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A comprehensive review on the role of Vitamin A on human health and nutrition

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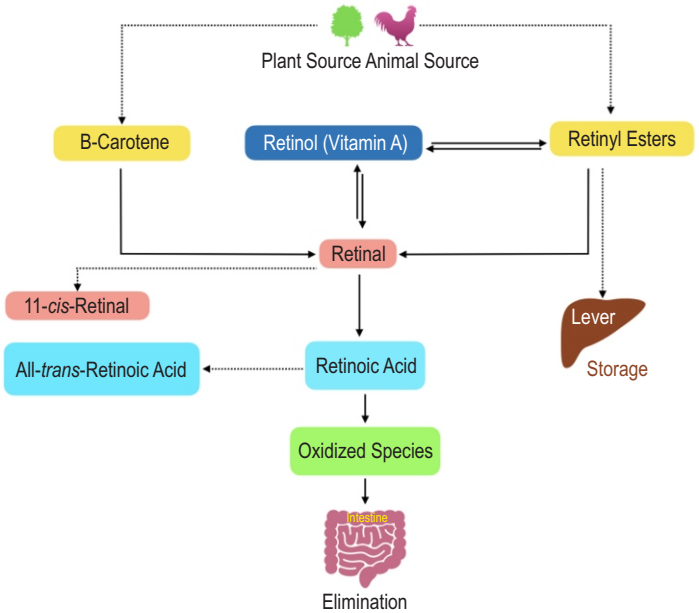
Abstract

Vitamin A is a crucial nutrient that protects the body from oxidative stress caused by free radicals, which are unstable molecules that can damage cellular components. Its antioxidant properties helps maintaining various physiological functions that depend on its presence, including vision, immune function and skin health. The human body can convert natural forms of vitamin A (retinol, retinal and retinoic acid) and provitamin A (β-carotene) into active forms, which interact with specific molecular targets, influencing gene expression, cell differentiation and cellular processes.

This comprehensive review provides an in-depth examination of vitamin A, covering its dietary sources, physiological roles and consequences of deficiency. In this research review explored the metabolic pathways of vitamin A, including absorption, transport and storage, as well as its potential applications, offering a thorough understanding of this essential nutrient. Furthermore, we have decreased the latest research on vitamin A's role in, maintaining healthy vision, immune function, and skin health, treating various diseases and conditions, such as retinal disorders, infectious diseases and cancer, mechanisms of action, including gene regulation, cell signaling, and antioxidant activity, relationships with other nutrients and health outcomes, including vitamin D, iron, and zinc, impact of deficiency on human health, including night blindness, impaired immunity, and skin disorders and emerging research on potential benefits and risks, including its role in chronic diseases and interactions with medications.

Key words: Nutrition, retinyl ester, Nyctalopia, Rhodopsin, Vitamin A, β-carotene,



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Introduction

Vitamin A is a fat-soluble vitamin found in various plant and animal foods, playing a crucial role in maintaining numerous critical bodily functions. These include supporting normal vision and eye health, particularly in low light conditions, through its role in rhodopsin regeneration; modulating immune function and inflammation; and promoting reproductive health and fertility by regulating gene expression and cellular differentiation. It also supports the growth and development of vital organs, such as the heart, lungs, and bones, through its involvement in cell growth, differentiation and morphogenesis; regulates energy metabolism and glucose synthesis; and maintains healthy skin and mucous membranes through its role in keratinocyte differentiation and epithelial integrity, ultimately making it an essential nutrient for overall health and well-being. Vitamin A is a group of unsaturated organic compounds, primarily associated with retinol, which exists in both natural and synthetic forms. Natural forms include retinal, all-trans retinoic acid (tretinoin), 9-cis-retinoic acid (alitretinoin), and 13-cis-retinoic acid (isotretinoin), while synthetic forms comprise etretinate, acitretin, adapalene, tazarotene, bexarotene and trifarotene (Carazo *et al.,* 2021).

These compounds play a crucial role in the growth and development, normal metabolic functioning, immune system regulation, and epithelial cell RNA synthesis, including the conjunctiva and cornea. Notably, 11-cis-retinal is essential for visual perception (Blaner *et al.,* 2016; Carazo *et al.,* 2021). Vitamin A deficiency (VAD) is a significant public health concern in developing countries. It can be obtained through diet in two forms: animal-derived products containing vitamin A (retinol and its derivatives) or plant-based provitamin A carotenoids, which are converted to vitamin A in the body (D'Ambrosio *et al.,* 2011). While the term "vitamin A" is often associated with retinol, and retinol is the predominant form of retinoids in the human body, the primary biologically active molecules are the oxidized derivatives 11-cis-retinal and all-trans-retinoic acid (ATRA) (D'Ambrosio *et al.,* 2011; Kam *et al.,* 2012).

Carotenoids, a group of vibrant yellow to orange pigments, are abundant in various fruits and vegetables. Beyond their connection to vitamin A, they possess potent antioxidant properties. Notable examples of carotenoids include β-carotene, α-carotene, lutein, lycopene and cryptoxanthin. Unlike animal-derived retinoids, carotenoids are tetraterpenoids that can be converted into retinol in the body. However, only specific carotenoids containing an unsubstituted β-ionone ring can be transformed into vitamin A, earning them the designation of provitamin A. Bael, a fruit rich in vitamins, minerals and bioactive compounds like marmelosin and psoralen, is a valuable source of essential nutrients. Products prepared from bael powder are rich in minerals and carotenoids, particularly Vitamin A. Notably, bael powder derived from fruits harvested between 180 and 245 days after fruit set (DAFS) is especially rich in marmelosin, psoralen and Vitamin A (Gurjar *et al.,* 2019). Yellow carotene, a precursor to vitamin A (retinol), is a pro-vitamin that plays a crucial role in nutrition. Carotenoids, are the pigments responsible for the red, orange and yellow hues in fruits and vegetables, they are abundant in various foods, including sweet potatoes, carrots, watermelons, peppers, apricots, nectarines, tomatoes, mangoes and corn. Additionally, they are present in leafy green vegetables like spinach, peas, parsley, pistachios, kale, broccoli, and Swiss chard, where the green color of chlorophyll masks the carotenoid pigments (Carazo *et al.,* 2021; Marzeda, 2019).

Visual impairment not only has a negative impact on individuals' vision but also hinders the growth and development of entire communities and society as a whole (Gordois *et al.,* 2012). At the global level, efforts have been made to address this issue, including the first collaborative and interdisciplinary global initiative to prioritize vision on the global health agenda, aiming to eradicate blindness-causing diseases such as trachoma and onchocerciasis, which has been successfully accomplished (Burki, 2021). Therefore, ensuring adequate nutrition, particularly sufficient vitamin A intake, is crucial for effectively preventing and treating such diseases. Since the late 1980s, there has been a significant expansion of knowledge regarding the various ways vitamin A functions, further highlighting its importance in maintaining good health. Vitamin A has been recognized as an essential nutrient with increasing therapeutic significance. The beneficial effects of carotenoids are attributed to their antioxidant properties. Beta-carotene may have additional benefits due to its convertibility to vitamin A. Lutein and zeaxanthin may also protect against eye diseases by absorbing harmful blue light that enters the eye (Gupta *et al.,* 2022). Proper metabolism of vitamin A in the human body plays a crucial role in reducing children's overall morbidity rates (Hall *et al.,* 2011; Sommer *et al.,* 2012).

Vitamin A can be consumed in two forms: preformed retinol, found in animal-derived foods like dairy, liver, eggs and provitamin A, found in plant-based foods like fruits and vegetables, including alpha (α)-carotene, beta (β)-carotene, and β-cryptoxanthin (Toti *et al.,* 2018). Mangos are rich in vitamin A, contains several bioactive compounds with anti-diabetic properties. Studies have suggested that hyperglycemia leads to increased oxidative stress-related indicators, elevated reactive oxygen species (ROS), and decreased antioxidant defenses in kidney cells, causing oxidative stress and potential cellular damage (Maritim *et al*., 2003). The mango peel is rich in polyphenols, carotenoids, dietary fiber, vitamin C, vitamin E and various beneficial plant compounds, including tri-terpenes and tri-terpenoids. These compounds have been shown to possess anti-cancer and anti-diabetic properties (Gupta *et al.,* 2022).

Vitamin A, an essential nutrient, in not synthesized in the human body and must be obtained through daily meals. The fat-soluble substances are readily absorbed by the liver and adipose tissue, stored as retinyl esters (O'Byrne *et al.,* 2013), and converted into all-trans-retinol, which interacts with retinol-binding proteins (RBPs) before entering the bloodstream. Dietary vitamin A comes in two forms: retinal esters (found in animal-based products like dairy, liver, and fish) and retinal (abundant in

vegetables, fruits, and plant-based products) (Schendel *et al.,* 2022; O'Byrne *et al.,* 2013). Although retinol is the common form of retinoids in the human body, the most physiologically active molecules are oxidized derivatives of 11-cis-retinal and all-trans-retinoic acid (ATRA) (Kam *et al.,* 2012). Carotenoids, such as α-carotene, β-carotene, cryptoxanthin, lutein, and lycopene, are yellow to orange pigments prevalent in fruits and vegetables, renowned for their antioxidant properties and link with vitamin A. The diverse functions of retinoids have led to the development of synthetic derivatives, classified into four generations: natural forms like retinol, retinal, tretinoin (ATRA), alitretinoin (9-cis-retinoic acid), and isotretinoin (13-cis-retinoic acid); etretinate and acitretin, derived from the first generation (Chiricozzi *et al.,* 2017); adapalene, tazarotene, and bexarotene (Dragnev *et al.,* 2007; Qu and Tang, 2010); and trifarotene, approved in the US (FDA, 2021). This research review will present a comprehensive analysis of vitamin A, shedding light on its significance and impact on human health as Vitamin A is an important source for proper growth and development of the human body.

Sources of Vitamin A

Vitamin A is an essential nutrient that cannot be produced by the human body, making dietary intake crucial. It can be obtained through preformed vitamin A or provitamin A carotenoids, with over 50 carotenoids identified. However, only β-carotene, α-carotene, and β-cryptoxanthin are present in significant amounts in human diet (Kelly *et al.,* 2018). These carotenoids are widespread in photosynthetic organisms, bacteria, fungi and animals (Barbosa *et al.,* 2008). β-carotene is abundant by found in the diet, primarily sourced from red and orange vegetables, as well as some similarly colored fruits and green vegetables (Table 1). In Europe, carrots, spinach, and tomato products are the main contributors to β-carotene intake, while β-cryptoxanthin is mainly obtained from citrus fruits juices (Beltrán *et al.,* 2015, Maiani *et al.,* 2009). Notably, β-cryptoxanthin and other carotenoids occur in plants as free and fatty acid esters, contributing to total vitamin A content due to their comparable bioavailability (Ma *et al.,* 2017). Rich sources of cryptoxanthin or its esters include various citruses, persimmons, chili peppers, red peppers, papaya, sea buckthorn, loquat, mango, and apricots (Maiani *et al.,* 2009, Jiao *et al.,* 2019). Completely ripe fruits have highest carotenoids concentration.

The sources of vitamin A from different vegetables are shown in Table 1. Adequate intake of vitamins and minerals is essential, varying by age. According to the Indian Council of Medical Research (ICMR), New Delhi, the recommended daily intake of vitamin A ranges from 350-600 µg for infants to adults (Singh *et al.,* 2023). Research shows that β-carotene is predominantly found in red and orange vegetables, as well as some similarly colored fruits and green vegetables (Kelly *et al.,* 2018). Specifically, β-carotene is rich in carrots, spinach and tomato products, while β-cryptoxanthin is abundant in various citrus fruits (Maiani *et al.,* 2009). A significant variation in carotene content was observed among different mango cultivars. A study quantified the total carotene content in raw mango candies, revealing a notable disparity. Specifically, Amrapali candy exhibited the highest carotene content (1.56 mg 100 g^{-1}), followed by Mallika candy (0.914 mg 100 g^{-1}), while Dussehri candy had the lowest content (0.672 mg 100 g^{-1}) (Singh *et al.,* 2021).

The carotenoid content in individual plant species exhibits significant variation, influenced by multiple factors. One notable indicator is the flesh color of a particular fruit or vegetable cultivar, as demonstrated in sweet potatoes and winter squash (Seroczynska *et al.,* 2006; Teow *et al.,* 2007). A strong correlation also exists between the degree of ripeness and carotenoid content in fruit, with fully ripe fruit containing the highest levels (Dragovic *et al.,* 2007; Zaccari *et al.,* 2015). Additionally, other factors such as cultivation method and location can impact carotenoid content (Dragovic *et al.,* 2007; Laurie *et al.,* 2012). Bael fruit is a nutrient-dense food, rich in beta-carotene, protein, riboflavin and vitamin C, as well as vitamins B1 and B2, thiamine, riboflavin, niacin, carotene, and essential minerals like calcium, potassium, fiber, and antioxidants (Gurjar *et al.,* 2019). Carotenoids, including β-Cryptoxanthin, occur in plants as free and esterified forms with fatty acids like lauric, myristic, and palmitic acids. Notably, these esters exhibit similar bioavailability and contribute to the overall vitamin A content (Ma *et al.,* 2017). Mango kernels are a rich source of various bioactive compounds, including caffeic acid, chlorogenic acid, catechins, mangiferin and quercetin (Gupta *et al.,* 2022). Mangiferin, a natural compound, has demonstrated anti-inflammatory and antioxidant properties, showing potential for treating eye diseases. The source of vitamin A in fruits and cereals are summarized in Table 2. The major vitamin A molecules present are β-carotene, cis-β-carotene, and violaxanthin isomers. Polyphenols play a crucial role in vision physiology and antioxidant protection of the eye, as supported by in vitro studies (Srinivasan, 2014). Flavonoids target various factors contributing to ocular diseases (Tilman *et al.,* 2010).

Mango byproducts, such as peel and seed kernel, are an excellent source of health-promoting compounds, including phenolic compounds, carotenoids, vitamins A, C, and E, and dietary fiber. Further research is needed to examine the nutritional and organoleptic aspects of these products to ensure consumer acceptance and optimal bioavailability of vitamin A (Gupta *et al.,* 2022). The mango seed kernel (MSK) is rich in nutrients as it contains carbohydrates, lipids, proteins and a variety of minerals (Singh *et al.,* 2021). Animal-derived foods, particularly milk and dairy products, meat, eggs, and fish, are significant sources of preformed vitamin A in human diet (Beltran *et al.,* 2015). While retinol content in milk from various livestock species shows minimal variation, factors like feed, seasonality, and breed can impact it. The source of vitamin A that is present in animal sources is mentioned in Table 3. Whole milk generally contains 20-80 micrograms of retinol per 100 ml, with higher milk fat content corresponding to higher retinol levels (Caprioli *et al.,* 2020). Similarly, dairy products' retinol content depends on milk fat levels (Ollilainen *et al.,* 1989). Livestock and poultry livers are rich in vitamin A, containing tens of milligrams of retinol and its

Table 1: Various kind of vegetables rich in β-Carotene content (µg 100 gm^{-1} of fresh weight) as source of vitamin A

Source	Tomato	Chilli pepper	Sweet potato	Pumpkins	Bitter gourd	Carrot	Coriander	Spinach	Cabbage	Broccoli
Botanical Name	*Solanum lycopersicum* L.	*Capsicum annuum* L.	*Ipomoea batatas* (L.)	*Cucurbita maxima Duchesne*	*Momordica charantia* L.	*Daucus carota* L.	*Coriandrum sativum* L.	*Spinacia oleracea* L.	*Brassica oleracea var. acephala DC*	*Brassica oleraceae var. italica Plenck*
Family	Solanaceae		Convolvulaceae	Cucurbitaceae		Apiaceae		Amaranthaceae	Brassicaceae	
β - Carotene	59-1500	100-15400	20-22600	70-6070	17040	4350-8840	4800	3100-4810	1020-10000	291-1750
References	Laur *et al.* (2011)	Seroczynska *et al.* (2006)	Laurie (2012)	Teow (2007)	Wall *et al.* (2001)	Laur (2004)	Booth *et al.* (1992)	Seroczynska *et al.* (2006)		

Table 2: Fruits and cereals rich in β-Carotene content (µg 100 gm^{-1} of fresh weight) as source of vitamin A

Source	Mango	Papaya	Red Grape fruit	Apricot	Persimmon	Dates	Maize
Botanical Name	*Mangifera Indica* L.	*Carica papaya* L.	*Citrus × paradisi*	*Prunus armeniaca*	*Diospyros kaki*	*Phoenix sp.* L.	*Zea mays* L.
Family	Anacardiaceae	Caricaceae	Rutaceae	Rosaceae	Ebenaceae	Arecaceae	Poaceae
β - Carotene content	109–3210	190-1050	2580	585–3800	3000	2950	171-1500
References	Maiani *et al.* (2009)	Veda *et al.* (2007)	Igual *et al.* (2013)	Dragovic-Uzelac *et al.* (2007)	Booth *et al.* (1992)		Laur *et al.* (2011)

Table 3: Various kinds of animal sources rich in vitamin A content (µg 100 gm^{-1})

Animal Source	Chicken liver	Chicken Leg	Beef liver	Hen Egg	Duck Egg	Duck Leg	Kembong Fish	Tenggiri Fish
β - Carotene	16,000	50	9000	304	209	69	8	8
Reference	Haytowitz *et al.* (2009)							

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esters per 100 g, with pig livers typically having the highest content (Alvarez *et al.,* 2015; Darwish *et al.,* 2016).

Metabolic Pathway of Vitamin A

Absorption: Vitamin A absorption in the human gut is highly efficient, with up to 90% of dietary intake being absorbed. This process is completed within 2-6 hours after digestion. The majority of stored retinol (over 90%) is absorbed in the form of retinyl ester within the lipid portion of chylomicrons (Ross *et al.,* 1999). During absorption, vitamin A, being fat-soluble, is incorporated into micelles and transported across the small intestine lumen. It then crosses the brush border (microvilli) into enterocytes, where carotenoids, precursors of vitamin A, are converted into active forms. These active forms are then packaged into chylomicrons and prepared for transportation throughout the body (Groff *et al.,* 1995).

Transport: After leaving enterocytes, chylomicrons carrying vitamin A metabolites (retinyl esters, carotenoids, unesterified retinol, and triglycerides) enter the lymphatic system and thereafter, general circulation. As they reach extra-hepatic cells, chylomicrons release triglycerides, but retain vitamin A. Vitamin A is then incorporated into chylomicron remnants (Groff et al., 1995). These remnants return to the liver for further metabolism and storage. When needed, retinol is mobilized from the liver through a process involving the carrier protein retinol-binding protein (RBP), enabling its recycling and reuse.

Storage: When serum vitamin A levels are adequate, the liver stores around 50-85% of the body's total retinol as retinyl esters. Hepatic stellate cells are the primary storage site, where retinyl esters are incorporated into lipid droplets due to vitamin A's fat-soluble properties (Groff *et al.,* 1995). However, the excessive accumulation of retinol in stellate cells can lead to hyper vitaminosis-A (Ross, 1999).

Excretion: Urinary system plays a crucial role in eliminating retinol and retinol-binding protein (RBP) from the body through renal catabolism and glomerular filtration (Ross, 1999). This process ensures the removal of excess vitamin A and its carrier protein from the body, maintaining optimal levels and preventing toxicity.

Physiological functions of vitamin A: Vitamin A exerts pleiotropic effects in the human body, with all-trans retinoic acid (ATRA) being the primary active form, despite retinol being the most abundant form (Hall *et al.,* 2011; Maden, 2002; Niles, 2003). ATRA performs various functions by binding to nuclear receptors and modulating gene expression. Retinoids are involved in several physiological processes, as illustrated in Fig. 1. Additionally, carotenoids, which contain antioxidants, play a crucial role in deactivating free radicals in the body, making vitamin A available (Sommer, 2003). Notably, retinoids have also been linked to various pathological conditions, including cancer, obesity, osteoporosis, cardiovascular disease and diabetes mellitus (Berry *et al.,* 2012; Gudas, 2012; Villarroya, 2004).

Vision: The retina, a complex region of the eye, plays a crucial role in regulating visual perception and transmitting information to the brain. Retinal, a mildly oxidized form of vitamin A with an alcohol-containing terminal group, is essential for this process. Two specific retinal structures, rods and cones, facilitate visual perception. Cones are responsible for high-intensity light detection, while rods are sensitive to low light conditions, making them vital for night vision and color vision. The ionone ring-based structure of retinal features a lengthy side chain with alternating single and double bonds, allowing for multiple cis-trans isomeric orientations (Fig. 2). A deficiency in retinol impairs low-light vision due to inadequate rhodopsin synthesis, leading to night blindness (nyctalopia) (Maian *et al.,* 2009). Fortunately, once plasma retinol levels return to normal, low-light vision can be restored.

Anti Cancer: The impact of carotenoids on cancer is disputed, especially for β-carotene. Despite its antioxidant properties and potential benefits for cardiovascular health and type II diabetes, research has yielded conflicting findings on cancer risk. A diet rich in fruits and vegetables, high in carotenoids, may reduce the risk of epithelial and lung cancers (Monsen, 2000). Conversely, β-carotene supplements have been linked to increased lung cancer risk and mortality in smokers (Omenn *et al.,* 1996). Importantly, this increased risk was only observed with supplements, not dietary intake (Middha *et al.,* 2019). In contrast, studies have shown that carotenoids can prevent oxidative stress, induce tumor cell death, and inhibit cancer development (Park *et al.,* 2020).

Immunity and Inflammation: Immune organs, comprising tissues with immunological functions, are responsible for the proliferation, differentiation and activation of immune-competent cells. Research highlights the essential role of consistent dietary vitamin A intake in maintaining the health of these vital organs. Vitamin A contributes significantly to the development and proliferation of regulatory tumor cells and modulates various immunological activities, including apoptosis regulation (Benson *et al.,* 2007; Kiss *et al.,* 2008). A deficiency in vitamin A impairs the immune system's ability to combat diseases like measles and parasitic infections, leading to increased severity and duration of these conditions (Adams *et al.,* 2005).

Diseases associated with vitamin A deficiency: Vitamin A is a crucial nutrient essential for various bodily functions, including healthy organ development (organogenesis), immunological competence, tissue differentiation, proper gastrointestinal function and adequate eyesight. The retinol and retinal forms of vitamin A play a vital role in maintaining healthy vision and reproductive processes. Vitamin A deficiency (VAD) is a widespread health issue that can lead to severe consequences, including blindness, impaired growth and development and increased susceptibility to infections.

Night Blindness: Nyctalopia, a disease that impairs vision, is another name for night blindness. Night blindness (nyctalopia) caused by vitamin A deficiency is a reversible condition that can be effectively managed and treated with retinal supplementation

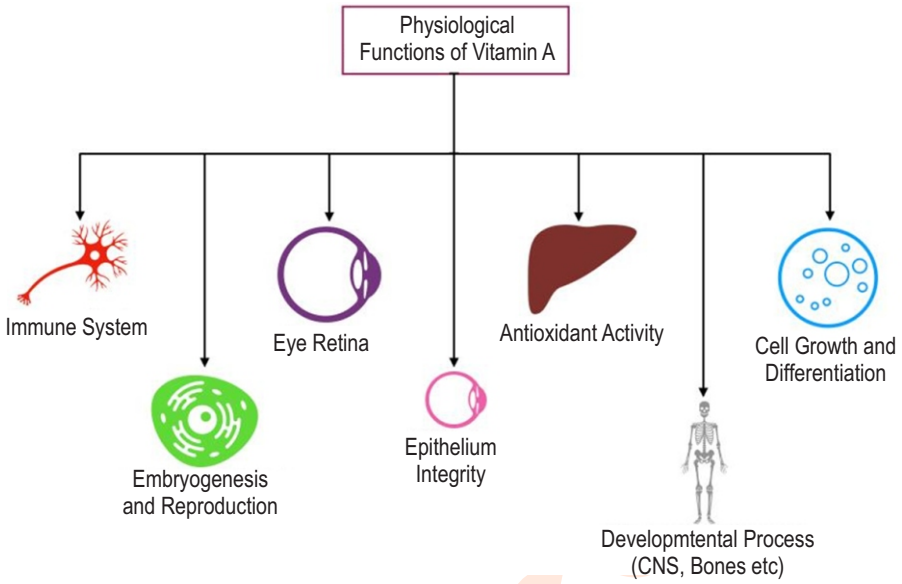

Fig. 1: Conceptual illustration of the physiological functions of vitamin A

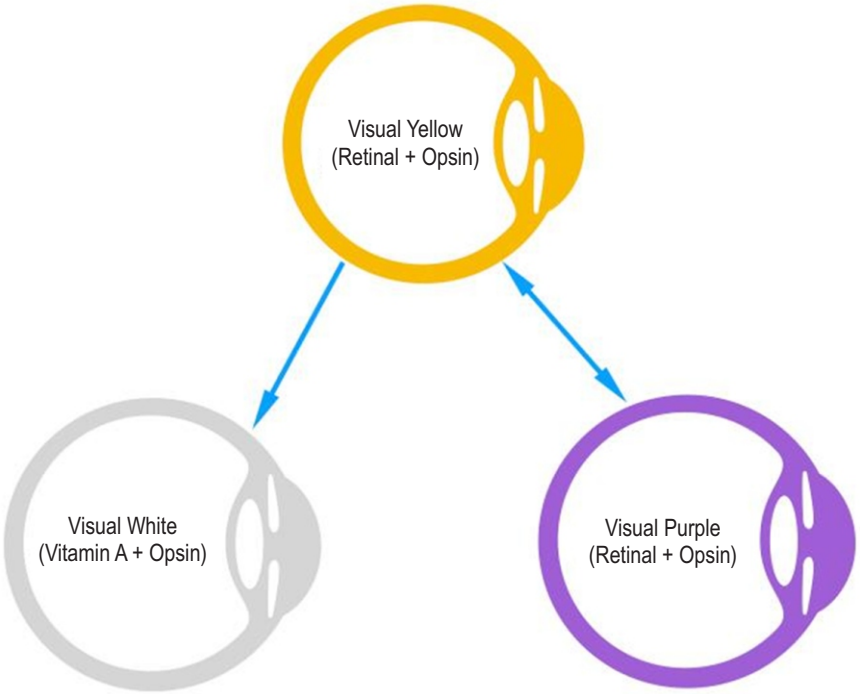

Fig. 2: Function of 11-cis retinal as progenitor of known visual pigments.

(Imdad *et al.,* 2017). People with night blindness have impaired night time or low-light vision. The deterioration of retina's rod cells may be the cause of this issue. Rod cells are crucial in the transmission of signals to the night light and neural transmission or brain cells, which are unable to function normally in the case of night blindness. Pregnant and lactating women may be at risk for night blindness. Neonates of vitamin A-deficient woman are born with decreased vitamin A baby.

Conjunctional Xerosis: Conjunctival xerosis, commonly known as conjunctivitis, is an inflammation or infection of the conjunctiva, a transparent, thin membrane that covers the sclera (the white part of the eye) and the inner surface of the eyelids. When conjunctiva becomes inflamed, its small blood vessels dilate, making them more visible and giving sclera a reddened or pink appearance, hence the nickname "pink eye." Conjunctivitis can be caused by a bacterial infection, viral infection or allergic reaction in the eye (Tarabishy and Jeng, 2008; Cronau *et al.,* 2010).

Bitot's Spots: Bitot spots are characterized by opaque, whitish triangular deposits that may form on the white interpalpebral area of the eye. These deposits consist of dried conjunctival tissue, which is a transparent layer covering the eye's exterior, and are unable to be moistened by tears due to impaired tear glands. This leads to an insufficient tear film and dry eyes. In cases of extreme eye dryness, foamy spots, commonly referred to as "Bitot spots," may appear on the conjunctiva (Han *et al.,* 2019; Dole *et al.,* 2009).

Corneal Xerosis: In individuals with corneal xerosis, the cornea appears dry and hazy. The condition often begins with superficial and punctate epithelial lesions, which can progress to the keratomalacia or corneal melting stage if left untreated. However, if addressed promptly, supplementation with high doses of vitamin A can lead to complete preservation of vision (Gilbert, 2013; Sommer *et al.,* 1983).

Keratomalacia: Conjunctiva is a membrane that lines the eyelids and covers the white part of the eye the cornea's surface can become dry and compromised leading to increased susceptibility to bacterial infections and corneal ulcers. Additionally, vitamin A deficiency can affect the retina, causing night blindness (impaired vision in low light environments). This condition is a common indication for keratoplasty (corneal transplantation) in the pediatric age group (Gilbert, 2013; Sommer *et al.,* 1983).

Xerophthalmia: Xerophthalmia encompasses the range of eye disorders resulting from severe vitamin A deficiency (VAD). Vitamin A plays crucial roles in maintaining eye health, and its deficiency can cause a variety of ocular signs and symptoms affecting the conjunctiva, cornea, and retina. Despite being preventable, xerophthalmia remains a leading cause of blindness in developing countries, highlighting the need for continued efforts to address vitamin A deficiency (Ifwat *et al*., 2022).

Vitamin A is a vital nutrient essential for growth, development, and overall health. Optimized intake is crucial in developing countries to prevent severe deficiencies. A balanced diet featuring diverse plant-based sources (sweet potatoes, carrots, dark leafy greens) and animal sources (fatty fish, eggs, chicken) can provide adequate vitamin A. However, certain derivatives (beta-carotene, retinyl palmitate) may exhibit pro-oxidant effects under specific conditions, highlighting the importance of a balanced approach.

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