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Beta Carotene -Therapeutic Potential and Strategies to Enhance Its Bioavailability

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Abstract

Background: Beta-carotene is a natural carotenoid that usually occurs as pigments in the plant kingdom. Ample evidence is available in the literature suggesting beta-carotene could possibly lower the risk of stroke, heart diseases, aging, vascular and other metabolic diseases. This mini review in this direction, focusses on the biological importance of beta-carotene and the impact of various factors on their bioavailability.

Methods: The goal of this work is to do a mini review on the available literature for the various therapeutic properties of beta carotene and also the current strategies that exist to enhance the bioavailability of beta carotene. Electronically accessible databases were searched, and the findings were collated for analysis and interpretation of the results.

Results: Bioavailability of such substances has been a topic of interest for several decades. Digestive aids play a crucial role in increasing the bio-absorption for carotenoids like beta-carotene. Some of these are, the use of vesicular systems, alteration of the physical structure and nano-formulations.

Conclusion: Owing to its therapeutic potential, the bioavailability of carotenoids has recently been described by several authors. Various strategies and techniques have been proposed and developed which can enhance the systemic absorption of such compounds.

Keyword: Carotenoids; Beta-carotene; Pro-vitamin A; Bioavailability

Introduction

Over the years nutraceuticals always played significant roles in improving human health and wellbeing. Nutraceutical products attracted huge interest due to their potential nutritional and health benefits. Nutraceuticals could be used to prevent chronic diseases and is believed to increase our life expectancy. Nutraceuticals comprise of rich sources of bioactive molecules which directly or indirectly upregulate / downregulate the molecular signals and prevent or delay onset of chronic diseases like diabetes, cancer, infective diseases and cardiovascular diseases. Recent market analysis data of nutraceutical products reflects that, carotenoids occupy a significant market share. There are more than 600 known carotenoids, among which few are found in our regular diet, like beta-carotene, cryptoxanthin, lutein, lycopene, zeaxanthin, and astaxanthin [1]. These group of compounds called carotenoids are primarily responsible for naturally painting certain vegetables and fruits with their rich, attractive eye-pleasing color.

Carotenoids are oil-soluble molecules. Most of these compounds are comprised of 40 branched carbon units bonded together [2]. Structurally, they're composed of conjugated double bonds. Carotenoids can absorb light and this property is depended on the chemical structure of the molecule. The amount of conjugated double bonds a carotenoid contain changes the wavelength of light that it can absorb and as a result it varies in color from red, orange, to yellow.

Carotenoids play a prominent role in protecting bodily cells and thereby act as powerful antioxidants. Moreover, they are proved to be vital for maintenance of proper eyesight and vision. There is a huge amount of published literature currently available on the mechanisms and roles of carotenoids in human health [3]. One among these carotenoids, beta-carotene has been studied elaborately by several researchers. It is now known that beta-carotene is the primary precursor for Vitamin A in humans. Moreover, the positive roles of beta-carotene in maintaining a proper vision and its role in other degenerative diseases are now known. It is believed that consumption of required amounts of food products containing these carotenoids may help to deal with diseases concerned with deficiency of vitamin A [4]. In addition to the above-

mentioned points, it is also worthwhile to mention here that several carotenoids are being currently developed as powerful agents for the promotion of health and wellbeing.

Current literature has provided enough evidence to support the claim that carotenoids are effective antioxidants. The effective roles of these substances in preventing degenerative diseases and other metabolic syndromes have renewed the interest in carotenoids (Figure 1).

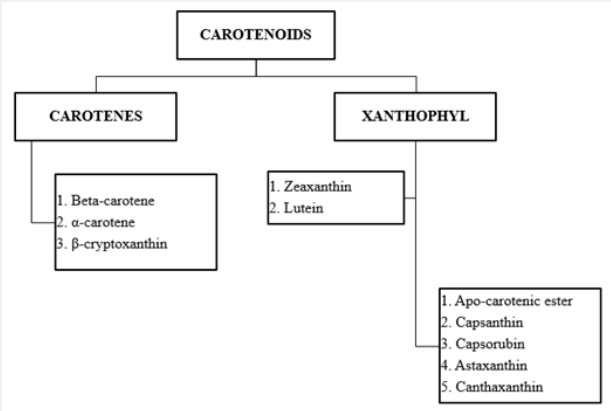

Figure 1: Schematic classification of carotenoids.

Carotenoids are classified into two major groups of substances (Figure 1). They are classified based on their basic moieties into carotenes and xanthophylls. The major compound among carotenes is beta-carotene, which are structurally made of cyclic hydrocarbons as one of their main components. On the other hand, a major example for xanthophylls will be lutein.

Beta Carotene

Among carotenoids, beta carotene is the most commonly found substance in dietary supplements [5]. Majority of the colours in fruits and plants are primarily due to this particular pigment. In Latin, the word 'carotene' stands for carrot. This is the origin of the present name. Apart from this, beta-carotene also is used as a coloring agent in several food products.

It is reported that these carotene compounds act as primary products in our body to produce vitamin A. Thus, these substances are also called as pro-vitamin A and thereby function as precursors. Studies have found out that majority of the vitamin A in our diet comes from these carotenoids like beta-carotene. On the other hand, there are also other sources for beta-carotene. This can be manufactured as a synthetic compound in laboratories or also can be isolated from different fungi or algal sources. Palm oil is another rich product containing beta-carotene. There are several glycoproteins that are formed from vitamin A, and these play a major role in humans for proper vision and eyesight. From these glycoproteins are then produced retinoic acid, which is essential in normal growth and cellular differentiation (Figure 2).

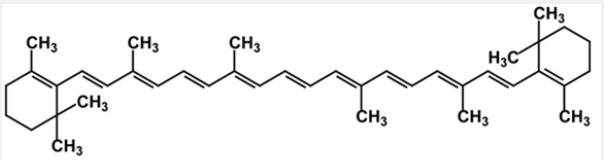

Figure 2: Chemical structure of beta-carotene.

Although, vitamin A can be beneficial for better eyesight, better night vision, for better immunity and for a glowing skin, it could be dangerous if consumed in excess [6]. Human bodies have a threshold of how much vitamin A is manufactured. This purely depends on the bodily and metabolic needs. Not all carotenoids can give raise to vitamin A. A number of carotenoids like lutein and lycopene cannot act as a precursor for vitamin A. Several studies have shown that beta-carotene, in addition to its effects on vision, also functions as a potent free radical scavenger. It is now known that much of the damage to the cells internally is caused by free radicals and sources of free radicals through oxidative reactions. Chronic exposure to damaging oxidative radicals can allow several diseases in the body. A number of authors have mentioned that antioxidants and free radical scavengers can enhance immunity and shield our bodies from several diseases [7].

Therapeutic Benefits of Beta-Carotene

There has been an extensive number of studies carried out and research papers published on the health benefits of beta carotene. Some of the therapeutic benefits based on the research data published have been summarized here. The USFDA approved beta-carotene as an effective therapy for erythropoietin protoporphyria. Several research studies conducted on animals have reported the anticancer activity of β-carotene [8-11]. There is plenty of evidence now that suggests carotenoids or food products rich in carotenoids are indeed beneficial in the prevention of several types of cancers and malignancies. Certain types of cancers namely, the cancers of prostate gland, urinary bladder and of the colon respond to a natural substance called lycopene. This substance is found in abundance in tomatoes. It was as early as in the 1960s when the initial findings of vitamin A as an anticancer agent started surfacing out. Subsequently, these findings led scientists and researchers to investigate on the anticancer potential of beta-carotene, as this substance was the precursor. There are two different studies that were conducted respectively in 1973 and in 1977, proved that beta-carotene itself had anticancer properties. The first study carried out by Dorogokupla and the second by Epstein, both showed that there was a reduction in the tumor size when supplemented with beta-carotene. The positive control groups and placebo groups which were not administered with beta-carotene showed the reverse. Both these studies were carried out on rodents. These studies proved that beta-carotene was effective in controlling cancers. Recent research conducted in the last two decades revealed

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the tumour controlling activity of beta-carotene in several tumor models that were tested. The mechanism of action of beta-carotene was later hypothesized, suggesting that, these substances bring about their therapeutic potential primarily through their free radical scavenging activity. This also corroborates with the earlier findings that suggested that beta-carotene has potent antioxidant potential.

Beta-carotene is found in most vegetables and fruits. Thus a number of studies have already been done on beta-carotene as a free radical scavenging agent. The studies have proved to be significant in terms of its antioxidant effect. Several in vivo studies done on animal models and other in vitro studies have shown that carotenoids as antioxidants have the ability to prevent chronic conditions. It was also found that the free radical scavenging activity of carotenoids was enhanced when combined with several other antioxidants like vitamin E. However, some studies involving animal models have reported that the pattern of metabolizing such carotenoids are different in animals from humans, and thus the findings may not be confirmatory [12].

One of the major vitamins that is required by our human bodies is vitamin A. Beta-carotene acts as a precursor for the production of vitamin A in our bodies. Thus it is also referred to as provitamin A. Vitamin A plays a major role in the normal functioning of our eyes, especially in the production of several pigments in the retina that helps with photoreception and night vision. Several problems arise when the body does not get the required amounts of vitamin A. This could be ranging from ocular degeneration to conditions like keratomalacia. Carotenoids like beta-carotene and lycopene have also been proved to prevent cardiovascular diseases. The risk of developing a cardiovascular disease and stroke is drastically reduced when sufficient vegetables and fruits rich in carotenoids are incorporated in the daily diet [13]. There are extensive studies done on the effects of carotenoids on stroke. However, there are no confirmatory studies or trials yet that prove that carotenoids protect the body from stroke. There are assumptions that carotenoids may protect the blood vessels from stroke as several studies have reported the reduced levels of homocysteine when tested with certain carotenoids and vitamins. Currently there is a clinical trial that is been carried out on a larger scale to study the effects of carotenoids on brain health and stroke [14-18].

Beta-carotene has been also studied for treating sun sensitivity. This condition called as erythropoietic protoporphyria, causes severe sensitivity to sunlight, which is painful. However, consuming large amounts of beta-carotene will render people with a decreased sensitivity towards sunlight. The consumption of beta-carotene is gradually tapered down over a certain period of time duration [19].

In one of the studies conducted among elderly males, it was found out that the ones who consumed a diet with beta-carotene and other carotenoids had a very less risk of developing diabetes and cardiovascular disorders. Such disorders are categorized under an umbrella term called metabolic syndrome. In general, this is defined as symptoms that are caused by problems associated with our metabolism. Metabolic syndrome primarily constitutes diabetes, cardiovascular disorders and lipid issues in the body. From the study it was also found that the participants had decreased lipid levels [19].

In another study involving participants with a condition termed as leukoplakia showed less number of symptoms when they consumed beta-carotene. On the other hand, people with same condition when they consumed placebo, the effects were discouraging. Leukoplakia is a condition usually found in people who are chronic smokers or alcoholics. It is characterized by white lesions in the oral cavity. However, it is cautioned that people should take the advice of a physician before consuming beta-carotene for this condition, as this could be associated with other risks as well [19].

Scleroderma is another condition which is portrayed by skin that is hardened. The condition also affects the connective tissues in the body. It is reported that this condition might arise when the levels of beta-carotene in the body gets lower than the required amounts. Researchers have significant evidence to prove that beta-carotene products can help people with this condition. However, more large scale studies are required before this can be formalised [19].

In a study conducted at the Harvard Medical School, involving 4,052 males, reported that longer consumption of beta-carotene on a regular basis have resulted in less probability for the participants to get mental slowdown or retardation. However, these results are observed only in participants who were on long term beta-carotene consumption. On the other hand, short term consumption, between the beta-carotene group and the placebo group, did not show any significant changes [20].

Bioavailability of Beta Carotene

There are various factors that come into play with regards to the bio-absorption of beta-carotene. These include the source of the product, process of extraction or isolation, quality and purity of the final product, cross interactions with other food substances in the system and the factors concerning the individual [21]. Carotenoids are known to be absorbed by duodenal mucosal cells by passive diffusion. Several other physico-chemical factors namely, particle size, flow properties, rheology, interaction with other additives and complexation also affect the bioavailability of beta-carotene. Biological barrier interactions also play a major role in the uptake of these substances [22].

There are several other factors that can affect the biosorption of beta-carotene. These could be the procedure or

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method how the food was prepared, and the ingredients used. Other factors related to diet like the amount of beta-carotene, amount of preformed vitamin A, presence of other carotenoids while preparation also play a major role [23-26]. It is reported that biosorption of beta-carotene is higher with fruits and red palm oil, whereas, with food products containing complex food matrices, the biosorption is observed to be lower [25]. It is worthwhile to note here that, for beta-carotene to be bio-absorbed, it needs to be first dismantled and released from the food matrix. Different cooking methods affect the release and absorption of beta-carotene into the system. Bioavailability can also be increased by making the food homogenized [27-29].

In human beings the bioavailability of pure beta-carotene is reported to be in the range of 8.7% to 65%. The interactions of plant material with micelle formation affects drastically the bioavailability of beta-carotene from natural products like fruits, vegetables and other natural sources. The first assessment on the bioavailability of beta-carotene was done on two hospitalized patients by administering them with radiolabeled beta-carotene. Radioactivity was measured later in these patients which gave an approximate idea on the amount of bioavailability [30].

Cheng et al., [31] have studied the possibility of an oral delivery system in the form of a microemulsion that could be suitable to deal with the difficulties and complications of delivering poorly aqueous soluble beta-carotene [31]. Microemulsions are usually comprised of an oily phase like natural oils, edible hydrocarbons or synthetic oil mixture of triglycerides with various chain length and saturation degrees. These also comprise of surfactants for which the molecular structure is mainly composed of a hydrophilic group, a hydrophobic group and a water phase, which include water and aqueous co-solvents. Incorporating beta-carotene into an oil-in-water ME as a functional beverage has several advantages including,

(1) solubilizing the poorly water-soluble beta-carotene.

(2) protecting beta-carotene from enzymatic degradation following oral administration.

(3) forming a thermo-dynamically stable product with a long shelf-life.

(4) improving the beta-carotene bioavailability by lymphatic adsorption.

(5) enhancing epithelial permeability through the use of surfactants such as medium-chain fatty acids [32].

In another work, researchers studied the possibility of microencapsulation methods to improve the release and bioavailability of beta carotene in vitro. In this study, alginate and chitosan-based formulations were evaluated [33]. A double-blind crossover study involving human subjects was studied for the effectiveness of an extract from the fruit of black pepper, consisting of a minimum of 98.0% pure alkaloid piperine, for its ability to improve serum response of beta-carotene during oral supplementation [34]. In another study, the effect of citric pectin on the bioavailability of synthetic beta-carotene was studied. The authors conclude that 7% citric pectin in the rat diet decreased the bioavailability of synthetic beta-carotene, reducing the liver reserves of vitamin A and beta-carotene [35].

Beta-carotene contains 40 carbons with 15 conjugated double bonds and 2 β-ionone rings at both ends of the molecule. These structural properties make beta-carotene highly hydrophobic and non-polar in nature.

In adult tissues, beta-carotene-15,15′-oxygenase (CMOI) is the main cytosolic enzyme that cleaves *β*-carotene to generate vitamin A *in vivo* [36-38]. Dietary fats, lipids and lipid-soluble vitamins, including *β*-carotene, are absorbed by the small intestine and then subsequently deliver them to the peripheral tissues for consumption. Although, the human intestines abundantly express the main *β*-carotene cleavage enzyme CMOI, complete intestinal conversion of all of the ingested *β*-carotene to vitamin A practically does not occur. As discussed above, the bioavailability of *β*-carotene, apart from genetic factors seems to be also affected by the nature of food matrix, type of preparation, fat content of the diet, type of fat, digestibility of fat-soluble components in the diet, bile acids, interactions with other carotenoids and individual variations due to endogenous activity of the digestive enzymes [39-42].

Formulations Containing Beta-Carotene

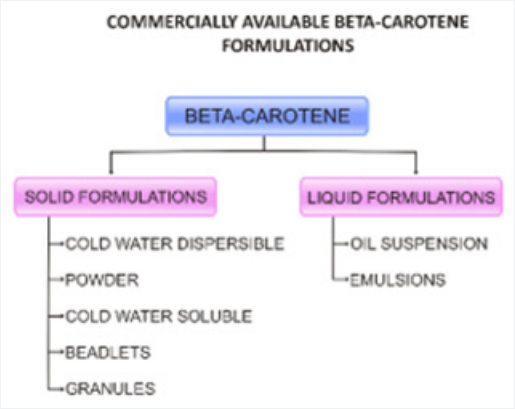

Figure 3: Commercially available beta-carotene formulations.

Both carotenes and xanthophylls are insoluble in water whereas in fats and oils a likewise only low solubility is found. This restricted solubility and also the high sensitivity to oxidation are an obstacle to direct application of the relatively coarse-grained products obtained by chemical synthesis in the coloring of foods and feeds, since the substances in coarsely crystalline form are not storage-stable and give only poor coloring results. Beta-carotene holds unique properties as a colorant, physiological antioxidant and provitamin A.

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This versatility means that it is used across many different segments, which include food, feed, supplements, cosmetics and colorants. To overcome the drawbacks of pure beta-carotene and make it viable commercially, various formulation designs were developed ensuring the product stability, solubility and bioavailability. Each segment demands different properties and stability of the beta-carotene formulations, which has led to the development of following major product groups like oil suspensions, powders, beadlets and emulsions (Figure 3).

Oil suspensions of beta carotene formulation have been widely used in the nutraceutical industry. Various concentrations of oil suspensions like 30%w/w to 10%w/w with bio-enhancers and solubilizers are marketed which shows relatively higher bioavailability than the raw synthetic beta carotene. These suspensions are manufactured with micronized beta carotene suspended in natural oil along with stabilizing and solubilizing agents.

Powders are another significant group of beta carotene formulation commercially available. Powders carry the handling advantages and ease of manufacturing compared to oil suspensions. Fine micronized grade of beta carotene are prepared majorly by adopting spray drying techniques.

Finely pulverulent carotenoid preparations are produced by dissolving a carotenoid in a volatile water-miscible organic solvent at elevated temperatures, if necessary at elevated pressure, precipitating the carotenoid by mixing the solution with an aqueous solution of a protective colloid and subsequently spray drying the solution as disclosed in European patent EP-B-0 065 193.

Most of the carotenoids, including beta-carotene and other carotenes, are relatively water insoluble and have also have high melting points. In the presence of an aqueous phase like water, they become highly sensitive to oxidation. The usual technique adapted to make it more water-dispersible is to formulate beta-carotene as a water-dispersible beadlet. These beadlets can be prepared by dissolving beta-carotene in a water-miscible organic solvent [43]. This could be followed by mixing the dissolved beta-carotene with an aqueous solution of a swellable colloid, like gelatin, then precipitating the β-carotene in a colloidally dispersed form and finally drying the colloidal dispersion.

Oil in water emulsions are another beta carotene formulation system used in the food, beverages and diary industries. Conventional homogenization techniques, including high-speed shearing, ultrasonic treatment, high pressure valve homogenization, etc. are widely applied to make beta-carotene emulsions. Among all the techniques, high pressure homogenization is the most used technique both in laboratories and industries, and emulsions with different particle size ranges can be produced depending on the pressures that the homogenizers can generate.

The bioavailability of the ingested nutrient is partially determined by its bio-accessibility, which is generally defined as the fraction of the ingested nutrient that is incorporated into the mixed micelles and thus becomes available for absorption in the body. The bio accessibility of beta carotene formulations is majorly influenced by the emulsion droplet size digestive oils, emulsifying agents. Hence during the formulation these factors are taken care of to ensure desired bioavailability.

Conclusion

Among the carotenoids, Beta-carotene is a precursor for vitamin A and essential for human health. Beta-carotene has been used widely in food, feed and other nutraceuticals commercially. Amidst the various therapeutic benefits of beta-carotene, it has got many drawbacks like poor bioavailability and its degradation tendency on exposure to light, heat and oxygen. Abundant studies and research were carried out to design delivery systems for beta-carotene to improve its bioavailability and chemical stability, and finally to enhance the functionality. However, the demands for beta-carotene formulations are on the rise, so are the research to address its functional draw backs.

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