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Review

Formulation and stability enhancement using vitamin A encapsulation in ocular abnormalities: A scientific review

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Abstract

The relationship between vitamin A, retinol activity, and eye health has been briefly elucidated. Based on certain reports, vitamin A and retinol activity can help overcome vitamin A insufficiency *i.e.*, xerophthalmia. The present review assesses vitamin A sources, β-carotene and β-cryptoxanthin in vitamin A metabolism, retinol and xerophthalmia, and new application of vitamin A in mitigating xerophthalmia. Vitamin A and its precursors are sensitive, and could lose their biological activity when exposed to light or oxygen. In this context, encapsulation may act as a protection strategy for enhancing vitamin A's biological functions under adverse conditions. With the belief that vitamin A and retinol activity have a long-term association with xerophthalmia, the present review discusses the relationship between vitamin A consumption and its precursors, as well as the physiological effects of vitamin A on xerophthalmia. In conclusion, further research using free and encapsulated forms of vitamin A to prevent vitamin A deficiency and manage xerophthalmia should be emphasised.

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Introduction

Vitamin A deficiency (VAD) is the main reason of visual impairment in adolescents around the world. It is particularly common in developing nations, with an estimated 228 million children suffering from moderate to severe deficiency (WHO, 1994). Malnourished adolescents raised by vitamin A-deficient mothers are more at risk, specifically, because they are impacted concurrently with other organic stresses such as diarrhoea or measles. VAD has been reported as a consequence of poor food intake, bosom ailments, and digestive malabsorption, though it is uncommon in the United States (Bishara *et al*., 1982).

Xerophthalmia is a term used to describe a range of ocular abnormalities due to VAD including conjunctival drying (xerosis), corneal ulceration accompanied by melting (keratomalacia), night blindness (nyctalopia), and retinopathy (Sommer, 1998). Vitamin A is compulsory for good immunological function as well as for the eyes. VAD, accompanied by an augmented risk of diseases or fatalities of affected precursors, is much more dangerous than respiratory or intestinal infections (Sommer *et al*., 1984; Sommer, 1998).

Vitamin A (VitA) is a class of monohydric unsaturated alcohols with an alicyclic ring. VitA is insoluble in water, and soluble in lipids (Sommer, 2008). VitA is also called an anti-inflammatory vitamin due to it being used to stimulate an organism's anti-inflammatory responses (Mellanby and Green, 1928). In the 1980s and 1990s, the anti-inflammatory properties of VitA were commonly recognised (Kolb, 1981; Muhilal *et al*., 1988; Semba, 1994). VitA is distinguished into three forms: retinol, retinal, and retinoic acetate (RA), with RA representing the closest organic activity. There are two most widely used derivatives of RA which are 9-*cis*-RA and all-*trans*-RA (ATRA) (Pino-Lagos *et al*., 2010). The

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most important roles of VitA are for visual maintenance, growth, and epithelium and mucous functions (Ross *et al*., 2000). However, the immuno-regulatory mechanisms governing VitA are still unknown. The present review provides an in-depth examination of the latest developments in VitA function in immunology. VitA's therapeutic abilities in the treatment of various contagious diseases are also compiled to provide theoretical support for VitA research in immunology and pharmacology.

VitA is found in various foods. Due to the operating efficacy of metabolic methods that put carotene within retinol differs from one to another, the bioavailability of carotenoids in diet are fluctuating. Milk products, eggs, butter, retinol-enriched margarine, and meat are examples of retinol-rich foods, while β-carotene-rich foods include vegetables and berries (carrots, dark-green vegetables, mangoes, candy potatoes, melons, and sweet crimson peppers). Several processed foods such as cornflakes, malted water dust, and lime water are also fortified with VitA (Field *et al*., 2002; Cusick *et al*., 2005; Erkelens and Mebius, 2017). Foods containing pro-VitA (carotenoids) have lower availability of VitA, but higher activity in the formulated VitA than natural foods, specifically in the treatment regimes of sick individuals. Retinol, in the form of retinyl esters and pro-VitA carotenoids, which are all components of nascent chylomicrons released by the lymphatic system, enters the human body. The majority of dietary retinol (in the form of chylomicrons or chylomicron remnants) is digested and stored in the liver, which is the primary position for retinol metabolism and storage. This is especially true after a protein called retinol-binding protein (RBP) circulating retinol out of the intestine.

Low water solubility and oxidation, on the other hand, directly influence the usage of VitA and its presence in foods, as well as the expansion of fat-soluble mixtures in commercial yields. Several techniques have been developed to enhance VitA activity, bioavailability, and water-solubility in specific situation. Carotenoids can be categorised by various methods including nanoemulsions, tiny emulsions, liposomes, strong lipid nanoparticles, and complicated assemblages with macromolecules (Gul *et al*., 2015). Since they contain lipids which can disintegrate bioactive chemicals, nanoemulsions are introduced as remarkable alternatives for safeguarding VitA and its precursors through encapsulation. They are also rather simple to work with, and can be included in various foods and beverages (Banasaz *et al*., 2020).

Recognising the importance of the association between VitA and xerophthalmia, the present review discusses the approach through a description and scientifically structured way of literature review. The relationship between the intake of VitA and its encapsulated precursors is also compared with the physiological properties of xerophthalmia.

Sources of vitamin A

Carotenoids such as β- and α-carotene (pro-VitA) are essential dietary sources of VitA. VAD is a common problem faced by many developing countries which encourages researchers to consider carotenoid-fortified food crops such as rice and corn as mitigation strategies (Sankari *et al*., 2018). Lycopene, an essential carotene (present in tomatoes), has high antioxidant activity, reduces the risk of cancers, and protects against heart diseases (Bhakta and Siva, 2010). Lutein and zeaxanthin are xanthophylls known to prevent macular degeneration (Lu and Li, 2008). Carotenoids and Apo carotenoids are used as dietary supplements in farm animals and fish feed, and as herbal colorants in the food and beauty industries (Umeno *et al*., 2005). As a result, these pigments have been extensively studied by organic chemists, food chemists, biologists, physiologists, doctors, and environmentalists.

VitA is quite possibly the most flexible nutrient, with roles in different capacities such as vision, immune system, upkeep of body linings and skin, bone and body development, and cell development and proliferation. VitA supports tissue in areas of the respiratory, urine, ligaments, and stomach as the primary protective measure against colds and infections. VAD can thus lead to poor vision, distress, death, and also in the case of pregnant women, can cause malnutrition in child in terms of child weight and size (Mayo Clinic, 2010).

Food sources

VitA exists in two forms: preformed retinoid and provitamin carotenoids. Different forms of VitA are shown in Figure 1. Pro-VitA is found in plant products with red, orange, and yellow colours, and converted by an antioxidant into VitA. Preformed VitA is found in animal products such as eggs, milk, liver, and immediately accessible to the body when ingested (Sizer *et al*., 1997).

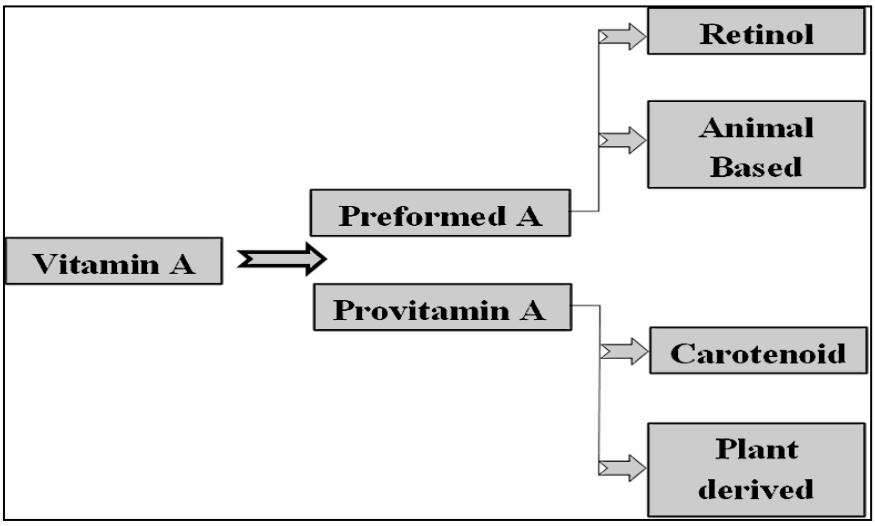

Figure 1. Derivatives of vitamin A.

β-carotene as vitamin A source

Since the effectiveness of transformation of β-carotene to retinol is not on a single factor, other transformation factors have been studied to assess the influence of β-carotene on total nutritional consumption of VitA. These studies showed that β-carotene plays a role in meeting the necessary intake of VitA. As reviewed by Grune *et al*. (2010), there are various functions, distributions, and absorption pathways of β-carotene into pro-VitA. There is widespread agreement that β-carotene is a source of VitA, and its pro-VitA's functions add to vitamin A intake (Grune *et al*., 2010).

β-cryptoxanthin as vitamin A source

Common carotenoid present in fruits, and human blood and tissues is β-cryptoxanthin. β-cryptoxanthin performs a number of vital functions for human health such as antioxidant defence and cell-to-cell communication. More significantly, β-cryptoxanthin is a precursor to VitA, a vital element for vision, growth, development, and immunological response. According to Burri (2015), β-cryptoxanthin has a higher bioavailability from typical food sources than α- and β-carotene. Although β-cryptoxanthin seems to be a worse substrate for β-carotene 15,15' oxygenase than β-carotene, animal model and human research indicated that β-cryptoxanthin-rich diets are as good as β-carotene-rich foodstuffs in terms of VitA content. These findings suggest that foods high in β-cryptoxanthin are potentially superior sources of VitA, and thus more vital for human health (Burri, 2015). Table 1 explains about the source, β-carotene equivalents, and VitA activity.

Recommended amount of vitamin A

VitA is a fat-soluble nutrient found in various food sources, and important for vision, immune system, and growth by supporting the proper functions of heart, lungs, kidneys, and various organs. Normal daily suggested amounts of retinol in microgram are given in Table 2.

Metabolism of vitamin A

Absorption

About 90% of VitA in the diet is absorbed in the gut. A linear relationship exists between absorption efficiency and intake. More than 90% of the body's retinol storage enters the absorption process as retinyl esters, within the lipids components of the chylomicron (CM) (Ross, 1999). VitA absorption is relatively fast, with maximal absorption happening two to six hours after ingestion. VitA, like other fat-soluble vitamins, is integrated into a micelle, and absorbed over the microvilli into the enterocytes in the small intestine. Carotenoids, the precursors of VitA, are transformed into active forms of the vitamin within the enterocytes. Freshly produced products, together with additional precursors, are subsequently packed into chylomicrons, and ready for distribution throughout the body (Groff *et al*., 1995).

Transport

When chylomicrons arrive at extra-hepatic cells, they release triglycerides while retaining VitA which is then incorporated into a chylomicron remnant. These residues are subsequently shuttled back to the liver, where they are metabolised and stored. When retinol is required, it recycles, *i.e*., it is

Table 1. Vitamin A activity in fruits (Booth *et al*., 1992).

Source	Description	β-carotene equivalent	Vitamin A activity
Ackee	Raw	560	93
Apple	Raw	43	7
Apricot	Raw	450 - 3,500	75 - 583
	Dried	1,260 - 6,540	210 - 1,090
Avocado	Raw	60 - 532	10 - 88
Banana	Yellow, Raw	60 - 130	10 - 21
	Red, Raw	90	15
Blueberry	Raw	60 - 170	10 - 28
Cashew fruit	Raw	760	127
Chile pepper	Raw	459	77
Currant	White, Raw	0	0
	Black, Raw	7 - 200	1 - 33
Guava	Raw	80 - 400	13 - 67
Loquat	Raw	1,580	263
Mandarin	Juice	250	42
Mango	Ripe, Raw	708 - 2,400	118 - 400
	Unripe, Raw	60	10
	Dried	4,400 - 5,621	733 - 877
Muskmelon	Raw	620	103
Papaya	Raw	300 - 2,500	50 - 417
Persimmon	Raw	3,000	500
Plantain	Raw	475	79
	Boiled	345	58
Raspberry	Juice	60	10
Sapote (diverse species)	Raw	48 - 100	8 - 17
Tamarillo	Raw	460 - 2,100	77 - 350
Watermelon	Raw	50 - 350	8 - 58
West Indian cherry	Raw	0 - 240	0 - 40

Table 2. Recommended amount of vitamin A intake by life stages (National Academy Press, 2001).

Life stage	Recommended amount
Birth to 6 months	400 mg RAE
Infants 7 - 12 months	500 mg RAE
Children 1 - 3 years	300 mg RAE
Children 4 - 8 years	400 mg RAE
Children 9 - 13 years	600 mg RAE
Teen boys 14 - 18 years	900 mg RAE
Teen girls 14 - 18 years	700 mg RAE
Adult men	900 mg RAE
Adult women	700 mg RAE
Pregnant teens	750 mg RAE
Pregnant women	770 mg RAE
Breastfeeding teens	1,200 mg RAE
Breastfeeding women	1,300 mg RAE

RAE: retinol activity equivalents.

mobilised from the liver. The carrier protein RBP is required for this mobilisation mechanism. This protein is the particular carrier for all *trans*-retinolins in the plasma. The holo-metabolite (retinol-RBP) then attaches to a transthyretin molecule (TTR). This newly synthesised macromolecule is not filtered by the nephronic glomeruli, thus circulating freely throughout the plasma. This mechanism allows tissues to absorb retinol *via* the cellular retinol-binding protein (CRBP) (Ross, 1999; Oruch and Pryme, 2012).

Storage

When VitA levels in the blood are sufficient, around 50 - 85% of total body retinol is stored in the liver as retinyl esters. Since VitA is fat-soluble, retinyl esters are often stored in hepatic cells where they are absorbed into lipid droplets. The VitA precursor, β-carotenoid, may be stored in the lipocytes of adipose tissues throughout the body, and when in excess, it can cause skin yellowing. The two enzymes β-carotene 15,15-monooxygenase 1 (BCMO1) and β-carotene 9,10-dioxygenase (BCDO2) are situated in distinct parts of the cell: BCMO1 is found in the cytosol, and its presence in organs other than the gut is crucial in embryogenesis and lipid metabolism, whereas BCDO2 is found in mitochondria, and useful in guarding against carotid-induced mitochondrial dysfunction (Groff *et al*., 1995; Ross, 1999).

Excretion

Retinol and RBP are excreted from the body *via* the urinary system, which includes renal catabolism and glomerular filtration. As a result, people with renal insufficiency may have higher levels of retinol and RBP in the blood, and they should be informed of the significant risk of developing VitA toxicity (Oruch and Pryme, 2012). The mechanism of VitA metabolism is explained in Figure 2.

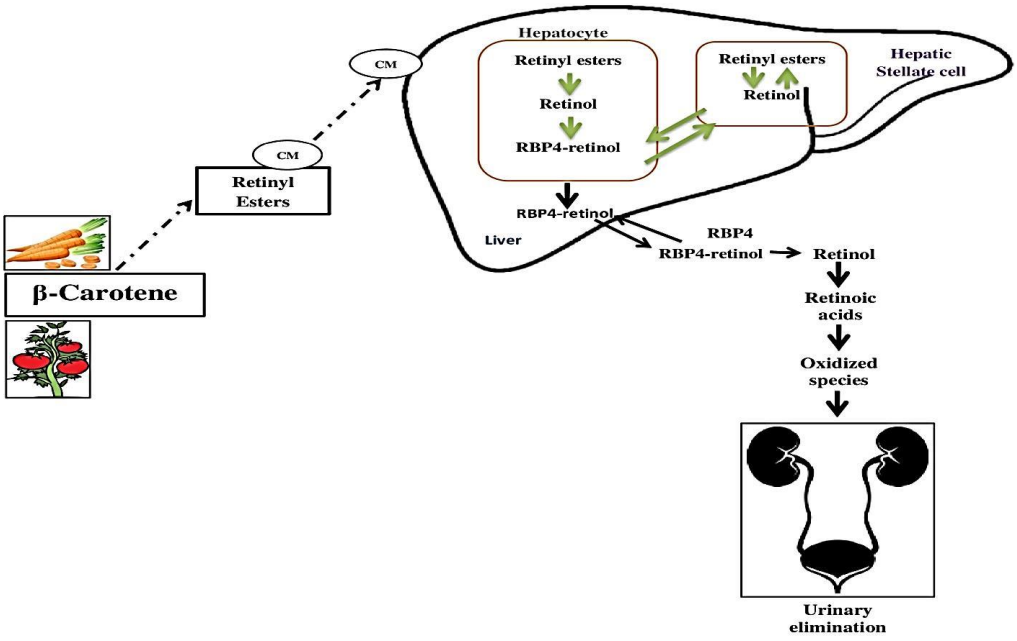

Figure 2. Metabolism of vitamin A.

Xerophthalmia signs of vitamin A deficiency (VAD)

The word "xerophthalmia" refers to broad ocular symptoms that are caused by VAD including diminished visual sensitivity to light (night blindness) and epithelial abnormalities of the cornea and conjunctiva such as conjunctival xerosis, Bitot spots, corneal xerosis, and keratomalacia (in order of their appearance and severity) (WHO, 1976; McLaren and Kraemer, 2012). These symptoms are linked to VAD, and vary in severity depending on age and the percentage of the deficiency.

The earliest clinical manifestation of VAD is night blindness, a condition in which a person cannot see in dim light. It is both a sensitive and specific diagnosis of low serum retinol levels (Sommer *et al*., 1980; Sommer, 1982). VitA, in the form of retinal, interacts with opsin in the eye to make rhodopsin, the rods' photosensitive vision pigment (DeLuca, 1978).

Night blindness is caused by a decrease in rhodopsin levels, and impaired rod function caused by VAD. In moderate cases, night blindness results from the interaction of colour vision stress caused by unexpected exposure to intense light, thus resulting in an accelerated rhodopsin turnover (Stephenson, 1896).

The WHO has classified various ocular indications of VAD in children including:

i. Night blindness: One of the most prevalent signs of VAD. This can impact adolescents as well as pregnant or breastfeeding women. When VAD is prominent in a community, it is often assigned a local name. It is a great way to learn what these terms mean, so that you can use those terms while enquiring about night blindness.

ii. Bitot's spots: Bitot's spots are a manifestation of VAD, and not caused by anything else. The bulbar conjunctiva near the limbus, at the three or nine o'clock locations, usually has a slightly elevated, white milky lesion. On the temporal side, Bitot's spots are more prevalent. The white deposit is keratin, which the conjunctiva proceeds to generate as a consequence of the insufficiency which induces 'squamous metaplasia', in which the cells in the conjunctiva mimic skin instead of mucous membrane cells.

iii. Corneal xerosis: This is ocular drying, which is an indication of a sudden, scarcity of lubrication. Since the glands in the conjunctiva are no longer functioning in a proper way, the cornea becomes dry. This leads to non-production of tears and also some mucus, which serve as a "wetting agent". The absence of mucus, combined with a lack of tears, causes a dry appearance and increases the chance of infection.

iv. Corneal ulceration: The cornea can get ulcerated and melt away if VAD is not treated as soon as possible. The ulcer may seem as a small, punched-out region in the cornea, or it may be puffier.

v. Keratomalacia: The eye can appear unexpectedly white / opaque in the absence of secondary infection. Unfortunately, recurrent ulcer infection is prevalent, thus resulting in an inflammatory eye.

vi. Corneal scarring: Depending on the depth of the corneal pathology, corneal scarring, staphylomas (forward bulging of a poorly injured cornea), or phthisis bulbi (shrivelled-up eye) are the end results of corneal ulceration and keratomalacia. The majority of symptoms in the eyes due to VAD are symmetrical and bilateral, and hence can result in blindness (Sommer *et al*., 1983; Cohen *et al*., 1985; Gilbert, 2013).

Different types of VAD based on the age groups are reported in the Table 3.

Table 3. World Health Organization (WHO) classification of vitamin A deficiency.

Xerophthalmia grade	Age group	Deficiency type
Night blindness	2 to 6 and in adult women	Not blinding, Long standing
Conjunctival xerosis	3 to 6	Not blinding, Long standing
Bitot's spot	3 to 6	Not blinding, Long standing
Corneal xerosis	1 to 4	Can be blinding, Acute deficiency
Corneal ulcer	1 to 4	Blinding, Severe Acute deficiency
Keratomalacia	1 to 4	Blinding, Severe Acute deficiency
Corneal scarring	> 2	Corneal ulceration consequence
Xerophthalmic fundus	Adults	Rare, Long standing, Not blinding also

Relationship between vitamin A, retinol, and xerophthalmia

VitA is produced for multiple functions in the human body, such as preventing night blindness, maintaining the outer layer of the skin, strengthening the body's defensive line, immune system, body growth, and development, and for the overall development of an infant. The preformed state of VitA (retinol) is essentially a precursor to two or more naturally basic moving parts of the element. All particles of *trans*-retinoic acid act as destructive substances, thus causing the formation of substances or mixtures of particle receptors. At retinoic acid receptors, the optic nerve pathway requires elfsis-

preformed (VitA) retinal (Blomhoff and Blomhoff, 2006; Sidra *et al*., 2020).

VAD is the cause of defects in the retinal pigment epithelium. Scotoma is caused by yellow and white patches in the peripheral retina. Xerophthalmia is a set of eye illnesses caused by VAD that manifests as Bitot's spots (abnormal squamous cell growth and keratinisation of the conjunctiva), advancing to corneal xerosis and keratomalacia (Alashry and Morsy, 2021).

Some carotenoids and their derivatives are involved in photoreception in both plants and animals. A typical example of complex interactions between plants and animals is the visual process, and the perception of neurons as vision depends on the plant chromophore. VitA usually binds to the Apo protein opsin to form rhodopsin (Esteban *et al*., 2015). Opsin, which contains complex retinol, is commonly found in flagellar green algae and metazoan eyes. They are usually not present in higher plants that represent different evolutionary patterns of visual and colour vision in plants and animals (Foster *et al*., 1984). Interestingly, the hormone abscisic acid is catabolised in plants by the same type of oxygenase that vertebrates use to break down retinoic acid. This indicates that animals store some unique enzymes from the ancestral gene pool for retinoic acid metabolism that meet the explicit requirements of visual photoreceptors. In plants, carotenoids are known to play an important role in photoreception because light-harvesting compounds do not have access to chlorophyll in the spectral range (Durchan *et al*., 2014; Manochkumar *et al*., 2021).

VitA (all-*trans*-retinol) is a precursor to the synthesis of rhodopsin, a photopigment found in rods. VitA must be transformed to 11-*cis*-retinal before rhodopsin is produced. One of two things can cause this. Isomerase converts all-*trans*-retinol (VitA) to 11-*cis*-retinol (VitA). Afterwards, the 11-*cis*-retinol can be transformed to 11-*cis*-retinal. Alternatives include converting VitA (all-*trans*-retinol) to all-*trans*-retinal, which can subsequently be transformed to 11-*cis*-retinal. After either mechanism produces 11-*cis*-retinal, it can be combined with scotopsin to produce rhodopsin. As rhodopsin absorbs light in the rods, 11-*cis*-retinal undergoes a constitutional shift, becoming all-*trans*-retinal. The opsin fragment undergoes a constitutional change to create metarhodopsin II, which is the activated form of rhodopsin. Transducin, a G-coupled protein located on the surface of the disc within the outer membrane of the rod cell, is then stimulated by metarhodopsin II. Activation of transducin results in activation of cGMP phosphodiesterase, which inhibits cGMP-mediated activation of cGMP-gated channels, allowing Na^+ ions to leak into the rod cytoplasm and causing hyperpolarisation. When Na^+ transportation into the rod cell is restricted in the presence of light, the rod cell becomes hyperpolarised, thus allowing messages regarding light detected during night vision to be delivered to the brain for final interpretation (Omenn *et al*., 1996).

Retinoic acid stimulates erythropoietin production by modulating the erythropoietin gene. It also affects iron metabolism; in VAD, iron is retained in the liver and spleen, and not freely available for erythropoiesis. Furthermore, VAD contributes to anaemia by lowering immunity, which leads to infection-related anaemia. There have been documented occurrences of xerophthalmia in the developed world as a result of poor nutrition, gastrointestinal malabsorption, and liver disease (Semba and Bloem, 2002; Chiu *et al*., 2016). The association between vitamin A, retinol, and xerophthalmia is explained in Figure 3.

Stability issues

Retinol is the most light-sensitive micronutrients. According to Allwood and Plane (1986), retinol is more vulnerable to light deterioration when exposed to frequencies less than 400 nm, with the most severe falling between 330 and 350 nm. Such frequencies are more usually seen in natural sunlight, whereas artificial light transmits only minor quantities of UV frequencies (Allwood *et al*., 2000b). A new study by Ferguson *et al*. (2013) observed massive loss of activity (more than 10%) when retinol is exposed to artificial lighting seen in emergency clinics and homes: cool and warm white light.

There has been a change in the attitude towards lighting after these investigations were conducted, with numerous units using energy-saving lights. Similar adjustments have taken place in homes which are attempting to cut expenditures. The influence of this illumination modification on retinol depletion has yet to be fully examined. The use of light is crucial until more studies are conducted about its influence on retinol loss of activity (Allwood *et al*., 2000a).

Apart from light deterioration, retinol sorption

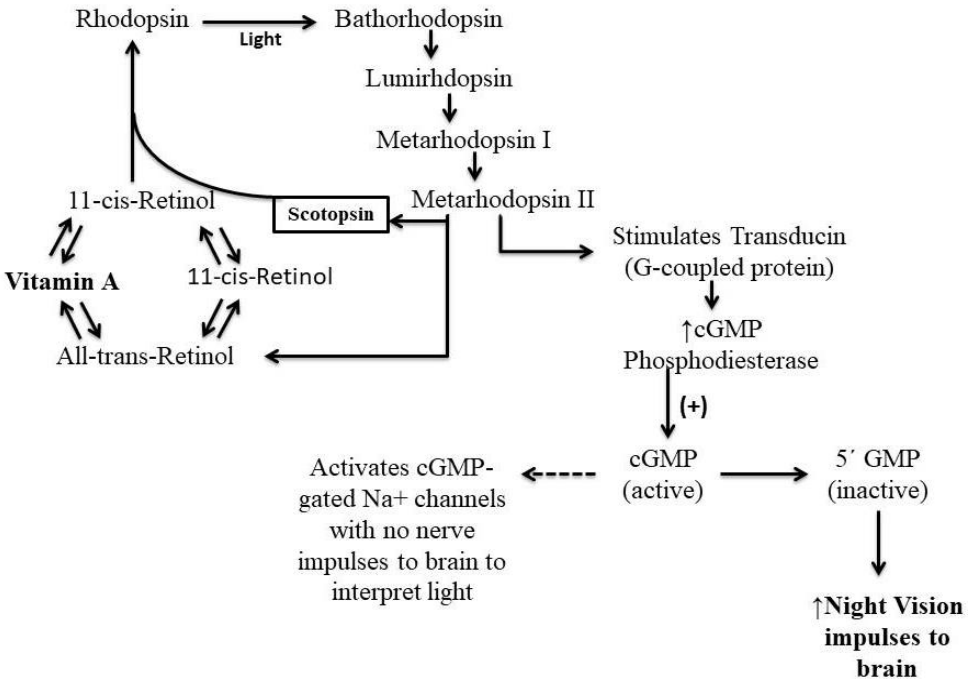

Figure 3. Mechanism of night vision.

can occur in hospital bags and tubes, thus lowering the amount of nutrition available to the patient (Allwood and Kearney, 1998). The less sensitive palmitate ester, as opposed to the acetic acid derivation ester, has greatly reduced this problem (Koletzko *et al.*, 2005). The use of tubing that contains polyolefin, which is derived from PVC, plasticisers, cement, or latex, can also reduce vitamin A retention (Henton and Merritt, 1990).

Peroxides produced by lipid emulsions are another source of nutritional contamination. Peroxidation is more likely in lipid emulsions containing polyunsaturated fatty acids (PUFAs). Peroxidation does occur in certain cases. The effect of various lipid emulsion arrangements on nutritional deterioration *via* peroxidation was investigated by Guidetti *et al*. (2008). When comparing soybean-medium chain triacylglycerol oil-based emulsions to soybean and olive/soybean oil-based emulsions after 24 hours of light-induced stockpiling at room temperature, Guidetti *et al*. (2008) discovered that retinol recovery was significantly augmented in soybean-medium chain triacylglycerol oil-based emulsions. Further examination is needed to comprehend the relationship between the organisation of lipid emulsions and nutrient deterioration.

The use of VitA as a nutraceutical or therapeutic ingredient containing foods is presently restricted by several factors *i.e*., poor water solubility, high melting point, chemical instability, lipophilic character, photodegradation, and low bioavailability which are caused by the chemical, mechanical, and thermal stresses during the time of food processing and storage, because when they are exposed to a stress, it may lead to degradation and loss of its properties. Encapsulation can be a protective method in order to enhance the activity of VitA as a nutraceutical or therapeutic ingredient containing foods.

Aspects of encapsulation in general

The process of encapsulating one ingredient (active agent) within an additional ingredient (wall material) is known as encapsulation. The encapsulated material is also known as core, fill, or internal phase. Coating, membranes, shell, capsule, carrier material, outer phase, or matrix are all terms used to define the encapsulating substance or wall material (Wandrey *et al*., 2009; Fang and Bhandari, 2010).

The encapsulation technique can be used for various reasons in the food industry. Encapsulation is a good way to get more bioactive chemicals (including antioxidants, minerals, vitamins, phytosterols, lutein, fatty acids, and lycopene) and living cells (like probiotics) into your foods (Desai and Park, 2005; Wandrey *et al*., 2009).

Encapsulation can also be used to change the physical properties of a substance to make it easier to handle, to separate distinct components of a mixture that could otherwise react, and to guarantee that an active agent has a suitable concentration and uniform dispersion (McClements and Lesmes, 2009).

The purpose of encapsulation is to preserve the bioactive compounds during processing and storage while avoiding interactions with the food matrix. The rapid deactivation of bioactive dietary components is the most important concern. These substances may benefit from encapsulation because it delays or prevents deterioration (such as oxidation or hydrolysis) until the product is delivered to the destination (Poornima and Sinthya, 2017).

Liang *et al*. (2013) used an oil-in-water approach to make nanoparticles with modified starch and β-carotene. They discovered that it retained far more pigment in nanoemulsion than free and dispersed pigment in oil. After *in vitro* digestion, nanoencapsulation increased β-carotene bio accessibility from 3.1 to 35.6%. They discovered that colloidal micronutrients have a greater surface area, which would promote lipase interaction (Rocha *et al*., 2018).

To prepare liposomes containing phosphatidylcholine and VitA, Sachaniya *et al*. (2018) employed a lipid film hydration approach followed by sonication and extrusion. Their results indicated that free VitA was released around 95% in 24 h, whereas encapsulated VitA was released around 50% (delayed) (Sachaniya *et al*., 2018).

Rocha *et al*. (2018) investigated the effect of nano-dispersion of β-carotene on antioxidant enzymes and cytotoxic characteristics. They discovered that encapsulation had advantages, and that loading β-carotene into nanoparticles increased its performance in aqueous settings, thus allowing for more efficient biological activity (Rocha *et al*., 2018).

Liu *et al*. (2019) studied Caco-2 cell lines *in vitro* and small intestine *ex vivo*. Nanoparticles were able to improve the absorption of active chemicals like β-carotene by using an oil/water emulsification process. According to the study, time, concentration, and temperature all affected the uptake. Encapsulated β-carotene had a higher absorption and transport rate than the free form (2.6 to 15%). There was also a better chance of retention and penetration in the gut tissue. Endocytosis allowed the particles to permeate Caco-2 cells more effectively. Particle size is inversely related to the existence of β-carotene in the cell monolayer (Liu *et al*., 2019).

Medeiros *et al*. (2019) encapsulated a carotenoid containing primarily β-carotene from a cantaloupe melon extract. They used this method to determine which encapsulating agent could aid water dispersibility and carotenoid stability in yogurt. Gelatine nanoencapsulation considerably increased water solubility and colour stability in yogurt throughout the 60-day shelf life. These effects were attributed to the particle size of roughly 60 nm, which increased the contact surface with water, and improved carotenoid function (Medeiros *et al*., 2019).

Baek *et al*. (2020) published their study on nanoemulsion loaded β-carotene in the enhancement of thermal and UV light stability. The study found that nanoparticles containing β-carotene were more stable, thus could be used in the food industry (Baek *et al*., 2020).

Liu *et al*. (2020) studied the structural characteristics, stability, antioxidant efficiency, *in vitro* gastrointestinal digestion, and release kinetics of vitamin C and β-carotene encapsulated in liposomes (L-VC-β-carotene). The storage stability of L-VC-β-carotene was better than that of L-β-carotene. The carotenoid in the two liposomes was gradually released throughout gastrointestinal digestion, with over 70% of the carotenoid liberated in simulated stomach fluid. During the gastric phase, the amount of β-carotene released was proportional to the amount of time it was in contact with stomach fluid. In the intestinal phase, liposomes were seen to be expanded, fractured, and fragmented, probably as a result of contact with bile salts or increased membrane fluidity to bile salt penetration, thus resulting in considerable lipase adsorption (Liu *et al*., 2020).

Resende *et al*. (2020) worked on vitamin A-containing NLCs for food fortification to ensure oral stability and bioaccessibility. The particles did not change in the stomach, and the biocompatibility of the formulations did not suggest fibroblast toxicity, based on *in vitro* trials imitating gastrointestinal digestion. In the digestibility test, the produced particles carried 80% of the extra vitamin to the stomach. The size of the particles in the stomach remained constant after two hours, thus showing that they were stable in the gut. Bile salts, when combined with pancreatic lipases, can help break down the di- and triacylglycerol that make up the particles (Resende *et al*., 2020).

Nanoparticles wrapped in gelatine were used by De Oliveira *et al.* (2021) to improve the antioxidant stability of a carotenoid-rich extract from the cantaloupe melon across a variety of storage conditions. Nano-encapsulated carotenoid improved antioxidant activity by roughly 60% due to the complex chemical interactions between porcine gelatine and crude carotenoid extract. As a result, encapsulated carotenoids had higher antioxidant capacity, and were better preserved than non-encapsulated carotenoids (De Oliveira *et al*., 2021).

The major goals of food encapsulation are to limit the rate of transfer of core components to surrounding materials, and to prevent incompatibility and reactivity of active chemicals. It alters the physical characteristics of the original materials for easier management, masks the undesirable taste or odour of the core materials, improves the quality of the core materials, controls the release of active materials, and betters the storage conditions by preventing degradative reactions such as dehydration and oxidation during storage encapsulation.

Conclusion

According to WHO research, VAD is a widespread health issue in developing countries, affecting not just preschool children but also children aged 8 and pregnant women. VAD affects around 250 million nursery children and significant number of pregnant women. Pregnant women and children from households with more than four children must be the focus of studies. Carotenoids are the most important natural pigment for the human body. Functions of VitA such as ensuring cancer immunity, UV light protection, and weight management are some of the health-promoting features of carotenoids that have attracted the attention of researchers and industry. The present review discusses the mitigation of VAD by supplementing carotenoids, and also the issues associated with stability and bioavailability. It also explains how encapsulated VitA has the most conserved biological activity, which promises better eye health.

Identifying the instability of VitA and carotenoid activity in the aspect of environmental circumstances, and integrating these bioactive chemicals in encapsulating agents that provide stability and increase favourable absorption effects, are subjects of substantial interest. It is possible to boost the usage of this nutrient in foods or pharmaceuticals in the treatment of VAD. Carotenoid will be a formula with high emphasis on antioxidant capacity, stability, and bioavailability. In spite of a large number of publications focusing on the properties that make carotenoids effective and their various potential health benefits, further research could explore VitA encapsulation and its consumption. Encapsulation technology, which preserves a certain quantity of carotenoids for long-term storage, can be used to solve these challenges. In recent years, there have been major advancements in encapsulation techniques. This strategy is incredibly useful and environmentally friendly for overcoming certain technological challenges. VAD can be easily solved in the future by taking carotenoid supplements. More research is needed to completely comprehend the mechanism in carotenoids as well as the best encapsulation technology for them. In conclusion, it is worth to give more importance for future studies related to the free and encapsulated forms of VitA to mitigate VAD.

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References

Alashry, A. I. A. and Morsy, T. A. 2021. Overview of vitamin A. Journal of the Egyptian Society of Parasitology 51(1): 29-42.

Allwood, M. C. and Kearney, M. C. J. 1998. Compatibility and stability of additives in parenteral nutrition admixtures. Nutrition 14(9): 697-706.

Allwood, M. C. and Martin, H. J. 2000b. The photo degradation of vitamins A and E in parenteral nutrition mixtures during infusion. Clinical Nutrition 19: 339-342.

Allwood, M. C. and Plane, J. H. 1986. The wavelength-dependent degradation of vitamin A exposed to ultraviolet radiation. International Journal of Pharmacy 31(1-2): 1-7.

Allwood,. M C., Ball, P. A., Driscoll, D. F. and Sizer,

T. 2000a. Light protection during parenteral nutrition Infusion: Is it really necessary? Nutrition 16: 234-235.

Baek, E. J., Garcia. C. V., Shin, G. H. and Kim, J. T. 2020. Improvement of thermal and UV-light stability of beta carotene-loaded nanoemulsions by water-soluble chitosan coating. International Journal of Biological Macromolecules 165: 1156-1163.

Banasaz, S., Morozova, K., Ferrentino, G. and Scampicchio, M. 2020. Encapsulation of lipid-soluble bioactives by nanoemulsions. Molecules 25: 3966.

Bhakta, D. and Siva, R. 2010. Determination of lycopene and its antioxidant activities in Indian tomatoes. Journal of Pharmacy Research 3(5): 933-937.

Bishara, S., Merin, S., Cooper, M., Azizi, E., Delpre, G. and Deckelbaum, R. J. 1982. Combined vitamin A and E therapy prevents retinal electrophysiological deterioration in abetalipoproteinaemia. British Journal of Ophthalmology 66: 767-770.

Blomhoff, R. and Blomhoff, H. K. 2006. Overview of retinoid metabolism and function. Journal of Neurobiology 66(7): 606-630.

Booth, S. L., Johns, T. and Kuhnlein, H. V. 1992. Natural food sources of vitamin A and provitamin A. Food and Nutrition Bulletin 14(1): 1-15.

Burri, B. J. 2015. Beta-cryptoxanthin as a source of vitamin A. Journal of the Science of Food and Agriculture 95: 1786-1794.

Chiu, M., Dillon, A. and Watson, S. 2016. Vitamin A deficiency and xeropthalmia on children of a developed country. Journal of Paediatrics and Child Health 52: 699-703.

Cohen, N., Rahman, H., Sprague, J., Jalil, M. A., Leemhuis de Regt, E. and Mitra, M. 1985. Prevalence and determinants of nutritional blindness in Bangladeshi children. World Health Statistics 38(3): 317-330.

Cusick, S. E., Tielsch, J. M., Ramsan, M., Jape, J. K., Sazawal, S., Black, R. E. and Stoltzfus, R. J. 2005. Short-term effects of vitamin A and antimalarial treatment on erythropoiesis in severely anemic Zanzibari preschool children. American Journal of Clinical Nutrition 82(2): 406-412.

De Oliveira, G. L. R., Medeiros, I., Nascimento, S. S. D. C., Viana, R. L. S., Porto, D. L. and Rocha, H. A. O. 2021. Antioxidant stability enhancement of carotenoid rich-extract from cantaloupe melon (*Cucumis melo* L.) nanoencapsulated in gelatin under different storage conditions. Food Chemistry 348: 129055.

DeLuca, L. M. 1978. Vitamin A. In Deluca, H. F. (ed). Handbook of Lipid Research, the Fat Soluble Vitamins (volume 2). New York: Plenum Press.

Desai, K. G. H. and Park, H. J. 2005. Recent developments in microencapsulation of food ingredients. Drying Technology 23: 1361-1394.

Durchan, M., Keşan, G., Slouf, V., Fuciman, M., Staleva, H., Tichý, J., … and Polívka, T. 2014. Highly efficient energy transfer from a carbonyl carotenoid to chlorophyll *a* in the main light harvesting complex of *Chromera velia*. Biochimica et Biophysica Acta (BBA) - Bioenergetics 1837: 1748-1755.

Erkelens, M N. and Mebius, R. E. 2017. Retinoic acid and immune homeostasis: A balancing act. Trends in Immunology 38(3): 168-180.

Esteban, R., Moran, J. F., Becerril, J. M. and García-Plazaola, J. I. 2015. Versatility of carotenoids: An integrated view on diversity, evolution, functional roles and environmental interactions. Environmental and Experimental Botany 119: 63-75.

Fang, Z. and Bhandari, B. 2010. Encapsulation of polyphenols - A review. Trends in Food Science and Technology 21: 510-523.

Ferguson, T. I., Price-Davies, R. and Cosslett, A. 2013. PP259-Mon vitamins - An unknown quantity. Clinical Nutrition 32: S219.

Field, C. J., Johnson, I. R. and Schley, P. D. 2002. Nutrients and their role in host resistance to infection. Journal of Leukocyte Biology 71(1): 16-32.

Foster, K. W., Saranak, J., Patel, N., Zarilli, G., Okabe, M., Kline, T. and Nakanishi, K. 1984. A rhodopsin is the functional photoreceptor for phototaxis in the unicellular eukaryote *Chlamydomonas*. Nature 311: 756-759.

Gilbert C. 2013. The eye signs of vitamin A deficiency. Community Eye Health 26(84): 66-67.

Groff, J. L., Gropper, S. S. and Hunt, S. M. 1995. Advanced nutrition and human metabolism. United States: West Publishing Company.

Grune, T., Lietz, G., Palou, A., Ross, A. C., Stahl, W., Tang, G., … and Biesalski, H. K. 2010. β-carotene is an important vitamin A source for humans. The Journal of Nutrition 140(12): 2268S-2285S.

Guidetti, M., Sforzini, A., Bersani, G., Corsini, C., Zolezzi, C., Fasano, C. and Pironi, L., 2008. Vitamin A and vitamin E isoforms stability and peroxidation potential of all-in-one admixtures for parenteral nutrition. International Journal for Vitamin and Nutrition Research 78(3): 156-166.

Gul, K., Tak, A., Singh, A. K., Singh, P., Yousuf, B. and Wani, A. A. 2015. Chemistry, encapsulation, and health benefits of β-carotene - A review. Cogent Food and Agriculture 1: 1018696.

Henton, D. H. and Merritt, R. J. 1990. Vitamin A sorption to polyvinyl and polyolefin intravenous tubing. Journal of Parenteral and Enteral Nutrition 14: 79-81.

Kolb, E. 1981. Recent findings on the importance of vitamin A and its metabolism in man and laboratory animals. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete 36: 897-902.

Koletzko, B., Goulet, O., Hunt, J., Krohn, K. and Shamir, R. 2005. Vitamins. Journal of Pediatric Gastroenterology and Nutrition 41: S47-S53.

Liang, R., Shoemaker, C. F., Yang, X., Zhong, F. and Huang, Q. 2013. Stability and bioaccessibility of beta carotene in nanoemulsions stabilized by modified starches. Journal of Agricultural and Food Chemistry 61: 1249-1257.

Liu, G., Zhou, Y. and Chen, L. 2019. Intestinal uptake of barley protein-based nanoparticles for beta-carotene delivery. Acta Pharmaceutica Sinica B 9: 87-96.

Liu, X., Wanga, P., Zoub, Y. X., Luoa, Z. G. and Tamer, T. M. 2020. Co-encapsulation of vitamin C and beta carotene in liposomes: Storage stability, antioxidant activity, and *in vitro* gastrointestinal digestion. Food Research International 136: 109587.

Lu, S. and Li, L. 2008. Carotenoid metabolism: Biosynthesis, regulation and beyond. Journal of Integrative Plant Biology 50(7): 778-785.

Manochkumar, J., Doss, C. G., El-Seedi, H. R., Efferth, T. and Ramamoorthy, S. 2021. The neuroprotective potential of carotenoids *in vitro* and *in vivo*. Phytomedicine 91: 153676.

Mayo Clinic. 2010. Vitamin A (retinol). Retrieved from website: http://www.mayoclinic.com/health/vitamin-a/NS_patientvitamina

McClements, D. and Lesmes, U. 2009. Structure-function relationships to guide rational design and fabrication of particulate food delivery systems. Trends in Food Science and Technology 20: 448-457.

McLaren, D. S. and Kraemer, K. 2012. Manual on vitamin A deficiency disorders (VADD). 3rd ed. Basel: Sight and Life Press.

Medeiros, A. K. O. C., Gomes, C. C., Amaral, M. L. Q. A., Medeiros, L. D. G., Medeiros, I., Porto, D. L., … and Passos, T. S. 2019. Nanoencapsulation improved water solubility and color stability of carotenoids extracted from cantaloupe melon (*Cucumis melo* L.). Food Chemistry 270: 562-572.

Mellanby, E. and Green, H. N. 1928. Vitamin A as an anti-infective agent. British Medical Journal 2: 691-696.

Muhilal, S., Permeisih, D., Idjradinata, Y. R., Muherdiyantiningsih, D. and Karyadi, D. 1988. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: A controlled field trial. The American Journal of Clinical Nutrition 48: 1271-1276.

National Academy Press. 2001. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. United States: National Academy Press.

Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., … and Hammar, S. 1996. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. The New England Journal of Medicine 334(18): 1150-1155.

Oruch, R. and Pryme, I. F. 2012. The biological significance of vitamin A in humans: A review of nutritional aspects and clinical consideration. Science Jet 1: 19.

Pino-Lagos, K., Guo, Y. and Noelle, R. J., 2010. Retinoic acid: A key player in immunity. BioFactors 36: 430-436.

Poornima, K. and Sinthya, R. 2017. Application of various encapsulation techniques in food

industries. International Journal of Latest Engineering Research and Applications 2: 37-41.

Resende, D., Lima, S. A. C. and Reis, S. 2020. Nanoencapsulation approaches for oral delivery of vitamin A. Colloids and Surfaces B - Biointerfaces 193: 111121.

Rocha, F., Sugahara, L. Y., Leimann, F. V., Oliveira, S., Brum, E. D. S. and Calhelha, R. C. 2018. Nano dispersions of beta-carotene: Effects on antioxidant enzymes and cytotoxic properties. Food and Functions 9: 3698-3706.

Ross, A. 1999. Vitamin A. In Shills, M., Olson, J., Shike, M. and Ross, A. C. (eds). Modern Nutrition in Health and Disease (9th ed), p. 350-313. Baltimore: Williams and Wilkins.

Ross, S. A., Mccaffery, P. J., Drager, U. C. and De Luca, L. M. 2000. Retinoids in embryonal development. Physiological Reviews 80: 1021-1054.

Sachaniya, J., Savaliya, R., Goyal, R. and Singh, S. 2018. Liposomal formulation of vitamin A for the potential treatment of osteoporosis. International Journal of Nanomedicine 13: 51-53.

Sankari, M., Rao, P. R., Hemachandran, H., Pullela, P. K., Doss, C G. P., Tayubi, I. A., … and Ramamoorthy, S. 2018. Prospects and progress in the production of valuable carotenoids: Insights from metabolic engineering, synthetic biology, and computational approaches. Journal of Biotechnology 266: 89-101.

Semba, R. D. 1994. Vitamin A, immunity, and infection. Clinical Infectious Diseases 19: 489-499.

Semba, R. D. and Bloem, M. W. 2002. The anemia of vitamin A deficiency: Epidemiology and pathogenesis. European Journal of Clinical Nutrition 56: 271-281.

Sidra, K., Aslam, M., Syed, F., Imran, M., Saad, B. and Noreen, S. 2020. An insight to Vitamin A: A neglected vitamin. EAS Publications Series 2(3): 107-123.

Sizer, F. S. and Whitney, E. N. 1997. Nutrition concepts and controversies. 7th ed. United Kingdom: Brooks Cole.

Sommer, A. 1982. Field guide to the detection and control of xerophthalmia. 2nd ed. Geneva: World Health Organization (WHO).

Sommer, A. 2008. Vitamin A deficiency and clinical disease: An historical overview. The Journal of Nutrition 138: 1835-1839.

Sommer, A., 1998. Vitamin A deficiency. In Duane, T. D. (ed). Clinical Ophthalmology on CDROM. Philadelphia: Lippincott-Raven.

Sommer, A., Hussaini, G., Muhilal, Tarwotjo, I., Susanto, D. and Saroso, J. S. 1980. History of night blindness: A simple tool for xerophthalmia screening. The American Journal of Clinical Nutrition 33: 887-891.

Sommer, A., Katz, J. and Tarwotjo, I. 1984. Increased risk of respiratory disease and diarrhea in children with preexisting vitamin A deficiency. The American Journal of Clinical Nutrition 40: 1090.

Sommer, A., Tarwotjo, I., Hussaini, G. and Susanto, D. 1983. Increased mortality in children with mild vitamin A deficiency. Lancet 2(8350): 585-588.

Stephenson, S. 1896. On epithelial xerosis of the conjunctiva. Transactions of the American Ophthalmological Society 18: 55-102.

Umeno, D., Tobias, A. V. and Arnoid, F. H. 2005. Diversifying carotenoid biosynthetic pathways by directed evolution. Microbiology and Molecular Biology Reviews 69(1): 51-78.

Wandrey, C., Bartkowiak, A. and Harding, S. E. 2009. Materials for encapsulation. In Zuidam, N. J. and Nedovic, V. A. (eds). Encapsulation Technologies for Food Active Ingredients and Food Processing. The Netherlands: Springer.

World Health Organization (WHO). 1976. Vitamin A deficiency and xerophthalmia. Geneva: WHO.

World Health Organization (WHO). 1994. Prevention of childhood blindness. Geneva: WHO.