]. Furthermore, recent research demonstrated that they have also considerable effects on human health nevertheless they are not considered as essential nutrients [3]. Laboratory studies have shown that these phytochemicals have the ability to block certain compounds in food, drink and breathe from becoming carcinogens. It will also, reduce the inflammation that triggers cancer growth. Moreover, the phytochemicals decrease the oxidative damage to cells that may cause various diseases and assist in hormonal regulation [1,3]. Scientists estimated that there are around 4,000 phytochemicals that have been identified so far, but only a small portion of them have been studied closely. These phytochemicals are usually found in a wide array of plants and are in most commonly consumed foods such as fruits, vegetables, coffee, green tea, beans, grains and so on[3]. The predominant objective of this review is to explain and focus on the five most common types of phytochemicals that have attracted remarkable scientific attention which are carotenoids, organosulfur compounds, curcumin, phytosterols and flavonoids by providing a bird's eye view of their biological activities, sources, deficiency, disease prevention, and safety.

Carotenoids

Carotenoids are plant pigments with 40 carbon atoms per molecule

(tetraterpenoids). They are a widely distributed group of more than 750 naturally occurring fat-soluble pigments that are synthesized by higher plants as well as some algae and photosynthetic bacteria. Due to their ability to absorb light in the 400-500nm region of the visible spectrum, they give plants, vegetables and fruit the yellow, orange and red pigments [4]. Carotenoids are divided into two major classes based on their structural elements; firstly, carotenes which consist only of carbon and hydrogen atoms such as α -carotene, β -carotene and lycopene, and secondly, xanthophylls which consist of carbon, hydrogen and one or more oxygen atoms such as lutein, β -cryptoxanthin and fucoxanthin⁵.

Sources of Carotenoids

Fruits and vegetables constitute the major sources of carotenoids in the human diet. They are present as micro-components and there are approximately 40 carotenoids existing in a typical human diet. Of these 20 out of 40 carotenoids have been identified in human blood and tissue. However, almost 90% of the carotenoids in the diet and human body are represented by β -carotene, α -carotene, lycopene, lutein and cryptoxanthin [4]. (Table 1) represents most common carotenoids and their sources in vegetables and fruit.

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Sub Date: 3 April, 2017, **Acc Date:** 4 April, 2017, **Pub Date:** 28 April, 2017.

Citation: Shuruq Almodaifer, Noura Alsibaie, Ghada Alhoumedan, Ghadeer Alammari, et al. (2017) Role of Phytochemicals in Health and Nutrition. BAOJ Nutrition 3: 028.

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Table 1. Most common types of carotenoids and their sources⁴

Carotenoid	Major Sources
β-carotene	Carrot, Mango, Spinach, Broccoli, Watercress
α-carotene	Peppers, Carrots
Lycopene	Tomatoes
Lutein	Green leafy vegetables

Absorption of Carotenoids

There are several factors, which influence the absorption of carotenoids. The first one is that carotenoids must be released from the food matrix, which can be done by food processing and cooking, and integrated into mixed micelles, a mixture of bile salts and lipids, to be absorbed intestinally. Furthermore, as carotenoids are fat soluble, they require the presence of fat as little as 4 g in the meal to ensure the absorption. Moreover, the rate and the extent of carotenoids' absorption is influenced by the type and amount of carotenoids, the type of fat and the presence of soluble fiber in the food [4,5].

Biological Activities of Carotenoids

Carotenoids as Provitamin A: There are more than 750 carotenoids found in nature and only about 50 of them have provitamin activity. Moreover, among the 50 provitamins, there are 3 carotenoids that are considered as the most significant precursors of vitamin A in human, which are β-cryptoxanthin, α-carotene and β-carotene that are converted and metabolized to vitamin A in the body. The importance of these provitamin carotenoids is that they serve as a source of vitamin A, which is needed for normal growth and development, immune system function and vision [4].

Carotenoids as Antioxidants: Carotenoids have the ability to function as antioxidants and promote oxidative stress resistance. In plants, the antioxidant activity of carotenoids is based on their singlet oxygen quenching properties. In humans, carotenoids are a part of an antioxidant defense system that works in two ways, either by singlet oxygen quenching properties as in plants or through scavenging oxidizing free radicals via giving the free radical, its missing electron instead of taking it from other macromolecules [4,5].

Deficiency of Carotenoids

Although consumption of provitamin carotenoids can help in reducing and preventing vitamin A deficiency, no obvious deficiency symptoms have been shown in people consuming low-carotenoids diet if they consume adequate vitamin A. However, consuming high carotenoids in diet can improve the health and lower the risk of having chronic diseases [6].

Disease Prevention and Toxicities

Many studies have shown that carotenoids have the ability to prevent the body from many chronic diseases through protecting

the cells against excessive oxidation that may cause damage to cell constituents. Thus, the carotenoids can prevent cell mutation and therefore the development of cancer and the formation of atherosclerosis, which is a major cause of cardiovascular disease. Moreover, they can protect the skin against photo-damage and prevent skin diseases as well as from eye diseases through its antioxidant activities [5, 7]. In general, consuming high doses of carotenoids is considered to be safe and there is no toxicities have been reported for both pregnant women and healthy people [8].

Organosulphur Compounds

Garlic has been used by different traditions and cultures for centuries for cooking and medicinal purposes. Garlic and onion contain high amounts of organosulfur compounds, which are important for their aroma, flavor and health benefits. Whole garlic cloves contain two classes of organosulfur [9] such as γ-glutamylcysteines and cysteine sulfoxides [9]. Garlic contains about 80% of the allylcysteine sulfoxide (allicin), which is a compound in cysteine sulfoxide group [9].

Metabolism and Bioavailability of Organosulphur Compounds

When raw garlic cloves are chopped or chewed the enzyme alliinase is released, which stimulate the synthesis of sulfuric acids from cysteine sulfoxides group found in garlic [9]. These sulfuric acids will then react with each other to form a compound called thiosulfinate (allicin), and this formulation will usually take about 10- 60 seconds to be completed after chopping the garlic. Later on, the catabolism of allicin will produce several fat-soluble organosulfur compounds such as diallyltrisulfide (DATS), diallyl disulfide (DADS), and diallyl sulfide (DAS) [10].

Studies have shown that allicin and allicin-derived compounds are absorbed intestinally because they have never been observed in human stool, blood or urine [9]. These findings indicate that allicin and allicin-derived compounds metabolism happens quickly [9]. The presence of allicin and ally methyl sulfide derived from allicin in breath points out the high bioavailability of Organosulphur compounds [9].

Biological Activities of Organosulphur Compounds

The organosulfur compounds have a preventive role in cardiovascular diseases [9]. Studies have shown that people living near the Mediterranean are less susceptible to have cardiovascular diseases because they use garlic as a major ingredient in Mediterranean cuisine [9]. Garlic and garlic-derived organosulfur compounds reduce the synthesis of cholesterol by inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG- CoA reductase), an enzyme which catalyzes the synthesis of cholesterol [9]. Also, they inhibit other enzymes in cholesterol biosynthesis pathway such as sterol 4- a methyl oxidase [9]. Moreover, garlic-derived organosulfur compounds inhibit platelet aggregation.

Another benefit of organosulfur compounds is anti-inflammatory activity by inhibiting inflammatory enzymes such as lipoxygenase and cyclooxygenase. Also, organosulfur compounds act as antioxidants by stimulation of synthesis of glutathione, an intracellular antioxidant [9].

Disease Prevention

In addition, organosulfur compounds can prevent cancer disease by affecting carcinogens' metabolism [9]. Organosulfur compounds have a major role in preventing gastric cancer and colorectal cancer [9]. Studies in China indicated that there is a relation between consumption of organosulfur compounds and gastric cancer. In an area of China, 82% of men and 74% women consume garlic three times per week, thus they were observed to have a lower risk of having gastric cancer when compared to another area of China where 1% of women and men consume garlic three times per week [9]. Also, studies in Italy and Switzerland found that 26% of people with high intake of garlic are less likely of having colorectal cancer than those who consume low intake of garlic [9].

Curcumin

Turmeric is one of the roots derived from the ginger family. It contains fat-soluble, polyphenolic pigments known as curcuminoids. Curcuminoids provide turmeric a yellow- orange color [11]. The major curcuminoid present in turmeric is Curcumin (Diferuloylmethane) is accountable for its yellow color. The anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant and anti-infective effects and wound healing properties of turmeric are due to the presence of curcumin. The medicinal properties of turmeric are made use in the Ayurveda system of medicine in India.

Biological Activity of Curcumins

Curcumin has many beneficial biological activities for the human health. Curcumin has the ability to enhance the synthesis of glutathione, which is an important intracellular antioxidant. It also has an anti-inflammatory activity, and it can inhibit cytokinase, chemo kinase, and cyclooxygenase (COX) and lipoxygenase (LOX) [11].

Disease Prevention: The anticancer properties of curcumin are well documented and are due to the inhibitory action of enzymes that are responsible for cancer growth. Likewise, it prevents the proliferation of cancer cells by regulation of DNA repair process. Curcumins can reduce the incidence of gastric and colorectal cancer [11].

Curcumin can be useful to treat and prevent type2 diabetes [12] by improving pancreatic β -cell function and reducing insulin resistance by its anti-inflammatory effects [11].

Curcumin is a useful phytochemical to reduce premenstrual

syndrome involving emotional and behavioral symptoms. An experiment has conducted on 70 women who have premenstrual syndrome by giving them 0.2g of curcumin per day during menstrual days and the results have shown that curcumin reduces physical, emotional and behavioral symptoms [11].

Earlier studies indicated that curcumin can protect from Alzheimer's disease by inhibiting the aggregation of β -amyloid ($a\beta$ peptide) in the brain, and thus stop neural inflammation [11]. An earlier experiment has been conducted on Chinese people with Alzheimer's aged 50+ year old and have been given an average of 4 g of curcumin daily for 6 months showed that the progression of Alzheimer's was nearly static compared to people who did not consume curcumin [13]. Curcumin acts on various stages of the natural wound healing and hasten healing.

Safety and Toxicity: Food and Drug Administration (FDA) consider curcumin as generally recognized as safe (GRAS) food additive in the United States of America [11]. However, some studies found that high consumption of curcumin can increase the risk of developing kidney stones as it is highly soluble in oxalates that can bind to calcium and forms calcium oxalate stones, which are insoluble calcium salt which is considered as the most common type of kidney stones [14]. Also, patients with biliary tract obstruction should consume curcumin carefully due to gallbladder contraction that can result from curcumin [14].

Phytosterols

Phytosterols are known as plant sterols that are similar in structure and function to cholesterol, and it is found in plant cell membranes [15]. There are more than 200 different types of phytosterols [16]. Phytosterols are classified into two classes: sterols, which have a double bond, and stanols, which lacks double bond [16, 17].

Sources of Phytosterols

The major source of phytosterols is from plants and plant oils [20]. An average, normal diet provides 250 mg/day of phytosterols; moreover, vegetarians have the highest intakes of phytosterols almost two times more than the normal [17]. Wheat germ, sesame oil, canola oil, and peanuts, as well as nuts and legumes, are good sources of phytosterols [20]. Phytosterols are usually added to fat-containing foods to low their effects of increasing low-density lipoprotein (LDL) concentrations in blood [21].

Biological Activities of Phytosterols

Phytosterols affect cholesterol absorption and lipoprotein metabolism. High intakes of phytosterols will lower cholesterol absorption and LDL concentrations in blood [18]. In the intestine, these phytosterols will eject cholesterol from mixed micelles, which can decrease cholesterol absorption resulting in low levels of cholesterol in the blood [19]. Hence the body synthesizes cholesterol

to meet its needs [19]. There are other biological activities, but scientists do not know their significance to humans so far. One of them is that phytosterols help to stimulate apoptosis in cancer cells that do not respond to the singles that trigger apoptosis [18].

Safety and Toxicities of Phytosterols: Phytosterols are generally recognized as safe substances (GRAS) based on available scientific evidence²². The recommended intakes of phytosterols are usually 3g/day[22,23]. However, people with phytosterolemia genetically were told to avoid any food supplements with phytosterol in order to reduce the risk of having premature atherosclerosis[24].

Disease Prevention: Plant sterols help to prevent some diseases like cardiovascular disease [25]. Clinical trials found that the consumption of phytosterols in the average of 2 g/day decreased the concentrations of serum LDL cholesterol by 9-14%[19]. The reduction in LDL cholesterol could reduce the risk of coronary heart disease (CHD) by 20% [19]. In other words, a balanced diet of plant sterol foods, which is rich in fiber, vegetables, whole grains, fruit, and low in saturated fat, is also important in reducing CHD risk [25].

Larges intakes of phytosterols in the diet can inhibit the growth of breast and prostate cancer [26]. In women with breast cancer, it shows that they have a higher LDL- cholesterol levels and triglyceride plasma levels than in normal women [26]. Consuming of plant sterols help to prevent breast cancer and to reduce the lipid levels [26]. Shown that treatment with phytosterols suppressed mitosis and encourage apoptosis for the prostate cancer cell [26]. However; most of the studies for cancer therapy using phytosterols are based on invitro and animal studies, so there is a need for human trials [26].

Flavonoids

Flavonoids are a large family, which contains over 5000 hydroxylated polyphenolic compounds. They are present in plants ubiquitously and synthesized by phenylpropanoid pathway in response to microbial infections [27]. Flavonoids are the major coloring component of flowering plants, and they are responsible for combating oxidative stress and they are also known as growth regulators.

Many studies have shown that flavonoids are responsible for various pharmacological activities and are mainly responsible for the taste, color, protection of vitamins and enzymes, and prevention of fat oxidation [27]. Although flavonoids are synthesized only in plants, they are an integral part of human and animal diet provided the diet is plant based. (Table 2) shows commonly consumed flavonoids.

Sources and Toxicity

National Health and Nutrition Examination survey (NHANES) reported an estimated intake of 200 to 250 mg/ day of flavonoids

among US adults. It was also observed that widely consumed flavonoid is Flavan-3oles which accounts for 80% of flavonoid intake while the least consumed flavonoids were isoflavones and flavones [28]. Flavonoids are found mostly in the fruits, especially citrus fruits, and vegetables, tea, red wine and legumes [28].

Bioavailability of Flavonoids

The amount of flavonoid present in indigested substances has little significance unless they are absorbed and become accessible to the tissue [28]. Moreover, flavonoids are rapidly metabolized in intestinal and liver cells after absorption. In addition, the biological activities may differ in some cases due to the influencing factors on the metabolic fate and the bioavailability [28]. One of the most influencing factors is the interaction with food matrix. The presence of macronutrients in food affects the bioavailability of flavonoids. Additionally, carbohydrates, protein, and fat are strongly connected with the physicochemical properties of flavonoids [28]. For example, protein in milk may decrease the absorption of polyphenols, which is found in black tea or cocoa because the milk protein will bind to flavonoids and reduce the flavonoid antioxidant capacity [28]. However, some carbohydrates increase the deglycosylation and absorption of flavonoids by enhancing the mucosal blood flow, gastrointestinal motility, and colonic fermentation [28].

Biological Activities of Flavonoids

Flavonoids have a variety of biochemical properties, but the major property of almost every class of flavonoids is their antioxidant activity including suppression of Reactive Oxidative Species (ROS) formation either by chelating trace elements that involved in the free radical generation or by inhibition of enzymes[29].

Flavonoids can protect the lipids from lipid peroxidation and the oxidative stress due to it by their antioxidant capacity. Flavonoids such as catechin, apigenin, naringenin, quercetin, rutin, and venoruton are recorded for their hepatoprotective activities [29].

Because of hepato protective property, the bioflavonoid protects the liver from the development of hepatic clinical manifestations due to lifestyle diseases such as diabetes. The different components of the flavonoid Silymarin such as silychristine, silibinin, and silydianine [29] are extracted from fruits and seeds of milk thistle (*Silybummarianum* (Compositae). Earlier studies have shown that silymarin can stimulate the enzymatic activity of DNA-dependent RNA polymerase 1 and the biosynthesis of RNA and protein, which stimulate the cell proliferation, and regeneration in damaged liver [29]. Hepatoprotective toxicity of Silymarin also involves cell membrane permeability and integrity regulation, collagen production, and inhibition of leukotriene [29]. Nowadays, Silymarin has become significant in the clinical field and the treatment of ischemic injury cirrhosis and toxic hepatitis caused by

Table 2. Common Dietary Flavonoids²⁷

Flavonoid Subclass	(Dietary Flavonoids (Aglycones)	Some Common Food Sources
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Red, blue, and purple berries; red and purple grapes; red wine
Flavan-3-ols	<i>Monomers (Catechins):</i> (+)-Catechin, (-)-Epicatechin, (-)-Epigallocatechin, (+)-Gallocatechin; and their gallate derivatives	Teas (particularly white, green, and oolong), cocoa-based products, grapes, berries, apples
	<i>Dimers and Polymers:</i> Proanthocyanidins [#]	Apples, berries, cocoa-based products, red grapes, red wine
	Theaflavins, Thearubigins	Black tea
Flavanols	Isorhamnetin, Kaempferol, Myricetin, Quercetin	Onions, scallions, kale, broccoli, apples, berries, teas
Flavones	Apigenin, Luteolin, Baicalein, Chrysin	Parsley, thyme, celery, hot peppers
Flavanones	Eriodictyol, Hesperetin, Naringenin	Citrus fruit and juices, e.g., oranges, grapefruits, lemons
Isoflavones	Daidzein, Genistein, Glycitein, Biochanin A, Formononetin	Soybeans, soy foods, legumes

various toxins such as the toxins in mushroom and acetaminophen [29].

Flavonoids at the concentration of 1–100 µg/mL can enhance the liver function, and are considered for safe and effective treatment of hepatobiliary dysfunction and digestive complaints [29]. Since flavonoids are synthesized by the plants in response to microbial infections, they have an ability to act as anti-bacterial agents. Several flavonoids such as flavones, flavanols and isoflavones have been reported for their potent antibacterial activity [29]. The special of antibacterial flavonoids is that they can act on multiple cellular targets rather than one precise target. Also, they have some antiviral activity. Since 1940, there are many researchers who approved the antiviral activity of several naturally occurring flavonoids [29]. They can work as inhibitors to various enzymes, which are associated with the life cycle of viruses. The significant synergistic effect is shown when flavones and flavanols are combined. For example, luteolin and kaempferol exhibit synergism on herpes simplex virus (HSV); moreover, the synergism of flavonoids with other antiviral agents has been reported [29]. Another biological activity of flavonoids is anti-inflammatory and analgesic activity. Flavonoids can affect the functions of the immune system and suppress the inflammatory cells. Also, flavonoids have been reported as cancer chemopreventive agents. For example, consuming apples and onions, which are the main sources of flavonol quercetin, can reduce the incidence of breast, prostate, stomach, and lung cancer. As red wine is a source of flavonoids, some available reports shown that moderate wine drinkers have a lower risk of cancer of the lung, colon, and endometrium [29]. The critical link between flavonoids and prevention of cancer is well known nowadays [30].

Conclusion

People from all around the world are depending on medicinal plants that contain phytochemicals for their health care needs as these plants result in lower adverse side effects compared

to synthetic drugs as well as their immense health effects on human body that associated with assisting in reducing the risk of having certain chronic diseases. Carotenoids, organosulfur compounds, curcumin, phytosterols and flavonoids are different types of phytochemicals that found in these plants that have a wide range of therapeutic indications with a great variety of biological properties such as antioxidant, provitamin, antibacterial, antiviral, anticancer and anti-inflammatory activities. Moreover, these naturally occurring compounds can be found in vegetables, fruits, nuts, and tea as well as grains which are readily available and cheap.

Chronic diseases such as heart disease, cancer and stroke are the top leading causes of death all over the world. The most common causes of cancer deaths could be easily avoided through a good and balanced diet and consumption of food containing phytochemicals is a wise strategy.

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