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Carotenoids: Updates on Legal Statutory and Competence for Nutraceutical Properties

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Abstract

Growing health disorders have increased the present-day research for developing health- promoting biomolecules. Carotenoids are one such prospective bioactive compound that has plenipotentiary health benefits. Carotenoids are yellow to red pigments that are naturally synthesized by plants and micro-organisms. Continuous research is being conducted to explore the wide range of activities of carotenoids so that it can be helpful for humankind in the near future. This might also pave a new arena in the nutraceutical research. The present review deals with the legal statutory status of carotenoids as nutraceuticals with relevance to their pro-vitamin A activity, anti-oxidant activity and protection from heart diseases. In a nutshell, the chapter describes the usefulness of carotenoids as a nutraceutical.

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Introduction

The global rise in human health problems has always been a major challenge to medical science. The advent of industrialization and urbanization has entailed a radical transformation of the environment. This thorough going reformation has often led to significant health implications. For instance, economic development has improved quality of life in terms of income and standard of living but has led to "Nutrition Transition" such as consumption of high calorie-low nutritious food, energy-dense high fat food, etc.[1] Moreover, the sedentary lifestyle is mostly mechanized and technology-driven, which has led to reduced physical activity, lack of exercise and increased mental stress.[2] As a result of these long-standing negative impacts on health, the global population is getting adversely affected by several types of chronic, age and lifestyle associated diseases. Obesity has been recognized as one of the leading health threats in most of the countries and has been proven to be associated with high socioeconomic status.[3] Researchers have reported

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that most of the cases of heart diseases and cancer which are the primary causes of mortality in many developed and developing countries are related to lifestyle factors and dietary pattern.[4,5] Furthermore, there is a growing prevalence of other lifestyle-related disorders like type II diabetes, inflammatory bowel disease, hyperlipidemia, hypertension, Non-alcoholic fatty liver disease (NAFLD) and lots more.[6,7] On the other hand, rapid industrialization has witnessed global population ageing.[8] Consequently, the quest for dealing with the health issues has simultaneously increased with increase in life expectancy. Frustrated with expensive disease treatments, consumers are now seeking for suitable alternatives. In a survey based on U.K., Germany and France, consumers rated diet higher than exercise or hereditary factors to achieve good health. This showed that the words were spoken by Hippocrates, the Father of Western Medicine, back in 5th century B.C. i.e., "Let food be thy medicine and medicine be thy food" was certainly the solution of today's problem. This scenario marked the entry of nutraceutical in the mainstream of science and technology. Nutraceuticals emerged as a non-conventional yet beneficial product to mankind. In this review, we will describe the general concepts of nutraceuticals. The primary focus will be given on the role of carotenoid as a nutraceutical. This chapter will give an overall impression about nutraceutical, from concept to its application.

The Concept of Nutraceutical

Nature has provided us with various chemicals in the form of phytochemicals and zoochemicals. Unlike essential nutrients (such as vitamins, minerals, carbohydrates, proteins or fats), phytochemicals and zoochemicals are non-nutritive secondary metabolites that are not essential to the human body for sustaining life but are produced by the plants and animals to protect their own self.[9] In the last few decades, researchers have demonstrated that these natural chemicals have various biological activities that may be helpful to human body.[10] The intake of plant-based foods such as fruits, vegetables, cereals, etc. as well as marine food such as sea cucumber, etc. have shown disease-modifying health effects along with reduced risks of onset of different lethal and chronic diseases.[11,12] These health-promoting effects are often attributed to the presence of bioactive chemicals in these natural sources.[13,14] This fact has encouraged several health organisations around the globe to conduct in-depth research on the naturally derived bioactive metabolites.

The concept of "nutraceutical" evolved as a new paradigm in the field of food science. The term "nutraceutical", a linguistic blend of the words "nutrition" and "pharmaceutical", was first coined by Stephen L. DeFelice, founder and chairman of the Foundation for Innovation in Medicine, New York, the United States in 1989.[15] The definition of nutraceutical as given by its inventers can be exactly quoted as "any substance that may be considered a food or part of a food and provides medical or health benefits including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and diet plans to genetically engineered 'designer' foods, herbal products and processed foods such as cereals, soups and beverages".[15] The Nutraceutical revolution began in early 1980s when potential benefits of different naturally occurring compounds supported with clinical evidence were being published in reputed medical journals. The array of natural products, showing benefits against different chronic and lethal diseases, started expanding. Examples include use of β-carotene as a photoprotective agent in erythropoietic protoporphyria.[16] Preventive effects of dietary β-carotene on cancer risks,[17] prevention of hypertension by fish oil,[18] cranberry juice as a prospective treatment for urinary tract infections,[19] protective effects of onion and garlic against atherosclerosis.[20] These reports on turn convinced US medical professionals which led to the acceptance of nutraceutical in the field of medical science, making it a pivotal part in the food industry.

Legal Statutory of Nutraceuticals

Since the early 1990s, nutraceuticals gained significant attention. The convergence of food research with medicine and pharmaceutical sciences led to the formation of different regulations and amendments. However, the legal status of nutraceutical differed country wise.

India

In India, manufacture, storage, distribution, sale and import of nutraceutical are regulated under the Food Safety and Standards Act 2006 (FSSA).[21] *Food Safety and Standards (Food or Health Supplements,* *Nutraceuticals, Foods for Special Dietary Uses, Foods for Special Medical Purpose, Functional Foods, and Novel Food) Regulations, 2015*, published in Gazette of India, Extraordinary, Part III, Section 4 defined nutraceutical as "a naturally occurring chemical compound having a physiological benefit or provide protection against chronic disease, isolated and purified from food or non-food source and may be prepared and marketed in the food-format of granules, powder, tablet, capsule, liquid or gel and may be packed in sachet, ampoule, bottle, etc and to be taken as measured unit quantities".

United States

U.S. legislation does not give separate legal definition for nutraceutical rather *Dietary Supplement Health and Education Act of 1994* defined a collective term called dietary supplement as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredient, viz., vitamin, mineral, herb or other botanical, amino acid, dietary substance, to be used by consumer to supplement the diet by increasing the total dietary intake or a concentrate, metabolite, constituent, extract, or combination of any of the aforesaid ingredients.

Europe

European Union Food Law also does not have a regulatory framework for nutraceuticals. Instead, European Food Safety Authority (EFSA) has laid down a "General Food Law Regulation" called "Regulation (EC) No. 178/2002" which applies for any foodstuffs including nutraceuticals. Regulation (EC) No. 178/2002 comprises of a range of complex regulations whose applicability depends on the nature of the foodstuff.[22]

Canada

In Canada, the Bureau of Nutritional Sciences of the Food Directorate of Health Canada defined nutraceutical as "a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food and is demonstrated to have a physiological benefit or provide protection against chronic disease" (www.canada.ca). Moreover, nutraceuticals are categorized under Natural Health Products Regulations, which came into effect on January 1, 2004. Under this regulation nutraceuticals are considered as safe over-the-counter products and do not need prescription for selling.

Australia and New Zealand

In Australia and New Zealand, nutraceuticals are termed as Complementary medicines. Until 2003, complementary medicines of both the counties were regulated by different bodies: Therapeutic Goods Act 1989 (http://www.tga.gov.au/) in Australia and Medsafe (http://www.medsafe.govt.nz/) in New Zealand. However, after a treaty was signed between the two countries in 2003 at Wellington, a single bi-national joint agency (namely, Australia New Zealand Therapeutic Products Agency, ANZTPA) was established to regulate the therapeutic products which included complementary medicines (http://www.anztpa.org).

Japan

In Japan, nutraceuticals fall under a specific category known as Food for Specified Health Use (FoSHU). FoSHU system was approved by Consumer Affairs Agency of the Government of Japan and started in 1991. FoSHU products are comprised of functional ingredients that help to maintain and regulate the structure/function of the body such as gastro-intestinal conditions, blood pressure, and blood cholesterol level. Currently, over 1250 FoSHU products have been approved by the Ministry of Health, Labour and Welfare of Japan.

China

In China, 'health foods' are an equivalent term for nutraceuticals. The Chinese regulation system defined health foods as "food that has specified health functions, suitable to be taken by specified group(s) of people and for the regulation of the functional state of the human body and is not used for the treatment of diseases". All the health foods sold in China are approved and registered with the State Food and Drug Administration (SFDA) (http://www.sfdachina.com). SFDA bears the responsibility for the assessment and review of food safety, effectiveness, quality control, and product labeling.

Hong Kong

On the other hand, Hong Kong does not have a legal definition for nutraceutical (http://www.legco.gov.hk). Different terms such as dietary supplements, functional foods, nutraceuticals, designed foods and natural health products are interchangeable depending upon the purpose of use (http://www.legco.gov.hk). Taiwan has well defined nutraceutical regulations. Nutraceuticals and functional foods are termed as Health foods and is regulated by Health Food Control Act (HFCA). According to HFCA 2006, health foods are food with specific nutrient or health maintenance effects which is specially labeled or advertised, and does not aim at treating or remedying human diseases.

South Korea

In South Korea, all the food supplements having nutritional and physiological effects are considered as Health/functional food (HFF).[23] The Korean Health/functional food Act mandates the marketing of the products in form of tablet, pill, powder, or liquid so that they could be consumed in measured doses. HFF has 37 ingredients listed as generic HFFs and any new active components are categorised as product-specific HFF after approval by the Ministry of Food and Drug Safety.[23]

Malaysia and Singapore

Malaysia does not have definition for nutraceuticals. However an official body named as Committee for the Classification of Food-Drug Interface Products interact with nutraceuticals and conclude whether the product is a drug or food. Similarly, Singapore does not have a legal definition of nutraceutical however, the working definition refers to substances derived from natural sources, including botanical materials in the form of extracts, isolates and concentrates (www.ava.gov.sg). Surprisingly, the Food Control Department of Singapore regulates conventional foods more strictly than nutraceuticals.

Russia

In Russia, nutraceuticals are categorised under a broader class, termed as Biologically Active Food Supplements (BAFS), which includes all the nutritive substances and minor food components that have health benefits like ameliorating deficiencies, decreases risk of debilitating diseases, improves quality of life, etc.[24] Nutraceuticals are referred to those biologically active substances, which are basic components of organisms, vitamins or their predecessors, macro and microelements (iron, calcium, selenium, zinc, etc.), dietary fibres and indispensable amino acids that are used for correction of chemical composition of food.[24] The health ministry of Russia is responsible for regulation of the nutraceuticals.

Thus, it could be well understood that the legal status of nutraceutical is dissimilar country wise. Despite of the differences, interest of nutraceutical is increasing in the research and development with a unified motto of better health.

Classification of Nutraceuticals

Dr. Steven L. DeFelice classified nutraceuticals into two broad categories – established nutraceuticals and potential nutraceuticals.[25] Established nutraceuticals have well-recognized health benefits, supported by sufficient clinical evidences. Nutraceuticals whose medicinal benefits are yet to be demonstrated by sufficient clinical data are characterized under potential nutraceuticals. For instance, folic acid became an established nutraceutical when sufficient evidences for prevention of neural tube defects were obtained. However, most of the bioactive products remain in the “potential” category due to lack of sufficient evidences such as ginseng tea, aloevera gel, etc.[26] Based on the availability and regular needs, nutraceuticals can also be divided into two broad categories, i.e., dietary supplements and functional foods. Vitamins, minerals, enzymes and other metabolites such as extracts of herbs, amino acids, etc., in the form of capsules, tablets or soft gels, are regarded as dietary supplements. Functional foods are claimed to provide additional health benefits through fortification or enrichment during processing in existing ingredients. For example, purple potatoes enriched with anthocyanin, golden rice enriched with carotenoids or fruit juices fortified with minerals have been designed to reduce health risk in accordance with conventional foods and consumed as part of a regular diet.[21]

Carotenoids as a Nutraceutical

Depending upon the convenience, nutraceuticals are organized in several ways. However, one of the classical methods of characterizing nutraceuticals is according to its sources such as dietary fibres, prebiotics, probiotics, polyunsaturated fatty acids (PUFA), antioxidants, polyphenols, spices and carotenoids.[27] Carotenoids are a large family of lipophilic tetraterpenoids consisting of long, highly conjugated chromophoric system. They are formed by condensation of isoprenyl units and can be categorized as carotenes (hydrocarbons) or xanthophylls (hydrocarbons containing oxygen). They are one of the most widespread and ubiquitous yellow-orange-red pigments in nature. Carotenoids are synthesized as secondary micronutrients in fruits, vegetables, algae, fungi and some bacteria. It has been estimated that over 100 million tons of carotenoids are synthesized in nature. Carotenoids are also classified into primary and secondary. Primary carotenoids are required by plants during photosynthesis (β-carotene, violaxanthin, and neoxanthin) and secondary carotenoids are ones localized in fruits and flowers (α-carotene, β-cryptoxanthin, zeaxanthin, antheraxanthin, capsanthin, capsorubin).[28] The vastness in distribution of carotenoids includes purple colour of *Proteobacteria*, greenish-brown color of *Phaeophyceae*, yellowish texture of birds' feathers, orange colour of carrots or autumn foliage of deciduous trees, coloration in mosses, ferns, algae, fungi, bacteria, marine animals or exoskeleton of crustaceans, night vision of vertebrate, even human skin coloration. It was previously assumed that animals are unable to synthesize carotenoids rather they sequester it from their diet. However, studies conducted by Moran *et al.,* (2010)[29] and Altincicek *et al.,* 2012[30] showed that three species of arthropods, namely pea aphids (*Acyrthosiphonpisum*), green peach aphids (*Myzuspersicae*) and two-spotted spider mite (*Tetranychusurticae*) are capable of synthesizing carotenoids as they have acquired carotenogenic genes through horizontal transfer from fungi. Furthermore, it was suggested that genomes of other arthropods might also consist of these genes and it is likely that carotenoid biosynthetic gene might have also transferred into the genomes of higher animals.[30] However, humans are unable to synthesize carotenoids *de novo* and must intake it through their diet as carotenoids fulfill a plethora of essential biological functions.[31] Till date, more than 750 naturally occurring carotenoids have been identified and described.[32] However only about 40 are present in a typical human diet of which 20 of them have been identified in human blood and tissues.[33] Close to 90% of the carotenoids in the diet and human body is represented by α-carotene, β-carotene, lycopene, lutein and cryptoxanthin.[34] Digestion and metabolism of dietary carotenoids by humans is a complex mechanism, possibly depending upon the genetic constituent of an individual.[35] Although, dynamics of carotenoids inside human body is mostly not understood, high concentrations of lutein, zeaxanthin, β-cryptoxanthin, lycopene, α-carotene and β – carotene are present in human plasma.[36] Adipose tissues and liver are generally considered as the main storage sites for carotenoids, however high per gram concentration of carotenoids accumulate in the adrenal gland, lungs, corpus luteum and teste.[37] Significant quantities of the colourless carotenoids, phytoene and phytofluene, are also found in human plasma and tissue.[38]

Over the last decades, interest for carotenoids as a bioactive compound has profoundly increased. In a research work conducted by Gouranton *et al.,* (2011),[39] it was observed that lycopene could decrease proinflammatory cytokine and chemokine expression in adipose tissue. Such kind of regulation might help to reduce obesity-related pathophysiology such as type 2 diabetes mellitus, cardiovascular disease. In a study by De Neve, (2014)[40], it was presumed that canthaxanthin possesses remarkable possibilities as nutraceutical due to its anti-carcinogenic, tumor suppressant characteristics and antioxidant properties. Likewise in another study, restorative potential of lutein was established against neuronal injury and degeneration diabetic-induced in rat model.[41] It was suggested that the anti-oxidant, anti-apoptotic, anti-inflammatory, neurotrophic growth of lutein has helped in preventing the deleterious effects of diabetes. Thus the inverse relationship between carotenoid intake and impending risks of number of different diseases including cancer, obesity, cardiovascular disease, age-related macular degeneration, photosensitivity associated with UV exposure etc. has made carotenoids an important player in the field of nutraceuticals. The following sections of the review will provide some vivid description on the different nutraceutical aspects of carotenoids.

Pro-vitamin A Activity

The pro-vitamin A activity is one of the most important function of carotenoids in terms of nutraceutical. Vitamin A and carotenoids are often considered as physiological modulators. Vitamin A (or retinol, 1) is an essential nutrient for the promotion of general growth, maintenance of visual function, regulation of epithelial tissues differentiation and development of embryo and immunity system.[42] Deficiency of vitamin A leads to series of ailments including xerophthalmia (dry eye), keratinization of eye leading to night blindness and eventually complete blindness, anaemia, growth retardation, increased incidence and severity of infections such as diarrhoea, urinary tract infection, measles, respiratory diseases, finally resulting into childhood deaths.[43] Since vitamin A is not synthesized in human body it should be supplemented through diet either as a preformed vitamin A (in form of retinyl ester, retinol, retinal, 3-dehydroretinol, and retinoic acid) from eggs, dairy products, fish and meat or as a pro-vitamin A which can be biologically converted to vitamin A. Carotenoids are one of the major pro-vitamin A in our diet. It has been found that in developing countries provitamin A carotenoids in vegetables and fruits provide more than 70% of daily vitamin A intake. Surprisingly, pre-formed vitamin A sources provide less than 30% of daily vitamin A intake (Press Conference of the State Council Information Office). However, in western societies, the provitamin A carotenoids derived from plants provide less than 30% of daily vitamin A intake, whereas preformed vitamin A derived from animal products provides more than 70% daily vitamin A intake.[44] For a carotenoid to exhibit pro-vitamin A activity, it is should have an intact, unsubstituted β-ionone ring and unsaturated hydrocarbon chain. Based on these structural considerations, almost 50 carotenoids can exhibit pro-vitamin A activity, of which only a few have been examined and estimated.[45] In 1930, for the first time, Thomas Moore discovered that β-carotene could be converted into vitamin A, *in vivo*.[46] Since then pro-vitamin A activity of other carotenoid has been investigated. Estimation of biopotency using rat assay exhibited 100% activity of β-carotene revealing it to be a potent provitamin A.[47] Among the other well-known carotenoids, α-carotene,β-cryptoxanthin are established precursors of vitamin A. Interestingly β-cryptoxanthinis the only xanthophyll possessing pro-vitamin A activity due to the presence of β-ionone ring structure in one half of its molecule.[48] Conversely, canthaxanthin, astaxanthin, zeaxanthin, lutein, violaxanthin consists of β-ionone ring substituted with hydroxy, epoxy, or keto substituents. Thus these carotenoids are unable to convert into vitamin A. In 1980, Ting SV gave a detailed description on nutrient content of citrus fruits and reported that carotenes (both in β and α form) and cryptoxanthins are the main vitamin A precursors. It was also reported that beta cryptoxanthin is the main provitamin A precursor in oranges and tangerine. In a recent study, lycopene ($C_{40}H_{56}$), which consists of a hydrocarbon structure devoid of β-ionone ring, was found to restore Vitamin A deficiency in mice indicating partial pro-vitamin A activity.[49] It was also found that Lycopene could compensate Vitamin A for retinoic acid receptor (RAR)-mediated signalling in the mammals and can restore vitamin A deficiency.[49] Till date, intensive research has been carried out on pro-vitamin A activity of carotenoids. In infants, breast milk is the primary source of vitamin A for the first 6 months of life. Thus, maternal vitamin deficiency can lead to decreased amount of vitamin A in breast milk which can cause vitamin A deficiency in children. In 1995, it was suggested that daily consumption of β-carotene in simpler matrix helped to combat vitamin A deficiency among Indonesian lactating women by increasing serum retinol, breast milk retinol and serum β-carotene rather than consuming equivalent amount of dark-green leafy vegetables.[50] Lactating Filipino women daily supplemented with low doses of β-carotene showed increase in milk retinol concentration.[51] A hypothesis proposed that formation of vitamin A from food sources of β-carotene could be a suitable alternative to high-dose capsules, which was further proved by the work of Fasli Jalal *et al.,* 1998.[52] Children of 3-6 years of age, fed with meals and snacks containing various amounts of β-carotene showed significant increase in retinol concentration. Moreover the combination of β-carotene and dietary fat had an additive effect which can be attributed to the fact that dietary fat plays a key role in absorption of vitamin A precursors.[52,53] In 2013, a study conducted on piglet model revealed that continuous dietary intake of provitamin A carotenoid biofortified orange maize during the gestation and lactation period of Vitamin A-depleted sows, increased the hepatic vitamin A reserves of the piglet.[54] A simulated analysis conducted by De Moura *et al.,* (2016)[55] concluded that substitution of white rice with β-carotene biofortified rice increased vitamin A intake and decreased the prevalence of vitamin A deficiency among women and young children in Bangladesh, Indonesia and Philippines. A study by Palmer *et al.,* 2016[56] suggested that impaired dark adaptation, an early symptom of vitamin A deficiency, could be prevented by regular consumption of provitamin A carotenoid containing food. It was also observed that regular intake of provitamin A carotenoid-fortified maize increased the pupillary response among children with vitamin A deficiency.[56] In Kenya, consumption of β-carotene fortified cassava modestly increased the serum retinol concentration and β-carotene concentration among children aged from 5 to 13 years.[57] The most important perspective from nutraceutical view point is to determine the bioconversion efficacy of pro-vitamin A carotenoids into vitamin A. It is essential to quantify the amount of ingested provitamin A carotenoid being absorbed, cleaved, reduced and finally available as retinol or retinyl ester. Over last few decades, lot of researchers have used different approaches to determine the bioconversion efficacy and retinol equivalence. Among the early studies, the intestinal conversion of β-carotene to retinyl ester was elucidated by Helen S. Huang, Dewitt S. Goodman and their team. Radioactive β-carotene (dissolved in oil) was fed to rat models, containing cannulae implanted in the thoracic duct. It was observed that 100% absorption of radioactivity occurred through lymphatic route, mainly in form of lymph chylomicrons. Moreover the lymph contained 89% of the radioactive retinyl esters which proved the occurrence of bioconversion.[58,59] This work was further designed to determine the events occurring in humans and it was found that the lymph consisted of 60-70% of radioactive vitamin esters and 20-30% of unchanged radiolabelled β-carotene (β-Carotene-15,15'-^{8}H). This showed that human intestine have extremely limited ability to absorb unchanged dietary β-carotene.[60] A year later, in a similar study by R. Blomstrand, β-carotene-15, 15^{1-14}C and β-carotene-15, 15^{1-3}H was provided to patients and 60-75% of labelled retinyl esters were obtained in the lymph. It was also inferred that conversion of β-carotene into vitamin A took place via central cleavage of β-carotene into two molecules of vitamin A alcohol.[61] These experiments were the milestones in the research on bioconversion of carotenoids to vitamin A. On the other hand, in 1949, a depletion study was conducted on healthy volunteers by depriving them of vitamin A and carotene for a long period. The resulting vitamin A deficiency was recovered by providing a daily dose of 1500μg of β-carotene or 390μg of retinol. Thus, from this study the β-carotene: vitamin A equivalence was determined to be 3.8 : 1 by weight.[62] A more extensive depletion study over a period of 359-771 days was conducted for estimating the β-carotene-vitamin A equivalence in 1974. The study showed that the amount of β-carotene necessary to cure vitamin A deficiency was approximately twice that of retinol.[63] However in order to overcome the confusion between 3.8 μg or 2 μg equivalence of β-carotene to 1 μg of retinol, the bioavailability of β-carotene from diet was considered as one-third of the provitamin A carotenoid ingested with 50% conversion of absorbed β-carotene.[64] Despite of this, due to the rising confusions, the depletion-repletion method for assessing bioconversion efficacy was no longer acceptable. Later on, different methods for studying the conversion of β-carotene to vitamin A were investigated. In one such method, population of low vitamin A status were fed with synthetic β-carotene or provitamin A carotenoid rich natural food and the changes in serum vitamin A concentration was measured. Using this approach a study was conducted to determine the relative conversion efficacy of β-carotene in vegetables and fruits.[65] The obtained results showed that the conversion factor of vegetable β-carotene into retinol was 26:1 by weight whereas, β-carotene from orange fruit was 12:1. Thus the effectiveness of orange fruit was found to be higher compared to that of vegetables, which indicated the importance of food matrix in bioconversion.[65] Next, deuterated retinol- dilution (DRD) method was used to measure the body stores of vitamin A in children with marginal or normal vitamin A status after feeding them dietary provitamin A carotenoids. The study reported that 27μg β-carotene from vegetables was equivalent to 1 μg retinol which was in accordance with the study of De Pee *et al.,* (1998).[65,66] In various studies, postprandial chylomicron (PPC) response curves of β-carotene and retinyl esters in blood were measured after supplementation of β-carotene in oil. In this method, the absorption efficacy of β-carotene was measured as area under the curve of β-carotene and retinylpalmitate in postprandial triacylglycerol rich lipoproteins fraction which contained the chylomicrons. Moreover, it was assumed that one molecule of β-carotene was converted into one molecule of retinylpalmitate. In one such study it was reported that mean absorption of 15mg β-carotene was 17% and the conversion of the absorbed β-carotene into retinylpalmitate was 52-83%.[67] In another similar study, however, 8% of mean absorption was observed from capsules containing 40mg β-carotene with a conversion of 40%.[68] Similarly in another study, no β-carotene was obtained in the triacylglycerol rich lipoproteins fraction after a dosage of 15mg carotenoid. This indicated that this uncertain for measuring β-carotene level.[69] In the subsequent year, Accelerator Mass Spectrometry (AMS) was used Dueker *et al.,* (2000)[70] for studying long term kinetics of β-carotene by estimating the presence of vitamin A in human plasma, urine and faecal samples of adult male volunteers after subjecting them to oral doses of β-[^{14}C] carotene. A lag period of 5.5h was found between the dosing and appearance of [^{14}C] retinyl esters and [^{14}C] retinol in plasma. Moreover, 57.4% of the dose was recovered in the stool within 48h postdosing which concluded that stool was the major excretory route for absorbed dose. In a nutshell the study suggested that 0.53 mol of vitamin A was obtained from 1 mol of β-carotene with a minimum of 62% of the absorbed β-carotene being cleaved to vitamin A.[70] However, it was noticed that gradual contradictions developed regarding the bioavailability of provitamin A carotenoids. Previously according to the report of FAO/WHO, β-carotene to retinol conversion ratio was 6:1 (FAO/WHO. Requirements of vitamin A iron folate and vitamin B12. Report of a Joint FAO/WHO Expert Consultation. FAO Food Nutrition Series No 23. Rome: UN FAO, 1988:29 –30). However after the studies of De Pee *et al.*,[50,70] US Institute of Medicine revised its recommended conversion factors to 12:1 for dietary β-carotene and 24:1 for other carotenoids in 2001.[71] Despite of this, argument persisted regarding the conversion ratio stating that β-carotene conversion ratio was closer to 21.1 which is much lower than the recommended ratio. In 2007, serum retinol concentration was measured after feeding Vietnamese lactating women with fruits and vegetables and it was concluded that the conversion factor for dietary β-carotene was 21.1.[72] However this method turned out to be inaccurate for well-nourished humans with high serum retinol concentration due to the inability to distinguish between the newly formed retinol from the retinols of body reserve .[73]

Most of the studies discussed till now cover the bioavailability of β-carotene. Relatively less study has been reported on pro-vitamin A activity of β-cryptoxanthin and β-carotene. However, it is generally assumed that the pro-vitamin A activity of β-cryptoxanthin is responsible for its nutraceutical and therapeutic properties.[74] In 2008, for the first time, β-cryptoxanthin bioavailability from β-cryptoxanthin fortified maize was studied on ninety four male Mongolian gerbils (age 40 days).[75] In the same investigation, bioconversion of β-cryptoxanthin to retinol from oil supplement was studied. It was found that β-cryptoxanthin bioavailability from both the sources was more or equally efficacious as that of β-carotene. Burri *et al.,* (2011)[76] conducted three human nutrition studies to compare the bioavailability of β-carotene, β-carotene and β-cryptoxanthin in western diet. The study suggested that bioavailability of β-cryptoxanthin was highest followed by β-carotene and finally β-carotene. It was also suggested that β-cryptoxanthin rich foods might be a better source for vitamin A compared to β-carotene. Several factors have been proposed that might be responsible for higher bioavailability of β-cryptoxanthin compared to β-carotene. Firstly, β-cryptoxanthin is extensively present in fruit while β-carotene is commonly present in green leafy vegetables. Moreover it has been already proved that conversion of pro-vitamin A carotenoids in fruits is better than vegetables. Thus it could be understandable that β-cryptoxanthin gets readily converted to retinol.[77] Secondly, facilitative transport involving scavenger receptor class B-type 1 (SRB 1) preferentially facilitates the absorption of xanthophylls (such as β-cryptoxanthin) than β-carotene.[78] This results into increased bioconversion of β-cryptoxanthin. Finally and most importantly, β-cryptoxanthin is less hydrophobic than α and β-carotene. Hence, during micelle formation in intestine, β-cryptoxanthin is positioned externally and thus it is more soluble in the aqueous environment of intestine which in turn enhances the absorption and bioavailability.

Antioxidant Activity

Epidemiological studies continue to suggest the different protective health benefits of carotenoids. One of the major reasons behind this protective activity is its antioxidant activity. Reactive Oxygen Species (ROS) such as superoxides, hydroxyl radical, peroxyl, alkoxyl radical and singlet oxygen are continuously generated as natural byproducts of normal oxygen metabolism in body.[79] It has been already documented that ROS plays a positive regulatory role in intracellular and extracellular signaling processes.[80] However a strict control on the cellular amount of ROS should be maintained to prevent oxidative damage to the cells. Body has its antioxidant defence and repair system to prevent accumulation of ROS but an imbalance between the ROS production and defence mechanism gives rise to a state called "oxidative stress". Oxidative stress leads to damage of biomolecules, cell death, tissue damage and also leads to critical pathogenesis like atherosclerosis, carcinogenesis, diabetes, cataract and accelerated ageing.[81] Long decades ago, it was suggested that β-carotene, canthaxanthin, astaxanthin and other carotenoids can serve as an effective antioxidant in peroxyl radical-dependent lipid peroxidation.[82] However further studies were required to establish the antioxidant activity of carotenoids. Kennedy TA proposed that beta carotene effectively exerted antioxidant activity at high oxygen partial pressure.[83] In a randomized doubleblind placebo-controlled study, β-carotene supplementation increased the plasma antioxidant capacity of older women.[84] In 1997, Carpenter *et al.,*[85] showed that β-carotene, canthaxanthin and zeaxanthin inhibited human monocyte- derived macrophages mediated LDL oxidation which in turn might also help in preventing arterial diseas.[85] β-carotene when added to conventional and high oleic canola oil, showed antioxidant activity during exposure to either autoxidative or photooxidative conditions.[86] Moreover, β-carotene was found to be highly effective in protecting oxidative stress induced by hypobaric hypoxia. Hypoxia is a condition in which organism is deprived of oxygen creating oxidative stress which eventually leads to tissue injury. β-carotene supplementation at 10 mg/kg body weight reduced the hypoxia induced oxidative stress by decreasing the levels of malondialdehyde (MDA) levels in plasma and tissues and concurrently increasing the levels of glutathione and glutathione peroxidase in albino rats.[87] In 2005, anti-oxidant effect of lycopene was studied on hazards induced by gamma radiation and it was found that lycopene could ameliorate the negative impacts of gamma radiation on serum and blood parameters, viz., the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase activity (GGT).[88] The radical scavenging activity of lycopene against carbon tetrachloride (CCl_4) was reported by Yaping *et al.,* 2002.[89] CCl_4 is a xenobiotic which gets reduced to highly reactive trichloromethyl radical (CCl_3.) and trichloromethylperoxyl radical (CCl_3O_2.) and eventually leads to hepatotoxicity in humans and animals. Lycopene increased the survival rate of CCl_3O_2. damaged rats. It was deduced that lycopene reacted with radical that caused bleaching of lycopene ground-state absorption.[89] In 2006, during an assessment of radical scavenging activity of retinal carotenoid, (viz., zeaxanthin and lutein) it was observed that the carotenoids scavenged hydroxyl more effectively than superoxide and moreover zeaxanthin had more pronounced effect than lutein.[90] In a study by Wang *et al.* 2010, carotenoids extracted from *Lyciumbarbarum* L were subjected to anti-oxidant evaluation and it was observed that the zeaxanthin fraction of the carotenoid extract showed highest hydroxyl radical scavenging activity.[91] Sindhu *et al*. observed that lutein extracted from marigold flowers (*Tageteserecta* L.) protected liver damage induced by hepatoxins (viz., paracetamol, Carbon tetrachloride, ethanol) by elevating the levels of antioxidant enzyme in liver tissue92. Microalgal biomass containing individual carotenoids, viz., β-carotene, astaxanthin and lutein were fed to rat model to evaluate the antioxidant efficacy of the carotenoids. It was observed that rat group fed with astaxanthin had highest levels of antioxidant enzymes in their blood and plasma than compared to the other two carotenoids.[93] Nowadays different anti-radical scavenging activities namely, DPPH, ABTS, Nitrite scavenging activity, Ferric reducing power assay are being frequently used for determining the radical scavenging efficacy of bioactive compounds.[94,95] A recent study on fucoxanthin extracted from *Odontellaaurita*[96] showed strong antioxidant activity in dose dependant way. The effective dose of fucoxanthin for 50% scavenging (EC_{50}) of DPPH radical and ABTS radical was found to be 0.14 and 0.03 mg mL^{-1}, respectively. Similarly, astaxanthin rich carotenoprotein extracted from shells of Pacific white shrimp (*Litopenaeusvannamei*) was subjected to ABTS, DPPH radical scavenging activities, FRAP assay and it was found that the antioxidative activity was concentration dependent.[97] Gharibzahedi *et al.,* (2013)[98] determined the strong antioxidant and free radical scavenging activity of natural canthaxanthin extracted from *Dietzianatronolimnaea* HS-1 through DPPH, NSA, RP, HRSA, TEAC assay. The study also suggested that the carotenoid would help human body to eliminate oxidative damages incurred by oxygen radical. In a recent study conducted by Saha *et al.,* (2015),[99] β-carotene extracted from a yeast strain *Sporidioboluspararoseus* DAGIII was subjected to DPPH assay and it was observed that the radical scavenging activity improved with rising concentration of extracted β-carotene and the highest activity was evident at 1000 mg/L with an IC_{50} value of 449.11mg/L. In a similar study, bacterial β-cryptoxanthin extracted from *Kocuria marina* DAGII was analysed for its anti-oxidant characteristics in terms of DPPH scavenging activity and ability to inhibit lipid peroxidation in a linoleic acid emulsion.[100,101] Interestingly, it was noted that the pigment exhibited greater efficacy in both the assay compared to synthetic β-carotene. Bera *et al.,* (2016)[102] enhanced the canthaxanthin production by Dietziamaris NITD through coconut water supplementation and observed that the extracted pigment had high radical scavenging activity in terms of DPPH and nitrite scavenging assay. Recently Foo *et al.,* (2017)[103] conducted a study on antioxidant capacity of microalgal biomasses and showed that the anti-oxidant property was directly correlated with the presence of fucoxanthin in it. Dunaliella species is considered as one of the rich source of carotenoid with β-carotene being the major product.[104] The antioxidant property of the D. *salina* extract on paracetamol-induced hepatotoxicity in Wistar rat was studied. Paracetamol induced significant decline in anti-oxidant markers like total antioxidant capacity (TAC), superoxide dismutase (SOD) with significant increase in the levels of Malondialdehyde (MDA) and nitric oxide (NO), the primary products of lipid peroxidation. But treatment with the D. *salina* extract caused significant elevation in the levels of TAC and SOD and reduction of MDA and NO levels104. Astaxanthin and astaxanthin esters extracted from Haematococcuspluvialis noticeably decreased the effect of carbon tetra chloride on albino wistar rat. Pretreatment of carbon tetra chloride treated rats with natural astaxanthin or its esters enhanced the levels of antioxidant enzymes which otherwise suffered a deterioration in the astaxanthin (or its ester) untreated group.[105] Moreover, the effect of the natural astaxanthin was more pronounced than the synthetic astaxanthin. In a recent study, Meng H *et al*. reported that astaxanthin increased the SOD, GSH-Px, and CAT activities in RWPE-1 prostate epithelial cell line for protecting it against $Cu^{2}+$ induced oxidative damage.[106] In another study revealed astaxanthin playing key function in mitigating oxidative stress developed during burn wound progression in Adult male Sprague-Dawley rats.[107] After an initial thermal insult, the wound might further progress and expand beyond the initial burn area. This condition, termed as burn wound progression, often results into oxidative stress. After the burn injury, MDA level significantly increased with a decrease in the activity of SOD and glutathione peroxidase (GPx). Moreover, the levels of Xanthine oxidase (XO) and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox), the factors leading to generation of free radical species, were increased. Astaxanthin reduced the disturbances in a dose dependent manner and reversed the trend of the concerned parameters.[107] The study suggested a novel strategy of combating burn wound progression by attenuating oxidative stress induced local inflammation and tissue cell apoptosis in and around burn wounds. In a recent study on protective effect of astaxanthin against cerebral ischemic injuries in rats it was revealed that the protective mechanism involved suppression of reactive oxygen species, activation of antioxidant defense pathway with inhibition of apoptosis and promotion of neural regeneration.[108] In another study, β-carotene pre-treatment prevented H_2O_2 induced oxidative damage and cell death in K562 cells.[109] A study conducted on crocin demonstrated that a dose of 30mg/d can significantly reduce pro-oxidant–anti-oxidant balance in individuals.[110]

Effect of Carotenoid on Heart

Consumption of fruits and vegetables can reduce coronary heart disease which tempted researchers to investigate the specific bioactive compounds responsible for the beneficial role. In 1994, analysis of a cohort study indicated that higher serum carotenoid levels had decreased risk of coronary heart disease.[111] In 1995, Gaziano *et al*.,[112] studied the effect of consumption of carotene rich fruit and vegetables on 1299 elderly Massachusetts residents and observed that increased dietary intake reduced the risk of cardiovascular disease. However, whether the effect was small, moderate or significant was not confirmed and required further studies. In the same year, experiments on hypercholesterolemic rabbits suggested β-carotene derivatives can protect from heart blockage. This may be due to some stereo-specific interactions with retinoic acid receptors in the artery wall.[113] A study conducted on middle-aged men of Finland demonstrated that low lycopene level in plasma increased the early manifestation of atherosclerosis.[114] Similar association was observed for serum carotenoid concentration and i atherosclerosis during investigation by Karppi, 2013.[115] In 2001, Rissanen *et al.*,[116] further studied the association between lycopene serum level and acute coronary disorder in men previously free of congenital heart defect and cerebrovascular disease. D'Odorico *et al.,* (2000)[117] observed an inverse relation for atherosclerosis risk with plasma α- and β-carotene concentration. Similarly, Lidebjer *et al.,* 2007[118] reported that significant reduction of lutein, zeaxanthin or β-cryptoxanthin in plasma may led to coronary artery disease (CAD) in adults. Furthermore, it was investigated that serum lycopene concentration had an inverse association with brachial-ankle pulse wave velocity (baPWV), which is a systemic marker of arterial stiffness mostly caused by oxidative stress and inflammation.[119] It was anticipated that the preventive effect of lycopene on LDL oxidation helped to reduce the arterial stiffness119. Likewise, Choi *et al.,* (2011)[120] demonstrated that astaxanthin administration significantly modulated the lipid profile and oxidative stress by lowering the levels of LDL cholesterol, apolipoprotein B and oxidative stress biomarkers (such as Malondialdehyde, isoprostane) among overweight and obese Korean adults. Other reports have also suggested that astaxanthin administration significantly decreased triglycerides and increased HDL cholesterol and adiponectic.[121] A study conducted among young adults (18-30 aged) showed that higher serum concentration of carotenoids was inversely related to the incidence of increased hypertension, the most prominent indicators of macrovascular disorder.[122] In another experimental study, LDL receptor knockout mice fed on high fat diet with alga *Dunaliellabardawil* containing 9-cis β-carotene to investigate atherogenesis.[123] It was observed that the powder inhibited the plasma cholesterol elevation by 40–63% and reduced the atherogenic VLDL and LDL. Moreover the atherosclerotic lesion area in the mice reduced by 60–83%. In 2011, a population based study in Singapore revealed that β-cryptoxanthin and lutein were connected to lowered risk of acute myocardial infarction.[124] In 2016, it was reported that intragastric administration of lycopene provided protection against Atrazine induced hepatic ionic homeostasis disturbance and cardiac dysfunction in Kunming mice by regulating ATPases' activities.[125,126] The authors further observed that modulation of nitric oxide and nitric oxide synthase content and blocking of TRAF6 dependent NF-κB pathway was also responsible for the protective effect of lycopene against Atrazine induced cardiac inflammation.[127] Pereira *et al.,* (2017)[128] demonstrated that both lycopene and tomato supplementation helped in cardiac remodelling after myocardial infarction by attenuating hypertrophy and improving diastolic dysfunction. The study by Tong *et al.,* (2016)[129] reported that ROS scavenging effect of lycopene helped to ameliorate Myocardial Ischemia-Reperfusion injury which in turn reduced the cardiomyocyte death in mouse model. During a survey on Systemic Lupus Erythematosus (SLE) patients, Han *et al.,* (2016)[130] observed that higher serum lycopene prevented cardiovascular disease related mortality in SLE patients. In addition, different meta-analysis have also supported the fact that higher consumption of lycopene has positive effects on blood lipid, blood pressure, endothelial function, cardiovascular disease.[131] Similar to lycopene, number of studies has been conducted on lutein which emphasises its role in preventing heart diseases. The inverse association of lutein and IL-6 were highlighted in the study of Chung *et al.,* (2017).[132] It was suggested that lutein has significant potential in combating chronic inflammation in coronary artery disease (CAD) patients. It was also affirmed that anti-inflammatory effects of lutein were mostly due to suppressing the secretion of inflammatory cytokines and metalloproteinase-9 from peripheral blood mononuclear cells.[133] A study by Howard *et al.,* (2017)[134] suggested that one of the possible mechanisms behind the protective effects of fruits and vegetables was the reduction of tissue oxidation and preventing the activation of damaging complement factors in blood by lutein. These evidences were further in accordance with the meta-analysis by Leermakers *et al.,* (2016)[135] which indicated that high dietary intake of lutein was associated with better cardiometabolic health. In another study, β-cryptoxanthin and β-carotene extracted from *Satsuma mandarin* had significant preventive effect on arteriosclerosis development.[136] In the subsequent year the randomized controlled trial performed by Nakamura *et al.,* (2017)[137] showed that consumption of β-cryptoxanthin rich *Satsuma mandarin* juice significantly lowered baPWV and serum concentration of MDA-oxidized LDL. These implied the fact β-cryptoxanthin enriched citrus fruits might be beneficial for cardiovascular discorders. A comparative analysis on the efficacy of β-cryptoxanthin and astaxanthin was also conducted by Pongkan, 2017[138] and it was observed that β-cryptoxanthin exhibited greater cardioprotective efficacy against cardiac ischemia-reperfusion injury by significantly reducing infarct sizes, mitochondrial swelling, mitochondrial depolarization, the Bax/Bcl-2 ratio TBARS levels in both plasma and heart of C57BL/6 mice model.

Conclusion

The growing health problems and change in lifestyle has necessitated the use of bioactive compounds as food components. Carotenoids hold a promising future in this aspect. The present chapter describes the health benefits of carotenoid with respect to some of the most prominent health issues. Owing to its pro-vitamin A activity and anti-oxidant activity, carotenoid has plenipotentiary benefits in curing various acute and chronic health diseases. Application of carotenoid as food additive will not only have good health impacts but will also reduce the various side-effects of synthetic additives. Moreover, different population based studies conducted by the researchers worldwide also clearly suggested that carotenoids can be used as potential therapeutic agent for cardiovascular diseases. Thus, use of carotenoid as a nutraceutical in the global market can be a beneficial step towards the humankind.

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Conflict of Interest

The author(s) do not have any conflict of interest.

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