A brief overview of carotenoids and their applications

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Abstract: Carotenoids are naturally occurring pigments found abundantly across various fruits, vegetables, and other foods that are plant-based. They impart variety of colors to the microorganism, fruits, vegetables with their striking red, orange, and yellow colors. Beyond contributing to the aesthetic appeal of these foods, carotenoids make a significant impact on human health. They are known for their antioxidant properties, offering protection against oxidative stress and damage caused by potentially harmful free radicals. Antioxidant property of carotenoids is due to presence of conjugated double bonds (CDB) that are present in their chemical structure. By reducing oxidative stress, carotenoids help protect the body against various chronic diseases, including cardiovascular diseases, and cancers. They are also well known for their pro-vitamin A activity, immune system modulation, and ability to scavenge free radicals while protecting against UV radiation. Because humans are not able to synthesize carotenoids, they must be obtained through diet or supplementation. Carotenoids' anti-cancerous/cancer preventative action is the main factor contributing to their pharmacological significances. Carotenoids also known for bacterial pathogenicity by acting as virulence factors. Carotenoids are also known to impart color hence beneficial for the food and beverage industries, textile industries etc. They are being used more frequently as substitutes for artificial colorants and additives as growing consumer interest in sustainable and natural products. Thus, the primary focus of this review is on the fundamental knowledge of carotenoids and its numerous applications in industries and human health.

Keywords: Carotenoids, human health, antioxidant, functions, industrial applications

1. Introduction: Carotenoids are a class of isoprenoid compounds, mainly composed of eight isoprene units (Fig.1.1) (C_5) forming a C40 carbon compound [1,2]. They have a characteristic polyene chain of conjugated double bonds (CDB) (Fig.1.2) is responsible for giving carotenoids distinguished absorption patterns and also impart a variety of colors to the microorganisms. CDB in carotenoids play a crucial role in their functional properties and energy transfer capabilities. The term "carotene" came into existence when Wilhelm Ferdinand Wackenroder in 1831 initiated the identification of carotenoid in the carrot. Within 50 years, Hartsen was able to isolate lycopene from *Tamus communis L. berries[3]*. Carotenoids are found in all organisms including phototrophic as well as in a variety of non-phototrophic organisms. It occurs widely in all three domains: Prokaryotes, Archaea and Eukaryotes [4]. Up until 2018, 1178 naturally occurring carotenoids with a wide range of structural variations and physicochemical characteristics have been documented and described in the literature[5]. It is synthesized by plants and microorganisms, while animals depend upon dietary sources since they are incapable of *de novo* synthesis[4]. Carotenoids are responsible for imparting various colours like yellow, red, orange to micro-organisms, algae, fungi, fruits, vegetables and plants. However, chlorophyll masks the colour of carotenoids in plants. This phenomenon can be observed in the autumn leaves as well as at the time of ripening of fruits [6]. Carotenoids are primarily located in hydrophobic regions of the cell since they are hydrophobic and cannot dissolve in water.

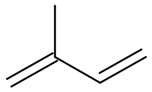

Figure 1.1: Isoprene (C5)

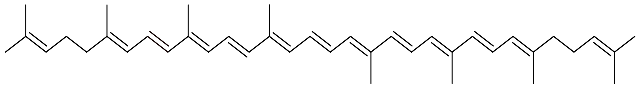

Figure 1.2: Lycopene

They can access the aqueous environment only when associated with proteins [7]. The polarity of carotenoids is altered by either polar functional groups or by the interaction of carotenoids with other molecules. Usually, a carotenoid molecule consists of 9-13 alternate single double bonds in a conjugated system which can exist in *cis* or *trans* isomeric forms. *Cis* forms do not aggregate or crystallize easily as compared to *trans* form. *Trans* form of carotenoids is more rigid. Carotenoids can be linear with no cyclic structures at the end of the molecule (acyclic carotenoids) or cyclic carotenoids with cyclic structures at the end [2,8]. Detailed explanations of the carotenoid's reactions i.e. oxidation, reduction, hydrogen abstraction, and addition properties have been reviewed [2,8]. Carotenoids have a variety of functions including the variation of colors in plants and animals, anti-oxidant molecules, protecting the reaction center from oxidative free radical species and also light-harvesting molecules. Animals use the carotenoid derivative in their retina as visual pigment, and it also functions as a chromophore in bacteriorhodopsin photosynthesis. Plants and animals use abscisic acid and retinoic acid respectively as antioxidant molecules to harvest light, shield the reaction center from oxidative free radical species, and shield egg protein from protease in some invertebrates[9]. It also acts as a vitamin A precursor and also plays a role in the prevention of human diseases such as cancer. Another important property of carotenoids is photochemical properties which is explained by their low-lying excited energy (both singlet and triplet)[10]. Carotenoid's ability to protect the reaction center from photo damage or reactive radical species as well as its function of light harvesting is all due to its long polyene chain structure [11].

2. Structure of carotenoids: Carotenoids are colored fat-soluble pigments sensitive to oxygen, heat and light[12,13]. Carotenoids are polyisoprenoid substances from a chemical perspective, and they can be generally divided into two classes (Fig.2) a) Carotenes, which are mostly composed of hydrocarbon molecules like lycopene, β-carotene, and b) xanthophylls, also contain oxygen atoms in the form of hydroxyl, methoxy, carboxyl, keto, or epoxy groups in their hydrocarbon chains[14]. Carotenoids are potentially strong antioxidant molecules due to the presence of an alternate single double bond conjugated system and thereby can quench the peroxy radicals[15]. Carotenoids are often identified using their chromophore and light absorption properties[16]. Carotenoid is a long C40 polyene structure with alternate single double bonds hence constitutes a conjugated system. More than nine alternate double single bonds in a conjugated system are responsible for the pigment properties of carotenoids. This conjugation property was demonstrated by Richard Kühn in 1935 and was awarded the Nobel Prize in chemistry[17]. Since they absorb wavelength between 400-600 nm, therefore, are pigmented molecules ranging from red, yellow, orange color [8]. The intensity and the depth of colors of these molecules depend upon the number of alternate single double bonds as well as the functional group present. C40 parent molecule is formed by the tail-to-tail linkage of two C-20 geranylgeranyl diphosphate molecules which further undergo several reactions to get a variety of different carotenoids. The primary changes in the parent C40 molecule include cyclization at one or both ends, which produces seven different end groups, a change in hydrogenation level, and the addition of functional groups containing oxygen, which results in a family of more than 750 compounds[8].

Initially, trivial names were assigned to carotenoids. These names were derived from their biological source, however, since such names do not give any information regarding their structure, therefore, IUPAC- semi systematic scheme was designed. All names are derived from the stem name "carotene" preceded by the Greek letter prefixes (Ψ, Φ, β, γ, ε, κ, χ) that designate the two end groups[2]. The IUPAC-IUB rules are given in detail in volume 1A of the series carotenoids. Those carotenoids which have lost CH_3, CH_2, or CH group from ends of the carotenoid molecules are known as nor-carotenoids while oxidative cleavage of carotenoids is known as apocarotenoids (less than 40 carbon atoms) e.g. Vitamin A, abscisic acid[18].

integral part of the membrane. They also influence membrane fluidity, increase rigidity and mechanical strength hence play a vital role in the structural properties of membrane[19]. Interaction with polar molecules is only possible when carotenoids either form a complex with protein or with its side functional polar groups. They also crystallize in aqueous media. In higher organisms, carotenoids are mainly found in chromoplast in the form of microcrystalline aggregates[20].

3. Pigments from Microbes: A diversity of pigments is available in the form of natural and synthetic pigments in the market. Due to the toxicity, carcinogenic and teratogenic properties of the synthetic pigments, attention has been drawn towards natural pigments derived from microbial sources. Carotenoids, anthocyanins, flavonoids, and tetrapyrroles (chlorophylls and phycobiliproteins) are known derived natural pigments from various species of fungi, algae and bacteria [21,22]. The favorable characteristics that should be present in the ideal pigment-producing microbes are mainly able to dissimilate a wide range of C and N sources, tolerant to pH, temperature, and minerals, produce adequate amounts of color,

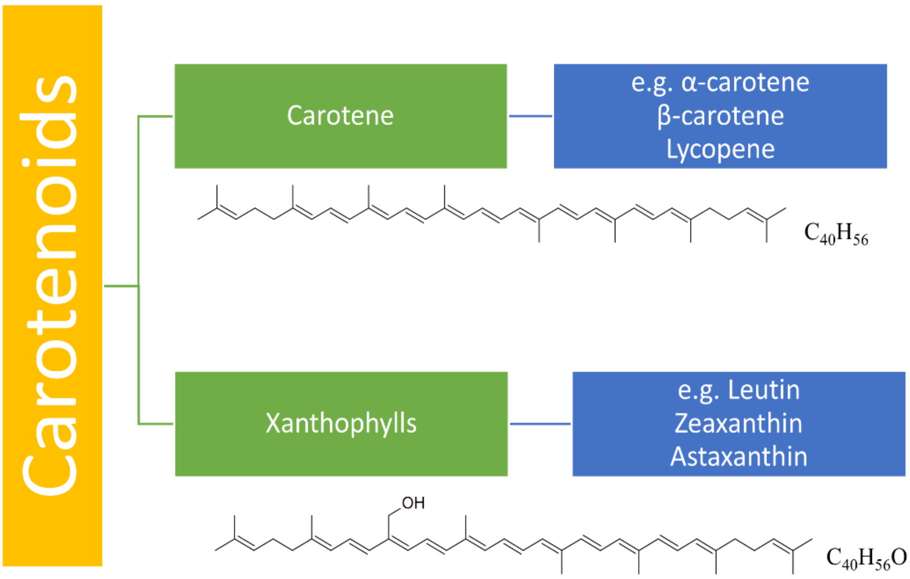

Fig 2. Classification of Carotenoids

2.1. Ultrastructural Organization of Carotenoids: Carotenoids being large and bulky form aggregates easily due to their hydrophobic nature mainly located at the be non-pathogenic, non-toxic, and easy to separate pigments from cell biomass[23]. The fermentation process is faster and more productive as compared to the chemical process. Utilizing microbial sources has several benefits, including the capacity to manipulate genes, growth independent of weather conditions, and ease of development on low-cost substrates. Additionally, microbial pigments have the key benefit of being significantly less hazardous than synthetic inorganic colors. As the public's awareness of "synthetic food additives" increased, industries are now focusing on extracting microbial pigments using genetic engineering and fermentation. If in-depth research is done on safe microbial pigments, the economics of natural food additives may be significantly improved[24]

4. Functions of carotenoids: Due to their anti-oxidant (anti-radical) properties, carotenoids are extensively used in the pharmaceutical industry for the manufacturing of medicines and supplements to boost immunity (Fig 3). According to experimental evidence, oxygen radicals are already thought to be a major factor in the development of many diseases[25,26]. It has been already established that carotenoids can significantly reduce infection by quenching radicals only if taken at threshold level[27] which is the case for lung cancer, arteriosclerosis, cataracts, age-related problems like macular degeneration, Parkinson's disease, multiple sclerosis, cardiovascular disease, and skin-related problems and eye diseases. In addition to their antioxidant properties, studies have revealed that carotenoids may also exert their effects by influencing enzymes that break down drugs in Phase I and II of their metabolism. These mechanisms include gap junction communication, cell growth regulation, gene expression regulation, immunological response, and cell growth regulation[28,29]. Dietary antioxidants are another name for carotenoids, which include lutein, lycopene, α-carotene, β-carotene, β-cryptoxanthin, and zeaxanthin.

4.1. Carotenoids as a precursor of vitamin A: Vitamin A is essential for humans since it is

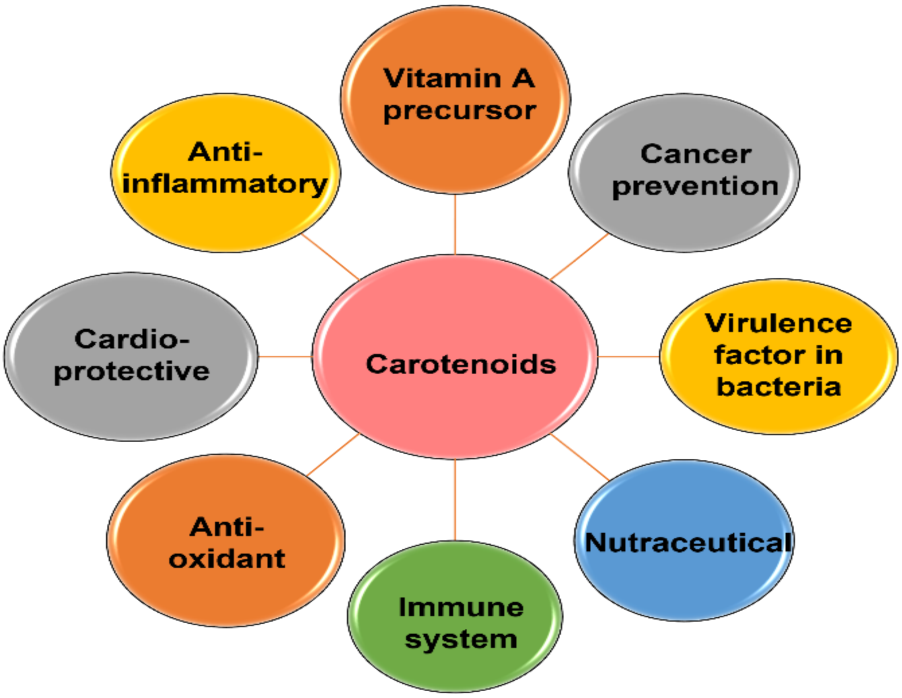

Figure 3: Functions of carotenoids

important for immune system health, eyesight, reproduction, and cellular communication. Since humans cannot synthesize vitamins on their own, they must get them from diet or supplementation. Carotenoids and Vitamin A share a lot of structural similarities[30]. Hence, some carotenoids like α-carotene, β-carotene, and β-cryptoxanthin can act as a precursor of vitamin A while others like lycopene, and zeaxanthin can't. Retinol, retinal, and finally retinoic acid are produced through the oxidation of provitamin A carotenoids. The retina must function as the precursor of 11-cis-retinal-dehyde, or as a crucial part of rhodopsin, which supports the appropriate differentiation and functioning of the cornea and conjunctival membranes. Deficiency may lead to xerophthalmia (dry eye) and ultimately to night blindness or total blindness [31]. Vitamin A and its active compound retinol, is widely known to influence the innate immune system and regulate the antibody response hence resist infections. In addition to supporting cell growth, vitamin A is essential for the regular development and functioning of the heart, lungs, and kidneys. It is known to maintain healthy skin, teeth, skeletal and soft tissue, and mucous membranes. It plays a vital role in the differentiation and proliferation of epithelial tissues[32,33]. Vitamin A also plays a crucial role in the male by maintaining genital tract and spermatogenesis while in the case of females, vitamin A is required throughout the lifetime as it plays a signal role for the initiation of meiosis in female gonads and helps in pregnancy i.e., fertilization, implantation, development of the embryo as well as placenta [33–35].

β-carotene is known to quench efficiently singlet molecular oxygen, peroxides, and peroxide radicals especially during lipid metabolism, due to the presence of conjugated alternate carbon-carbon single double bonds. β-carotene is known for its 100% conversion from pro-vitamin A to vitamin A which is later converted into retinoid compounds in the intestine and liver by the enzyme 15-15'- β-carotenoid dioxygenase and by alcohol dehydrogenases respectively. Conversion may be enhanced by α-tocopherol & zinc [34,36].

4.2. Carotenoids and nutraceuticals (nutrition + pharmaceutical): The term nutraceutical was defined as "any substance that is a food or part of a food that provides medical or health benefits, including the prevention and treatment of disease" by Stephen DeFelice[37]. Due to their many advantageous properties like antioxidant activity, ability to modulate the immune system, scavenging free radicals, and Pro-vitamin A activity, carotenoids could be exploited for pharmaceutical purposes against many diseases as well as for health maintenance. Additional epidemiological research has demonstrated that carotenoids protect people from a variety of illnesses, including cardiovascular diseases[38,39]. The antioxidant properties of carotenoids like lycopene, β-carotene, canthaxanthin, zeaxanthin, and astaxanthin, which are widely used in a variety of foods, cosmetics, vitamin supplements, health products, and feed additives for fish, crustaceans, poultry, and other livestock, could be utilized and exploited by the nutraceutical industries to make enormous profits. According to Globe Newswire, Feb 2023, it is expected that feed carotenoids will surpass the revenue of USD 2.75 billion by growing at a CAGR of 2.2%. For human health, β-carotene along with supplementation of canthaxanthin was used for patients suffering from erythropoietic protoporphyria to reduce some of the deleterious effects of light[40,41]. β-carotene is known to inhibit progressive carcinogenic pathways. Certain cancers like oral, mammary tumors, and skin cancers were reduced[42]. Lycopene quenches the reactive oxygen species which is the causative agent for sperm damage and hence can be used to treat infertility in men. The best approach to lower the risk of prostate cancer is to consume lycopene, which can be found in processed tomatoes [43,44]. Carotenoids further protect the cell membrane lipids, proteins, lipoproteins and DNA from oxidative damage [45]. It is given as a supplement to patients with liver diseases for lowering LDL cholesterol and is thought to help prevent atherosclerosis[46,47]. Another significant carotenoid to be utilized as a supplement for a variety of ailments is lycopene, which has been shown *in vitro* and *in vivo* research that slow the growth of breast, lung, cervical, ovarian, prostate and pancreatic cancers[48–52]. Lycopene also suppressed insulin-like growth factor-I-stimulated growth. This growth factor is a key hormonal regulator that controls the proliferation of endometrial and breast cancer cells[52]. It is advised to include carotenoids, particularly lutein and zeaxanthin, in a balanced diet or take pure supplements to lower the risk of developing acquired illnesses such retinal degeneration, neurological diseases, cataracts, and coronary heart disease.[53,54]. It also helps in improving eyesight as they absorb blue light thereby often recommended to eye patients by ophthalmologists[55]. Carotenoids can also be taken as supplements to reduce inflammation especially astaxanthin as it is known as an anti-inflammatory and work against inflammatory cytokine interleukin-6, tumor necrosis factor-alpha (TNF-a), interleukin 1B (IL-1b), nitric oxide (NO), Cox-2 enzyme, prostaglandin E-2 (PGE-2), and nuclear factor kappa-B. Hence, there is no argument that carotenoids as a part of whole foods or taken as supplements can benefit human health by protecting from UV radiation, cell health, eye health and cancers.

4.3. Role of carotenoids in Immunity: The free radicals created during metabolic and immunological processes are quenched by carotenoids' scavenging action [56,57]. Acquired immunity consist of lymphocytes that invariably generate reactive oxidative products (ROS) to oxidize contaminants and kill infections by damaging their cell membranes, proteins, and nucleic acids. But reactive species do not differentiate between self and non-self hence as a defense mechanism, the body utilizes antioxidant molecules to quench them effectively and safeguard the "self" cells. The dietary antioxidants that are most frequently used are zinc, selenium, carotenoids, flavonoids, vitamin E, and vitamin C. Furthermore, it is well recognized that carotenoids are important for signal transduction, gene regulation, apoptosis, and the disease etiology [58,59]. By promoting effector T-cell activity, boosting macrophage and cytotoxic T-cell capacity, and promoting T- and B-lymphocyte proliferation, carotenoids strengthen vertebrates' immunity. Additionally, it has been discovered to have immunomodulatory benefits in mammals [60,61]. Carotenoids are known to modulate and influence the functioning of the immune system by reducing the reactive species that immune-suppressive peroxides and immune-active cells can produce[4,62]. They are also known to protect membrane receptors; control the release of lipid compounds that have immunomodulatory properties like prostaglandins and leukotrienes; also known to improved gap junction communication and immunological function *in vitro*; decreased or stopped cell transformations and mutagenesis[7,62,63].

4.4. Role of carotenoids in prevention and protection from cancers: Numerous studies have established a plausible link between carotenoids and their effect on therapy and prevention of cancer. Several meta-analysis studies have further verified the role played by carotenoids in cancer pathogenesis. The carotenoids having anti-cancerous activity include α and β carotenes, lycopene, lutein, zeaxanthin, fucoxanthin, canthaxanthin, astaxanthin etc. The anti-cancerous activity is primarily attributed to their anti-oxidant activity, however, a few of them modulate signaling pathways involved in apoptosis, cell proliferation, and autophagy[64–66]. Numerous carotenoids e.g. α and β-carotenes are known for their anti-cancerous activity[67]. However, α-carotenes are believed to possess higher antioxidant activity while β-carotenes are known for their anti-tumor activity [68]. Lycopene has been described to protect and prevent a variety of cancers including colon cancer, prostate cancer[69], lung cancer[70], mammary tumors [71], cancers of urinary bladders [72], ovarian cancers [73] and hepatocarcinoma [74]. Lutein has been associated with the chemoprevention of cancer [75] however its role in specific cancers remains to be established. Fucoxanthin, canthaxanthin and astaxanthin have been demonstrated to possess anti-cancerous activity in several cell lines and animal models [76–78]. Astaxanthin is known to inhibit cell proliferation and induce apoptosis and both could be used for potent anti-cancerous activities [79].

4.5. Carotenoids as virulence factor in bacteria: By virtue of their antioxidant properties carotenoids could impart survival advantage for intracellular pathogens that are exposed to toxic levels of reactive oxygen species and reactive nitrogen species. The role of the carotenoids as virulence factors was first described in *Staphylococcus aureus* [80]. This pigment was demonstrated to function as an anti-oxidant inside neutrophils and protect the bacterium from ROS [80]. The role of carotenoids in the virulence of the bacterial pathogen is further exemplified in Group B *Streptococcus* which has hemolytic and cytolytic toxins. Interestingly, it was observed that the c*ylE* gene enables bacteria for both the toxin and the pigment production [81,82]. Interestingly, several mycobacterial species also produce small amounts of carotenoids. While their exact function in the pathophysiology of tuberculosis remains unknown, carotenoids are crucial for the intracellular survival of *Mycobacterium marinum* [83]. Even in phytopathogens, the carotenoids are key players. For instance, carotenoids are crucial for both neutralizing ROS and protecting from UV light in *Pantoea stewartii.* Interestingly the pigmentation in this phytopathogen is regulated by virulence and quorum sensing regulator EsaI/EsaR. Du et al proved that carotenoids accumulated during the formation of biofilm in *Rhodococcus sp.* SD-74 *Cronobacter sakazakii* [84]. Carotenoids play an important role in the virulence of parasites affecting humans. *Toxoplasma gondii* which causes fatal toxoplasmosis in immuno-compromised individuals is known to produce abscisic acid. Abscisic acid plays a major role in pathogenesis and transmission [85]. Similar to *T. gondii*, *Plasmodium falciparum*, which causes malaria in humans also possesses machinery to synthesize carotenoids[86].

5. Industrial applications of Carotenoids: Carotenoids are highly pigmented chemicals that impart bright hues to fruits, vegetables, and other natural sources. Owing to their distinct qualities as colouring agents and possessing antioxidant properties, they are employed in a variety of industry sectors (Fig 4). It is reported that the market for carotenoids is expected to expand from its 2021 valuation of \$1.8 billion to \$2.7 billion by 2031, with a compound annual growth rate (CAGR) of 3.9% from 2022 to 2031[87]. Carotenoids are a natural food colouring ingredient that the food industry uses extensively because they can produce a wide range of vivid tones. Additionally, as dietary supplements, carotenoids offer significant health advantages by serving as antioxidants that shield the body from oxidative stress[63]. Carotenoids act as natural antioxidants in food preservation, extending the shelf life of items. They are also excellent flavour enhancers, enhancing the visual appeal of a variety of foods[63]. Carotenoids are used by the pharmaceutical industry for medical purposes in addition to food. Their anticancer qualities have been found by research, which makes them useful in the creation of cancer therapies[88]. Carotenoids also exhibit anti-inflammatory

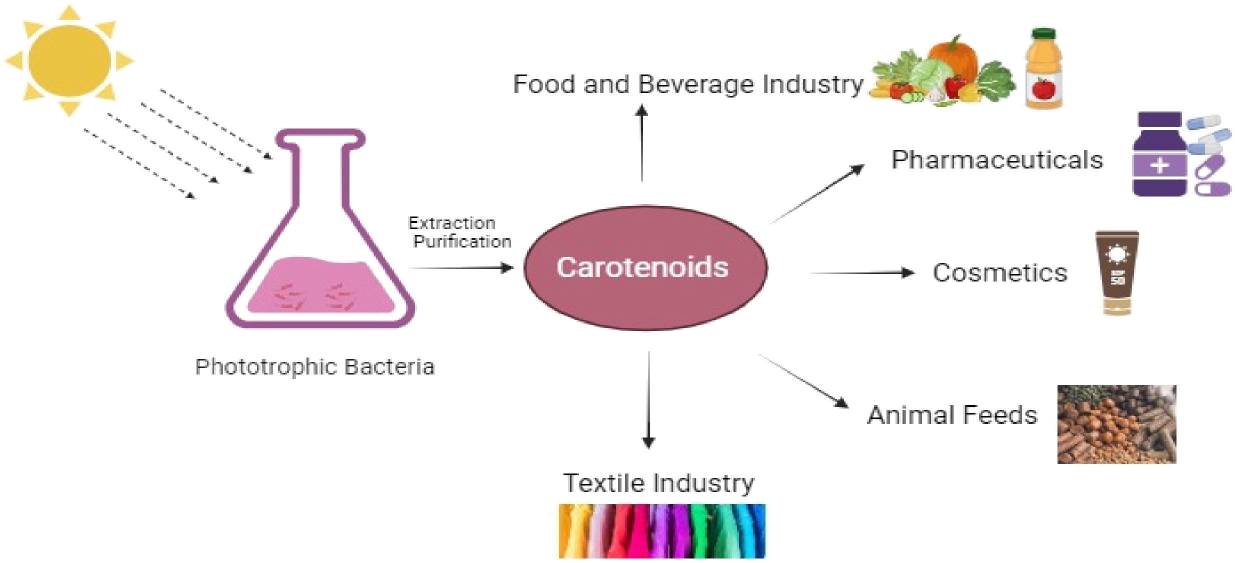

Figure 4: Applications of carotenoids in various industries

properties, which may be advantageous in the treatment of inflammatory diseases[89]. Finally, carotenoids are now present in the cosmetics sector. Because of their antioxidant qualities, they are utilized in skincare products; in hair care products because they strengthen hair; and in makeup and beauty boosters because of their vivid pigmentation[90]. All things considered, carotenoids are essential to many different businesses because they offer several benefits and uses. Carotenoids are useful in a wide range of industrial applications, from food and cosmetics to pharmaceuticals and biotechnology. Carotenoids are also being used more frequently as substitutes for artificial colourants and additives due to the growing consumer interest in natural and sustainable products[87].

6. Conclusions: Owing to carotenoids' numerous applications due to the presence of long hydrocarbon chains with conjugated systems led to the exploitation and search of novel carotenoids for the benefit of human society. Carotenoids are not only anti-cancerous molecules but also utilized as natural food colorants, in cosmetics as they protect the skin from UV light, quenching excessive reactive species formed by immune-active cells, protecting the cells from peroxides and maintaining membrane fluidity, acting in the release of immunomodulatory lipid molecules such as prostaglandins and leukotrienes [91] and so forth. Owing to its industrial application and despite the availability of natural and synthetic carotenoids, there is currently a resurgence of interest in microbial sources. As a response to a variety of environmental challenges, microorganisms tend to collect a variety of carotenoids. By doing this, they defend themselves from free radicals and play a significant role in photoprotection. Microbes like algae, fungi, and bacteria generate carotenoids, but only a few of them are used economically [92–96]. It's intriguing to learn that different microorganisms produce variety of carotenoids, which can neutralize the effects of toxic dietary additives. The discovery of unique, stable, and highly anti-oxidant active carotenoids from the bacterium is therefore of interest to the researchers.

Conflict of Interests: The authors declare that there is no conflict of interest regarding the publication of this paper.

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