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REVIEW

An Overview on the Effects of Some Carotenoids on Health: Lutein and Zeaxanthin

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Abstract

Purpose of Review In this review, the chemical properties, nutritional sources, absorption mechanisms, metabolism, biosynthesis and promising health-related benefits of lutein and zeaxanthin were emphasized and some recommendations for the future studies are suggested.

Recent Findings Lutein and zeaxanthin are phytochemical compounds in the carotenoid group and are synthesised only by plants. All mammals get lutein and zeaxanthin into their bodies by consuming plant-based foods. Especially leafy green vegetables, broccoli, pumpkin, cabbage, spinach and egg yolk are rich in lutein and zeaxanthin. Lutein and zeaxanthin have potential health effects by preventing free radical formation, exhibiting protective properties against oxidative damage and reducing oxidative stress. These compounds have neuroprotective, cardioprotective, ophthalmological, antioxidant, anti-inflammatory, anti-cancer, anti-osteoporosis, anti-diabetic, anti-obesity, and antimicrobial effects.

Summary The preventive properties of lutein and zeaxanthin against numerous diseases have attracted attention recently. Further clinical trials with large samples are needed to make generalisations in the prevention and treatment of diseases and to determine the appropriate doses and forms of lutein and zeaxanthin.

Keywords Lutein · Zeaxanthin · Carotenoid · Antioxidant · Anti-inflammatory · Ophthalmological

Abbreviations

AchE	Acetylcholine esterase
ADI	Acceptable daily intake
AMD	Age-related macular degeneration
DHA	Docosahexaenoic acid
DMAPP	Dimethylallyl pyrophosphate
DNA	Deoxyribose nucleic acid
EFSA	European Food Safety Authority
FPP	Farnesyl pyrophosphate
FPPS	Farnesyl pyrophosphate synthase
GGPP	Geranylgeranyl pyrophosphate
GGPPS	Geranylgeranyl pyrophosphate synthase
Glu	Glutamate
HDL	High-density lipoprotein
HMGCoA	Hydroxy-methyl-glutaryl-coenzyme A
HO-1	Heme oxygenase 1
HPA	Hypothalamic-pituitary-adrenal
ICAM	Intracellular adhesion molecule
IDF	International Diabetes Federation
IL-1β	Interleukin1-beta
IL-6	Interleukin-6
IL-8	Interleukin-8
IPP	Isopentenyl pyrophosphate
LDL	Low-density lipoprotein
MPOD	Macular pigment optical density
MS	Multiple sclerosis
nAMD	Neovascular age-related macular degeneration
NFATc1	Nuclear factor of activated T-cells
NF-κB	Nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
Nrf2	Nuclear factor erythroid 2-related factor
OC	Ovarian cancer
OH^-	Hydroxyl

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PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
RCC	Renal cell carcinoma
ROS	Reactive oxygen species
RRMS	Relapsin-remitteng multiple sclerosis
SR-B1	Scavenger receptor class B type 1
T2DM	Tip-2 diabetes mellitus
TBI	Traumatic brain injury
TFAM	Mitochondrial transcription factor a
TNF- α	Tumor necrosis factor-alpha
UV	Ultraviolet
VLDL	Very low-density lipoprotein

Introduction

Carotenoids are a group of natural tetraterpenoid pigments found in plants, fungi, bacteria, and algae [1] and have a significant role in many physiological functions of a human body. There are more than 1100 naturally occurring carotenoids identified [2]. Carotenoids are classified as carotenes and xanthophylls according to their chemical structure. Carotenes are non-oxycarotenoid substances that have cyclic hydrocarbons at one or both ends of the molecule. On the other hand, xanthophylls are carotenoids that contain oxygen. While the carotene group includes α-carotene, β-carotene, β-cryptoxanthin and lycopene, the xanthophyll group includes zeaxanthin, meso-zeaxanthin lutein, canthaxanthin and astaxanthin [3, 4]. The impact of dietary lutein and zeaxanthin intake on health has attracted attention in recent years [3]. Lutein and zeaxanthin have neuroprotective, cardioprotective, ophthalmological, antioxidant, anti-inflammatory, anti-cancer, anti-osteoporosis, anti-diabetic, anti-obesity, and antimicrobial effects [5, 6]. Moreover, lutein and zeaxanthin contain properties that protect the skin from ultraviolet (UV) rays, thus preventing certain skin diseases [7]. These positive effects of lutein and zeaxanthin on health are related to their characteristics such as preventing the formation of free radicals, being protective against oxidative damage and reducing oxidative stress [8].

This review was conducted to examine the clinical effects and modes of action of lutein and zeaxanthin, taking into account all their potential properties, and their effectiveness on health by analysing in vivo, in vitro, animal, and human studies.

Chemical Structure and Sources of Lutein and Zeaxanthin

Xanthophylls, an oxidized version of the carotenoid, are yellow pigments that account for the majority of carotenoids in nature. The term xanthophyll is originated from two Greek vocables: xanthos inferred "yellow" and phyllon inferred "leaf". Moreover, leaf pigments appear as a yellow band on chromatography. Lutein and its isomer zeaxanthin are compounds in the group of xanthophylls [9], (Fig. 1).

The chemical structure of lutein contains unsaturated polyene hydrocarbon containing 8 isoprene residues, 40 carbon atoms, 9 double bonds, and two hydroxyl (OH^-) groups in the β-ionone rings. Zeaxanthin is the isomer of lutein. The position of the double bond in the cyclic ring in the structure of zeaxanthin differs from that of lutein [4], (Fig. 2).

Lutein and zeaxanthin, unlike other carotenoids, have hydroxyl groups at both ends. The hydroxyl groups give these two compounds hydrophilic properties. The hydrophilic affinity of lutein and zeaxanthin enables them to react better with singlet oxygen. Therefore, lutein and zeaxanthin's capability to remove free radicals is better than non-polar carotenoids [9].

Since lutein and zeaxanthin are synthesised only by plants, all mammals get lutein and zeaxanthin into their bodies through nutrition. In nature, these compounds exist in esterified and non-esterified forms with fatty acids [3]. Especially leafy green vegetables contain plenty of lutein and zeaxanthin. Their content in vegetables varies between 0.01 and 40 mg/100 g on average. The foods with the highest

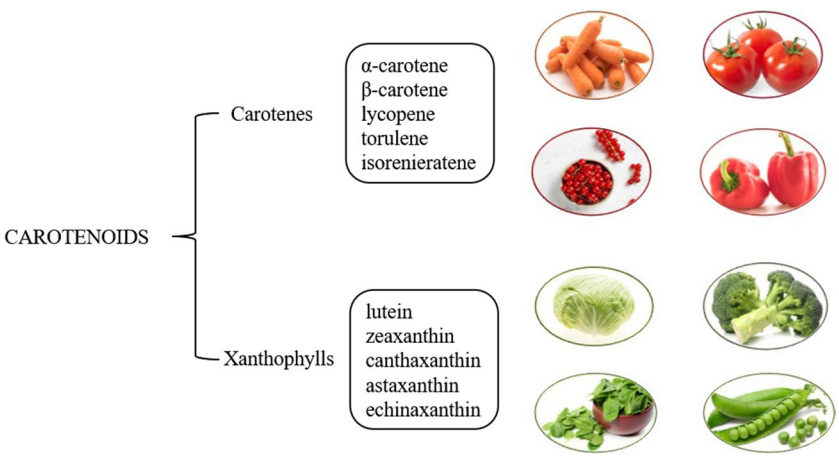

Fig. 1 Carotenoid subclasses and sources [9]

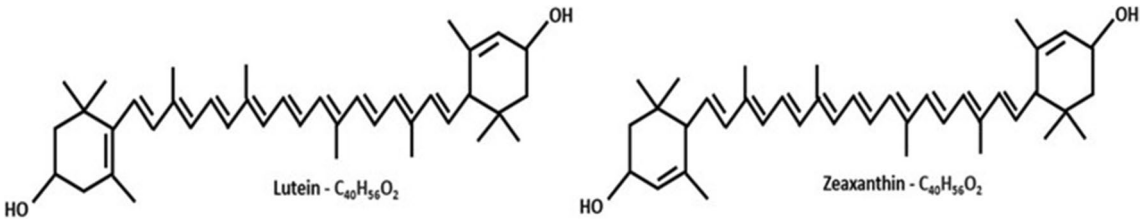

Fig. 2 Structural formula of lutein and zeaxanthin [4]

Table 1 Lutein and zeaxanthin content of some foods (mg/100 g) [4, 10]

Nutrient	Lutein/zeaxanthin	Nutrient	Lutein/zeaxanthin
Kale	39.55	Green peas (canned)	1.35
Spinach	11.93	Corn (canned)	0.88
Lettuce	2.63	Green beans	0.64
Broccoli	2.44	Carrot	0.35
Brussels sprouts	1.59	Cabbage	0.31

lutein and zeaxanthin content are kale and spinach. Lettuce, peppers, parsley, broccoli, Brussel's sprouts, pumpkin and egg yolks also contain lutein and zeaxanthin. Fruits contain less lutein and zeaxanthin than vegetables. Additionally, nectarines, kiwis, blackberries, raspberries, avocados and black currants are other foods with high lutein and zeaxanthin content [4], (Table 1).

Biosynthesis, Absorption and Metabolism of Lutein and Zeaxanthin

Mevalonate is the biosynthesis pathway of lutein. In this pathway, the hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) compound is reduced to mevalonic acid via the HMG-CoA reductase enzyme. Mevalonic acid is the precursor of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) [11]. Farnesyl pyrophosphate synthase (FPPS) transforms into isoprenoid farnesyl pyrophosphate (FPP) by enzymatic activity, leading to the catalytic extension of DMAPP. The enzyme geranylgeranyl pyrophosphate synthase (GGPPS) catalyses the extension of FPP to the isoprenoid geranylgeranyl pyrophosphate (GGPP) [5]. Dimerase enzymes dimerize GGPP molecules into phytoene. The reductase enzyme oxidizes phytoene to α-carotene via lycopene. Finally, the hydroxylation reaction at the third position of the two α-carotene rings, catalysed by a hydrolase, provides the constitution of lutein [12]. Since there are no genes encoding the enzymes required for biosynthesis of carotenoid in the animal organism, these compounds are obtained from foods [4].

Since lutein is hydrophobic, it is absorbed like fatty acids and fat-soluble vitamins. Fat-soluble lutein (free or esterified) and zeaxanthin also require fat for absorption and transport. Cholesterol esterases hydrolyze lutein esters before they can be absorbed by enterocytes [13]. This absorption process is thought to occur via scavenger receptor, class B type 1 (SR-B1). It is known that carotenoids encapsulated in the interior space of micelles carry out the stages of hydrolysis, absorption, binding to chylomicrons, and release into lymph [3]. Carotenoids are released from chylomicrons by lipoprotein lipase. They are carried by high-density lipoprotein-carrying cholesterol (HDL-C), low-density lipoprotein-carrying cholesterol (LDL-C), and to a lesser extent, very low-density lipoprotein-carrying cholesterol (VLDL-C). Primarily, lutein is stored in adipose tissue and hepatocytes. Lutein is excreted through bile and kidneys [14]. There are roughly 20 various types of carotenoids in human plasma or serum. The concentration of lutein and zeaxanthin in serum varies between 0.1–1.44 and 0.07–0.17 µmol/L, respectively [3]. Retinas contain only lutein and zeaxanthin. The human retina and lens contain much higher concentrations of xanthophylls than other tissues. However, they are not discovered in high concentrations in the blood or in the average diet [15].

Genetic factors, gender, age, health and nutritional status, as well as its type, number and the environment in which it is absorbed affect lutein bioavailability [4]. Thermal processing applied to plant-based foods increases the bioavailability of carotenoids by destroying the cell membranes and protein complexes of carotenoids. Lutein and zeaxanthin are relatively resilient to high temperatures. The bioavailability of lutein and zeaxanthin is increased by finely chopping and cooking foods [13].

The Effects of Lutein on Health

Carotenoids exhibit a strong antioxidant activity with the conjugated double bond system. Photoreceptor membranes are prone to peroxidation because they are rich in polyunsaturated fatty acids. Macular xanthophylls show an antioxidant activity in the photoreceptor membrane. Carotenoids are involved in many processes such as modulation of intercellular signalling pathways, regulation of the cell cycle,

stimulation of the immune system and growth factors, apoptosis and the fight against viruses [9].

Anti-diabetic Effects

Type 2 diabetes (T2DM) is a disease accompanied by high blood glucose levels that causes multiple organ dysfunction and affects the health and life of individuals [16]. The International Diabetes Federation (IDF) Diabetes Atlas (2021) reports that there are 537 million people with diabetes worldwide, constituting 10.5% of the adult population (20–79 years) [17]. IDF predictions show that 643 million people will develop diabetes by 2030. That figure is expected to rise by 46% by 2045 accounting for 1 in every 8 adults (approx. 783 million people).

Diabetes plays an important role as a risk factor in eye diseases such as cataracts, glaucoma and diabetic retinopathy [18]. In addition to producing reactive oxygen species (ROS), hyperglycemia impairs antioxidant capacity by damaging enzymes and antioxidants, causing oxidative damage and chronic inflammation, and leading to various complications [19]. Lutein may alleviate microvascular complications in T2DM patients through antioxidant and anti-inflammatory mechanisms, as well as the regulation of relevant genes and signalling pathways [18]. In a study, it was determined that lutein (up to 1.0 μM) blocks glucose-mediated increases in intracellular ROS, protein carbonyl and malondialdehyde content in retinal pigment epithelial cells [20]. A study in obese rats reported that the combination of lutein and orlistat effectively reduced high blood glucose levels caused by a high-fat diet [21]. Hyperglycemia leads to diabetic retinopathy by reducing mitochondrial biogenesis through the downregulation of nuclear transcription factors peroxisome proliferator-activated receptor-γ coactivator-1 (PGC-1α) and mitochondrial transcription factor A (TFAM) [22]. Lutein increases mitochondrial biogenesis in hyperglycemia-induced cell culture and rat retina [23]. Lactucaxanthin found in lettuce is a structural isomer of lutein and the anti-diabetic property of lactucaxanthin has been reported [24]. Lactucaxanthin or lutein was administered to diabetic rats at 200 μM for 8 weeks. Like lutein, lactucaxanthin was found to increase the expression of antioxidant activity, reduce oxidative stress markers, suppress the expression of endoplasmic reticulum (ER) stress and inflammatory markers in the diabetic retina, and improve glucose tolerance and lipid profile [25]. A study reported a negative correlation between serum lutein levels and blood glucose and urine microalbumin/creatinine ratio in elderly patients with T2DM and nephropathy. Additionally, low serum lutein levels indicated a high risk of T2DM and nephropathy in these patients [26]. In another study, no association was found between lutein/zeaxanthin intake and gestational diabetes [27]. However, another study reported that an increase in lutein levels could be beneficial for fasting glycemia in pregnancy [28]. A systematic meta-analysis revealed that dietary intake of lutein and zeaxanthin decreased the risk of T2DM [29]. Considering the studies, it seems that lutein and zeaxanthin may have positive effects on diabetes. However, more comprehensive clinical studies are needed before definitive conclusions can be reached.

Cardioprotective Effects

Cardiovascular diseases, including peripheral arterial diseases, ischemic heart disease, stroke, heart failure, and other cardiac and vascular diseases, are one of the leading causes of global deaths and negatively affect quality of life [30]. Lutein and zeaxanthin are transported in the body by HDL-C particles. This transport system increases HDL-C, which is known to have anti-atherogenic activity, and allows more cholesterol to be transported from hepatic tissues to the liver [5]. The cardioprotective effects of lutein can be explained by its modulatory properties on oxidative stress, inflammation, glucose homeostasis, lipid metabolism, insulin resistance and blood pressure [31]. In a meta-analysis study evaluating the effect of lutein and zeaxanthin on dyslipidemia, it was observed that lutein and zeaxanthin improved HDL-C levels [32]. In their study, Leemarkers et al. [33] stated in their review of 70 articles, including 387.569 participants, that dietary lutein intake and an elevation in serum lutein level had positive effects on cardiovascular health. Hajizadeh-Sharafarad et al. [31] reported in their meta-analysis study that lutein may protect against risk factors of atherosclerosis, including inflammation and endothelial dysfunction. It was found that lutein supplementation in rats reduced reactive oxygen species and lipid peroxidation, and lowered the level of inflammatory biomarkers such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) [34]. Lutein and zeaxanthin supplementation in rats fed a high-fat diet was shown to lower the levels of intercellular adhesion molecule-1 (ICAM), nuclear factor-kappa B (NF-κB), and vascular endothelial growth factor, thereby modulating genes associated with oxidative stress and inflammation [35]. In rats with isoproterenol-induced myocardial infarction, 40 mg/kg lutein supplementation applied for 28 days improved lipid peroxidation products, cardiac biomarkers (lactate dehydrogenase, creatine kinase-MB), inflammatory markers (IL-6, TNF-α, and NF-κB), and apoptotic markers. It has been reported that lutein supplementation has a cardioprotective effect [36]. In recent years, animal and human studies have reported that lutein and zeaxanthin may have cardioprotective properties with their positive effects on blood lipids and inflammatory biomarkers.

Neuroprotective Effects

Lutein is a carotenoid found in small amounts in human brain tissue. Although other carotenoids, such as β-carotene, are more widely consumed in the diet than lutein, lutein collects in greater amounts (up to 5 times) in the brain. Lutein and its isomer zeaxanthin, which have anti-inflammatory and antioxidant activities, cross the blood–brain barrier and are absorbed by cerebrovascular cells [37]. The function of lutein in brain tissue is ambiguous. However, lutein concentrations in the brain have been shown to be related to other antioxidants, lipid and energy pathway metabolites, amino acid neurotransmitters, and brain osmolytes. Further, lutein can promote brain function and structure by preventing the oxidation of docosahexaenoic acid (DHA). Therefore, lutein is associated with neurodegenerative diseases [37].

Epilepsy, one of the most common neurological disorders, occurs due to neurodegeneration caused by oxidative stress [38]. The Racine scale is an assessment tool commonly used to measure the severity of epileptic seizures in animal studies. In a study conducted on albino rats with epilepsy, it was observed that lutein supplementation alone or in combination with antiepileptic drugs was associated with reduced Racine scale scores, delayed seizures, and improved motor performance. Additionally, lutein supplementation alone has been associated with the inhibition of cerebral damage by reducing oxidative stress in hippocampal homogenate and serum TNF-α concentrations [39].

Depression is a chronic, multifactorial and life-threatening mental disorder in which increased glucocorticoid levels and oxidative stress occur as a result of dysfunction of hypothalamic–pituitary–adrenal (HPA) axis [40]. A study reported that lutein treatment provided an antidepressant-like effect by improving oxidative stress markers and neurochemical abnormalities caused by corticosterone in rats [41].

Lutein nanoparticles have been reported to ameliorate locomotor damage, dopamine levels, acetylcholinesterase (AChE) activity, and oxidative stress markers of the Parkinson's model in Drosophila [42]. In a meta-analysis that included 3 dose–response studies using 1 mg/day lutein supplementation stated that high lutein intake increases the risk of Parkinson's disease [43].

Antioxidants such as lutein, which is known to be localized in brain tissue, may provide neuroprotective effects in multiple sclerosis (MS) by downregulating inflammatory molecules [44]. In a study, lutein intake positively affected attention and memory by improving carotenoid status in individuals with relapsing–remitting multiple sclerosis (RRMS), but had no important impact on cognitive function [37].

In a cohort study conducted in middle-aged and older adults, cases of dementia were wrongly associated with serum lutein + zeaxanthin and β-cryptoxanthin levels. It was determined that this preservative effect was less in antioxidant vitamins and other carotenoids [45]. As a result of a meta-analysis, it was stated that lutein and zeaxanthin levels in plasma and serum were inversely associated with the risk of Alzheimer's disease [46].

20 mg/kg of lutein and zeaxanthin was administered to rats with induced traumatic brain injury (TBI). Lutein and zeaxanthin significantly reduced infarct volume, blood–brain barrier permeability, NF-κB, interleukin1 beta (IL-1β), and IL-6 levels in brain samples collected after 24 h [47].

Glutamate (Glu) neurotransmitter, which is effective in regulating brain functions, is an important stimulant of the central nervous system. Excessive accumulation of intracellular Glu increases ROS concentration in neurons [48]. A study conducted on the effects of glutamate on SH-SY5Y neuroblastoma cells in the presence of lutein reported that lutein had positive effects on lipid peroxidation, iron metabolism, glutamate-induced ROS, and inflammation [49]. When the effects of lutein and zeaxanthin on neurological diseases are evaluated, it is thought to be difficult to reach a definitive conclusion. Extensive in vivo, in vitro, animal and human studies are needed in this area.

Anti-obesity Effects

The World Obesity Federation states that obesity is not only a risk factor for chronic diseases, but also obesity itself is a chronic, recurrent progressive disease. While the prevalence of obesity has increased three-fold in adults since the 1970s, it has also increased dramatically in children and adolescents [50]. Carotenoids, including lutein and zeaxanthin, are of great interest in the treatment of obesity [51]. This effect of carotenoids on obesity is based on the fact that the storage, metabolism, and biological activity of carotenoid compounds occurs in the fat tissue [51, 52]. Adiposopathy is defined as impaired adipose tissue accompanied by adipocyte hypertrophy, metabolic and endocrine disorders, and visceral adiposity. Carotenoids have been also reported to reverse the phenomenon of 'adiposopathy' in adipose tissues [51].

In the NHANES (National Health and Nutrition Examination Survey) 2007–2018 study, which evaluated the dietary carotenoid intake of obese adults, it was reported that the intake of total carotenoids, β-carotene, β-cryptoxanthin, α-carotene, and lutein + zeaxanthin was inversely associated with the risk of obesity [53]. Another study reported that lutein oxidized products may have an anti-obesity effect by inhibiting pancreatic lipase activity [54]. In a study of 60 rats fed a normal or high-fat diet, 100 mg/kg zeaxanthin supplementation and an exercise programme reduced fat mass in the internal organs of the rats, had a therapeutic effect on dyslipidemia and blood glucose, and as a result, had an anti-obesity effect [55]. Plasma carotenoid levels in

obese individuals are associated with impaired antioxidant capacity. As a result of a six-week weight loss programme applied to obese adult individuals, it was observed that a 4-kg decrease in fat mass resulted in a important elevation in plasma lutein and zeaxanthin levels [56]. Hajizadeh-Sharafabad et al. [51] reported that applying a low-energy diet along with lutein supplementation in obese individuals provided a significant decrease in body fat mass, waist circumference, and visceral fat mass, and lean body mass was preserved. In another study, in which lutein and lycopene supplementation was administered to slightly overweight and obese individuals for eight weeks, it was observed that the intervention increased serum carotenoid levels and reduced visceral fat mass [57]. When studies in the literature are examined, it is thought that lutein and zeaxanthin may have antiobesity properties by reducing body weight, visceral fat and body fat mass.

Ophthalmological Effects

The rate of population aging is increasing worldwide. This is accompanied by an increase in eye diseases that cause preventable vision loss. The main causes of vision loss include age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, retinopathy of prematurity, and many other eye diseases [58]. Oxidative stress, apoptosis, inflammation, and mitochondrial dysfunction cause the specified eye diseases. Antioxidants play a role in the prevention and treatment of many eye disorders related to oxidative stress [4, 59]. The macula and lens are the most important two tissues involved in the vision process, and lutein and zeaxanthin are located in these tissues but their distribution in the retina varies. While lutein is more concentrated in peripheral part of the retina, zeaxanthin is dominant in its central part [4]. Lutein and zeaxanthin show protective properties against ophthalmic diseases with their antioxidant properties [5]. A study reported that higher dietary intake of lutein and zeaxanthin was associated with a decrease in the prevalence of visual impairment [60]. Lutein and zeaxanthin play a significant role in maintaining the integrity of the retina along with optimizing central visual acuity [61]. Lutein increases visual acuity and macular pigment optical density (MPOD) [6]. A study showed that there was a moderate positive correlation between MPOD and plasma lutein and zeaxanthin levels [62]. MPOD is associated with the risk of retinopathy and visual impairment [6]. Carotenoids protect the retina tissue by acting as antioxidants, neutralizing free radicals, reducing oxidative damage, and increasing MPOD, which allows them to act as an optical filter against blue light, a type of high-energy light with a wavelength of 400–500 nm in the visible light portion of the electromagnetic spectrum [61].

During the third trimester of pregnancy, lutein and zeaxanthin supplementation to the mother are transferred to the baby via the placenta. It is known that lutein and zeaxanthin supplementation to the mother can improve the baby's visual development and performance and prevent retinopathy of prematurity [63]. Lai et al. [64] concluded that mothers' serum lutein and zeaxanthin levels during pregnancy may affect the visual acuity and early vision development of babies. Richer et al. [65]. administered 14 mg zeaxanthin and 7 mg lutein to elderly individuals who had difficulty driving in twilight and low brightness levels for a period of six months. Lutein and zeaxanthin supplementation increases MPOD in individuals having hardship with night vision and show measurable benefits in many visual functions significant for driving at night [65]. In another study, it was observed that applying supplementation of 10 mg lutein, 2 mg zeaxanthin, and 10 mg meso-zeaxanthin in patients diagnosed with glaucoma for 18 months increased MPOD [66]. Fitzpatrick et al. [67] reported that lutein and zeaxanthin supplementation had no clear effect on MPOD. Visual screen terminal syndrome is a syndrome characterized by hand coordination and eye movement disorders caused by the increase in the use of devices such as computers, tablets and smartphones in recent years. In another study, it was observed that supplementing 2 mg/day zeaxanthin, 10 mg/day lutein, and 6 mg/day astaxanthin for eight weeks to participants who underwent surgery due to visual display terminal syndrome increased MPOD and alleviated the decrease in eye-hand coordination [68]. In their study, Lawler et al. [69] reported that higher lutein and zeaxanthin in serum and retina were associated with larger central retinal vascular calibre on an elderly female individual. Another study showed that 16-week supplementation containing 4 mg/day zeaxanthin, 20 mg/day lutein, and antioxidants (zinc, copper, vitamin E, vitamin C,) increased MPOD volume and carotenoid levels [56].

Li et al. [70] observed that lutein and zeaxanthin supplementation increased visual acuity. In another systematic review, it was stated that 10–20 mg/day lutein supplementation was an effective treatment in those with AMD by increasing MPOD. In addition, supplementation in higher doses and for a longer period of time increased the effect [71]. In another systematic review, it was reported that high-dose (20 mg/day) and long-term (> 6 months) supplementation of lutein may have positive effects on patients with AMD [72]. In a study in which the relationship of lutein and zeaxanthin with AMD was observed for eight years on average, it was reported that the risk of AMD was lower in individuals with higher plasma lutein levels [73]. In another study, it was stated that excessive intake of foods rich in lutein would significantly decrease the risk of AMD [74]. Majeed et al. [75] stated that supplementation containing lutein, zeaxanthin and piperine for individuals aged 50 and over with early-stage dry-type AMD prevented the progression of early-stage dry-type AMD and protected eye health.

In another study, it was observed that applying zeaxanthin supplementation to patients with unilateral neovascular age-related macular degeneration (nAMD) at 20 mg/day for five years or longer reduced two-year unilateral nAMD in the fellow eye by 23% [76]. More prospective clinical studies are needed to make generalizations about whether or not lutein and zeaxanthin supplements are effective in preventing vision loss.

Anti-cancer Effects

The assumption that carotenoids, a class of carotenoids, may have beneficial effects on health due to their limited absorption is incorrect. However, it has been reported that xanthophyll carotenoids, especially astaxanthin, are natural compounds with strong antioxidant activity [77]. In a study, there was a significant reduction in total tumour burden in rats with breast carcinoma fed lutein (50 mg/kg/day) and p-sitosterol (50 mg/kg/day), without significant toxicities. Additionally, a secondary tumour development was prevented [78]. A systematic study concluded that every 1 µmol/L increase in circulating lutein and zeaxanthin concentrations decreased the risk of bladder cancer by 56% [79]. Another study investigated whether or not dietary lutein and zeaxanthin intake affected the risk of colorectal cancer in patients with DICER1 rs3742330 polymorphism. It has been determined that dietary lutein and zeaxanthin intake reduces the risk of colorectal cancer [80]. Dietary micronutrients could have a preservative effect on the development of renal cell carcinoma (RCC) by preventing oxidative deoxyribose nucleic acid (DNA) damage and tumour growth. It has been determined that increasing the dietary lutein and zeaxanthin intake reduces the risk of RCC, regardless of race, gender, age, and smoking status [81]. Zeaxanthin levels in ovarian cancer (OC) patients were found to be significantly lower in early and advanced stage patients [82]. When studies investigating the effects of lutein and zeaxanthin on cancer are examined, it is thought that they may have positive effects on tumor cells with their strong antioxidant effects, but more clinical studies are needed to be able to generalize on this subject and reach clearer conclusions.

Anti-osteoporosis Effects

It has been reported that lutein and zeaxanthin carotenoids, which have anti-inflammatory characteristics, may be protective in conditions such as fragility, sarcopenia and osteoporosis, which have inflammatory and oxidative stress aetiology [83, 84]. A cell study reported that lutein suppressed bone resorption and IL-1-induced osteoclast differentiation [85]. Lutein prevents bone destruction and stimulates bone formation in rats. In this way, it has been determined that it increases bone mass [86]. In a study, it was stated that lutein supplementation may protect against osteoporosis by downregulating osteoclast-specific marker (NFATc1) expression and inflammation through activating Nrf2-induced antioxidant gene expression (HO-1, NQO1) in ovariectomized rats [34]. In another study, high blood zeaxanthin levels were found to have an independent positive relationship with femoral neck strength in middle-aged and elderly individuals [87]. In a previous study conducted with adults aged fifty years and older, it was detected that higher plasma lutein and zeaxanthin concentrations were associated with decreased frailty after 8 years of follow-up. However, it was not associated with hand grip strength and sarcopenia [83]. In a study, it was found that high lutein and zeaxanthin intake was associated with a lower risk of osteoporosis [88]. Lutein and zeaxanthin, which are in the carotenoid group, have anti-inflammatory effects and can have a positive effect on bone diseases such as osteoporosis.

Other Diseases

Antioxidants reduce oxidative damage caused by UV rays on the skin [6]. Lutein and zeaxanthin protect eyes and skin from blue light and oxidative damage, which has the shortest wavelength of the visible spectrum. It prevents free radical formation, mitochondrial dysfunction and skin inflammation [5]. In their animal study in which lutein, zeaxanthin and rosemary formulation was applied to skin dehydration caused by UV light for 12 weeks, Heo et al. [89] concluded that the application of lutein, zeaxanthin and rosemary formulation may have positive effects on skin dehydration caused by UV light [89].

With the accumulation of ROS, the antioxidant capacity of the cells decreases, which is frequently seen in chronic kidney disease. Carotenoid compounds, including lutein and zeaxanthin, prevent ROS formation via their antioxidant properties. All these mechanisms show that carotenoids may have a therapeutic effect for chronic kidney disease [90]. Pan et al. [26] found a negative relationship between serum lutein level and diabetic kidney disease in elderly individuals.

Gao et al. [27] administered alcohol supplementation to rats and then 10 mg zeaxanthin supplementation every day for 2 weeks. Ethanol supplementation caused an increase in alanine aminotransferase and aspartate aminotransferase concentrations in rats and zeaxanthin supplementation showed a healing effect against alcohol-induced hepatic damage [27]. In another study, 12.5, 25.0 and 50.0 mg/kg lutein supplements were administered to rats exposed to 2.5 µm particulate matter and the intervention played a protective role in lung tissues [91]. Yang et al. [92] stated that respiratory disease mortality was lower in individuals with high serum total carotenoids, α-carotene, lycopene and lutein/zeaxanthin levels. In a previous study, ovalbumin was administered to rats, causing them to show asthma-like

Table 2 Effects of lutein on health: in vivo-in vitro, animal and human studies

Type of study	Pharmacological effects	Study subjects	Intervention	Outcomes	Reference
In vivo/in vitro studies	Ophthalmological	Retinal pigment epithelial ARPE-19 cells	1 µM lutein	Lutein and lycopene protected ARPE-19 cells from oxidative damage caused by tBHP by showing antioxidant effects against oxidative damage caused by ROS ($p < 0.05$)	[96]
	Cardioprotective	Peripheral blood mononuclear cells	1, 5 and 25 µM lutein	IL-6, IL-1β, and TNF concentrations in cell supernatants were dose-dependently reduced by lutein. 25 µM lutein was shown to suppress mRNA expression of IL-6, IL1-β, and TNF ($p < 0.05$)	[97]
	Anticancer	Human breast cancer cell line T47D	Control group and 6.25, 12.5, 25 and 50 µg/mL lutein	Lutein reduced breast cancer cell proliferation via activating the NrF2/ARE pathway and blocking the NF-κB signaling pathway ($p < 0.05$)	[98]
	Antiobesity	3T3-L1 cells in rat abdominal adipose tissue	40 µM lutein	It has been reported that lutein reduced excessive lipid accumulation ($p < 0.001$) and may have antiobesity effects ($p < 0.05$)	[99]
Animal study	Ophthalmological	Albino male rat ($n = 42$)	6 days a week for 2 months, comparison of product supplement containing 63.75% lutein and 11.25% zeaxanthin isomers and placebo group	Lutein/zeaxanthin supplementation prevented premature photoreceptor cell degeneration	[100]
	Ophthalmological	Albino rat ($n = 24$)	Oil supplement containing lutein and zeaxanthin in a ratio of 10:1, twice daily for 42 days Group 1: placebo Group 2: 1.028 mg/kg Group 3: 0.514 mg/kg Group 4: 1.028 mg/kg	Antioxidant enzyme levels increased dose-dependently and long-term supplementation could prevent phototoxic damage to the eye ($p < 0.005$)	[101]
	Cardioprotective	Hyperglycemic rat ($n = 33$)	Comparison of lutein (39 nmol/day/rat) supplementation, control group, and placebo group for 8 weeks	Lutein supplementation prevented heart and kidney damage in hyperlipidemic rats by acting on oxidative stress	[102]

Table 2 (continued)

Type of study	Pharmacological effects	Study subjects	Intervention	Outcomes	Reference
	Antidiabetic	Sprague Dawley diabetes male rat	For 4 weeks Group 1 (control, nondiabetic): 2.0 mL/kg sterile saline Group 2: 2.0 mL/kg sterile saline Group 3: 100 mg/kg metformin Group 4: 200 mg/kg zeaxanthin Group 5: 400 mg/kg zeaxanthin	Zeaxanthin supplementation showed hypoglycemic ($p < 0.05$), hypolipidemic ($p < 0.05$) and antidiabetic ($p < 0.05$) effects in diabetic rats	[103]
	Antiobesity	In vivo, male C57BL/6 J rat ($n = 60$)	Standard diet was applied to the control group for 4 weeks, and HFD was applied to the intervention groups for 4 weeks. Then, the rats were divided into 3 different groups for four weeks; HFD, HFD + 20 mg/kg zeaxanthin, HFD + 40 mg/kg zeaxanthin	Zeaxanthin supplementation inhibited adipocyte differentiation ($p < 0.05$) and intracellular lipogenesis ($p < 0.05$) in rats, reduced fat weight ($p < 0.05$), and showed anti-adipogenic and antiobesity properties	[104]
	Neuroprotective	Male wistar rat ($n = 48$)	Rats; They were divided into 4 groups: control, Aβ, Zeaxanthin, Zeaxanthin + Aβ Zeaxanthin: 60 mg/kg/day	Zeaxanthin reduced Aβ level by regulating Aβ transport receptors and inflammatory cytokines ($p < 0.05$). Zeaxanthin supplementation prevented learning and memory problems caused by Aβ1-42 in rats	[105]
	Lung damage	Albino male wistar rat ($n = 18$)	Group 1: MTX + lutein (1 mg/kg lutein) Group 2: MTX + 0.9% NaCl Group 3: healthy group 0.9% NaCl	It was observed that the levels of MDA, MPO, IL-1β and TNF-α in the lung tissues of Group 2 were significantly higher than the other groups ($p < 0.0001$). Lutein ameliorated MTX-induced oxidative lung damage, biochemical and histopathological outcomes	[106]
Cross sectional study	Neuroprotective	25–45 aged overweight and obese adult ($n = 94$)	The relationship between serum lutein levels and memory assessment in blood taken after a 10-h fast was investigated	Serum lutein was found to be positively related to accuracy in tying objects ($p < 0.05$) and inversely related to misplacement error ($p < 0.01$). Macular carotenoids have no relationship with memory performance. Serum lutein plays an important role in hippocampal function in overweight or obese adults	[107]
Cross sectional study	Bone health	Young healthy adult ($n = 63$)	Retinal lutein/zeaxanthin, serum lutein/zeaxanthin, bone mineral density and dietary physical activity were evaluated	Serum lutein/zeaxanthin was not found to be associated with bone mass, but a significant relationship was found between retinal lutein/zeaxanthin and bone density in the proximal femur and lumbar spine ($p < 0.05$)	[108]

Table 2 (continued)

Type of study	Pharmacological effects	Study subjects	Intervention	Outcomes	Reference
Case–control study	Anticancer	25–70 aged, female ($n=1042$)	Group 1: 521 female with breast cancer Group 2: 521 female with healthy	It has been revealed that Lutein/zeaxanthin plays a protective role in breast cancer risk	[109]
Meta-analyse study	Anticancer	10 study ($n=7$ case–control, $n=3$ cohort study)	Associations between intake of specific carotenoids and risk of NHL have been analyzed	Dietary lutein/zeaxanthin intake was associated with a 0.82 (0.69–0.97) reduction in NHL risk ($p<0.05$)	[110]
Randomized controlled trial	Ophthalmological	Postmenopausal women ($n=72$)	Group 1: anthocyanines (60 mg/day) Group 2: xanthophylls (6 mg lutein + 2 mg zeaxanthin/day) Group 3: anthocyanines (60 mg/day) + xanthophylls (6 mg Lutein + 2 mg zeaxanthin/day)	Baseline concentrations of lutein, zeaxanthin, lutein + zeaxanthin / cholesterol/triglycerides increased in Group 2 (2.8-and 1.6-fold in lutein and zeaxanthin concentrations) and in group 3 (2- and 1.4-fold in lutein and zeaxanthin concentrations). MPOD was not modified in any of the groups at the end of the study. There were no differences in the dietary intake of lutein + zeaxanthin and anthocyanin at any point in time in any group	[111]
Meta-analyse study	Ophthalmological	3 randomized controlled trials ($n=406$)	Comparison of oral lutein/zeaxanthin administration at any dosage and duration with placebo for the prevention of retinopathy of prematurity in preterm neonates with ≤ 32 weeks' gestation	Lutein/zeaxanthin supplementation did not reduce the incidence of retinopathy of prematurity, sepsis, mortality, necrotizing enterocolitis, or bronchopulmonary dysplasia	[112]
Multicenter, randomized, observer-blinded trial	Ophthalmological	Patients aged 50 years or older diagnosed with AMD	Age-related eye disease group (AREDS) formulation at doses approved (control group; $n=59$) DHA, lutein, zeaxanthin, resveratrol and hydroxytyrosol to the formula (intervention group; $n=50$)	At month 12, the intervention did not have a significant differential effect on visual acuity compared with the control group, with an estimated treatment difference in Early Treatment Diabetic Retinopathy Study (ETDRS) of -1.63 (95% CI -0.83 to 4.09; $p=0.192$)	[113]
Randomized controlled trials	Ophthalmological	Healthy normolipemic adults aged 45–65 years ($n=29$)	Total 1.8 mg lutein for 4 weeks Group 1: 500 g/day of kiwi, orange, and avocado ($n=14$) Group 2: 180 g/day of green beans, sweet corn, and squash ($n=15$)	Serum lutein concentration increased by 37%. Serum lutein/HDL-cholesterol level increased by 29%. Lutein + zeaxanthin/HDL-cholesterol increased and this effect was greater in the vegetable group. MPOD did not change and did not correlate with contrast threshold	[114]

Table 2 (continued)

Type of study	Pharmacological effects	Study subjects	Intervention	Outcomes	Reference
Randomized controlled trials	Neuroprotective	Healthy, non-demented elderly Japanese individuals with memory complaints	Trial 1 (n = 120, 24 weeks) Group 1: placebo group Group 2:, LCPUFAs (120 mg/day ARA, 300 mg/day DHA and 100 mg/day EPA) + dietary supplement Group 3: LCPUFAs (120 mg/day ARA, 300 mg/day DHA and 100 mg/day EPA) + 10 mg lutein, 2 mg zeaxanthin Trial 2 (n = 192, 12 weeks) Group 1: placebo group Group 2: LCPUFAs (120 mg/day ARA, 300 mg/day DHA and 100 mg/day EPA) + 10 mg lutein, 2 mg zeaxanthin	LCPUFAs + lutein/zeaxanthin supplementation did not significantly affect memory function in healthy, non-demented elderly individuals with memory complaints but improved memory function in healthy, non-demented elderly individuals with cognitive decline	[115]

Aβ amyloid beta, *AMD* age-related macular degeneration, *IL-6* interleukin-6, *IL1-β* interleukin-1 beta, *MDA* malondialdehyde, *MPO* myeloperoxidase, *MPOD* macular pigment optical density, *mRNA* messenger ribonucleic acid, *MTX* methotrexate, *LCPUFAs* long-chain polyunsaturated fatty acids, *NF-κB* nuclear factor kappa B, *NHL* non-Hodgkin lymphoma, *NrF2* nuclear factor erythroid 2-related factor, *ROS* reactive oxygen species, *tBHP* tert-butyl hydroperoxide, *TNF* tumor necrosis factor

symptoms, and then zeaxanthin was administered. Zeaxanthin alleviated ovalbumin-induced allergic asthma in rats by modulating the p38 MAPK/β-catenin signalling pathway [93]. In a study conducted on ulcerative colitis patients, it was observed that the frequency of gastrointestinal symptoms, especially constipation, was lower in individuals with higher lutein and zeaxanthin intake [94]. Another study reported that there was a dose-dependent inverse relationship between dietary lutein and zeaxanthin intake and the incidence of dental fluorosis, and high dietary carotenoid intake may prevent dental fluorosis [95]. In the literature, the number of studies evaluating the effects of lutein and zeaxanthin on skin diseases, kidney and liver diseases, gastrointestinal diseases, and tooth and gum diseases is limited. Prospective clinical studies evaluating the relationship between lutein and these diseases are needed.

Table 2 summarizes important in-vivo, in-vitro, animal and human clinical studies to evaluate the effects of lutein and zeaxanthin on health.

Safe Level and Toxic Effect

According to the European Food Safety Authority (EFSA), the Acceptable Daily Intake (ADI) value for lutein is 1 mg/kg and that for zeaxanthin is 0.75 mg/kg [116]. According to EFSA, no acute or chronic toxicity has been reported to date in various studies conducted to define the upper daily limit and side effects of lutein supplementation [117]. Overdosing on dietary supplements can have negative effects on health, so it is recommended to consume 400–500 g/per day of vegetables and fruits as per daily requirement [118, 119].

Conclusion and Recommendations

Lutein and zeaxanthin reduce oxidative stress by reacting better with ROS than other types of carotenoids such as alpha-carotene, beta-carotene and lycopene due to the difference in their chemical structures. Therefore, they have high antioxidant and anti-inflammatory capacity. Along with these properties of lutein and zeaxanthin, the lack of observed toxic effects makes them promising molecules for treating and preventing many diseases. Lutein and zeaxanthin provide potential benefits, especially by showing ophthalmological, neuroprotective, anti-diabetic, anti-obesity, anti-cancer, anti-osteoporosis and cardioprotective effects. There is evidence from both human interventions and epidemiological reports for the health benefits of lutein and zeaxanthin. Lutein and zeaxanthin have beneficial effects on biomarkers that play a role in the pathogenesis of many diseases. However, there is also large heterogeneity among biomarkers. Therefore, there is a need for appropriate evidence

and studies to demonstrate the therapeutic effects of lutein and zeaxanthin in the treatment and prophylaxis of the diseases and complications examined in this review.

Future Perspective

In light of the recent published studies, the health effects of lutein and zeaxanthin and their use in the treatment of certain diseases are a subject of strong and growing debate. There is great interest in the effects of dietary lutein and zeaxanthin in the prevention and treatment of diseases. While most studies on the prevention and treatment of diseases have shown positive effects of lutein and zeaxanthin, some studies have not found any association. Therefore, the existing evidence needs to be clarified and strengthened. In this context, more comprehensive in vivo, in vitro, animal and human studies are needed to evaluate the efficacy and safety of lutein and zeaxanthin and to demonstrate their pharmacological and clinical effects and modes of action and the risks associated with high intakes of lutein and zeaxanthin.

Key References

32. •• Ghasemi F, Navab F, Rouhani MH, Amini P, Shokri-Mashhadi N. The effect of lutein and zeaxanthine on dyslipidemia: a meta-analysis study. Prostaglandins Other Lipid Mediat. 2023;164:106,691. https://doi.org/10.1016/j.prostaglandins.2022.106691
This article is a meta-analysis study examining the effect of lutein and zeaxanthin supplementation on dyslipidemia. The intervention has been reported to reduce HDL-C levels.

55. • Al-Thepyani M, Algarni S, Gashlan H, Elzubier M, Baz L. Evaluation of the anti-obesity effect of zeaxanthin and exercise in HFD-induced obese rats. Nutrients. 2022;14(23):4944. https://doi.org/10.3390/nu14234944
This article investigated the effect of zeaxanthin supplementation and exercise program on obese rats. An antiobesity effect of the intervention was observed in rats.

62. •• McGwin G Jr, Kar D, Berlin A, Clark ME, Swain TA, Crosson JN, Sloan KR, Owsley C, Curcio CA. Macular and plasma xanthophylls are higher in age-related macular degeneration than in normal aging: alabama study on early age-related macular degeneration 2 baseline. Ophthalmol Sci. 2022;3(2):100,263. https://doi.org/10.1016/j.xops.2022.100263
This article examines a cross-sectional study of retinal xanthophyll carotenoids on age-related macular degeneration (AMD) progression in AMD. Results indicate that there was a moderate positive correlation between macular pigment optical density and plasma lutein and zeaxanthin levels.

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Declarations

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References

1. Sun T, Yuan H, Cao H, Yazdani M, Tadmor Y, Li L. Carotenoid metabolism in plants: the role of plastids. Mol Plant. 2018;11(1):58–74. https://doi.org/10.1016/j.molp.2017.09.010.
2. Demmig-Adams B, Polutchko SK, Adams WW III. Structure-function-environment relationship of the isomers zeaxanthin and lutein. Photochem. 2022;2(2):308–25. https://doi.org/10.3390/photochem2020022.
3. Giordano E, Quadro L. Lutein, zeaxanthin and mammalian development: metabolism, functions and implications for health. Arch Biochem Biophys. 2018;647:33–40. https://doi.org/10.1016/j.abb.2018.04.008.
4. Mrowicka M, Mrowicki J, Kucharska E, Majsterek I. Lutein and zeaxanthin and their roles in age-related macular degeneration-neurodegenerative disease. Nutrients. 2022;14(4):827. https://doi.org/10.3390/nu14040827.
5. Murillo AG, Hu S, Fernandez ML. Zeaxanthin: metabolism, properties, and antioxidant protection of eyes, heart, liver, and skin. Antioxidants (Basel). 2019;8(9):390. https://doi.org/10.3390/antiox8090390.
6. Mitra S, Rauf A, Tareq AM, Jahan S, Emran TB, Shahriar TG, Dhama K, Alhumaydhi FA, Aljohani ASM, Rebezov M, Uddin MS, Jeandet P, Shah ZA, Shariati MA, Rengasamy KR. Potential health benefits of carotenoid lutein: an updated review. Food Chem Toxicol. 2021;154:112328. https://doi.org/10.1016/j.fct.2021.112328.

7. Fiedorowicz J, Dobrzynska MM. Lutein and zeaxanthin - radio- and chemoprotective properties. Mechanism and possible use. Rocz Panstw Zakl Hig. 2023;74(3):257–264. https://doi.org/10.32394/rpzh.2023.0266.
8. Zafar J, Aqeel A, Shah FI, Ehsan N, Gohar UF, Moga MA, Festila D, Ciurea C, Irimie M, Chicea R. Biochemical and immunological implications of lutein and zeaxanthin. Int J Mol Sci. 2021;22(20):10910. https://doi.org/10.3390/ijms222010910.
9. Aziz E, Batool R, Akhtar W, Rehman S, Shahzad T, Malik A, Shariati MA, Laishevtcev A, Plygun S, Heydari M, Rauf A, Ahmed AS. Xanthophyll: health benefits and therapeutic insights. Life Sci. 2020;240:117104. https://doi.org/10.1016/j.lfs.2019.117104.
10. Ulusoy HG, Sanlier N. A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities. Crit Rev Food Sci Nutr. 2020;60(19):3290–303. https://doi.org/10.1080/10408398.2019.1683810.
11. Waller DD, Park J, Tsantrizos YS. Inhibition of farnesyl pyrophosphate (FPP) and/or geranylgeranyl pyrophosphate (GGPP) biosynthesis and its implication in the treatment of cancers. Crit Rev Biochem Mol Biol. 2019;54(1):41–60. https://doi.org/10.1080/10409238.2019.1568964.
12. Niu G, Guo Q, Wang J, Zhao S, He Y, Liu L. Structural basis for plant lutein biosynthesis from α-carotene. Proc Natl Acad Sci U S A. 2020;117(25):14150–7. https://doi.org/10.1073/pnas.2001806117.
13. Hirdyani H, Sheth M. Lutein-the less explored carotenoid. World J Pharm Res. 2017;6(6):528–553. https://doi.org/10.20959/wjpr20176-8671.
14. Vyas S, Patel A, Nabil Risse E, Krikigianni E, Rova U, Christakopoulos P, Matsakas L. Biosynthesis of microalgal lipids, proteins, lutein, and carbohydrates using fish farming wastewater and forest biomass under photoautotrophic and heterotrophic cultivation. Bioresour Technol. 2022;359:127494. https://doi.org/10.1016/j.biortech.2022.127494.
15. Maoka T. Carotenoids as natural functional pigments. J Nat Med. 2020;74(1):1–16. https://doi.org/10.1007/s11418-019-01364-x.
16. Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, Yin X, Xu Q. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol (Lausanne). 2023;14:1161521. https://doi.org/10.3389/fendo.2023.1161521.
17. IDF, International Diabetes Federation. IDF Diabetes Atlas. In: IDF Diabetes Atlas. 10th ed. 2021. https://idf.org/about-diabetes/diabetes-facts-figures/. Accessed 30 January 2024.
18. Rehman K, Akash MSH. Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? J Cell Biochem. 2017;118(11):3577–85. https://doi.org/10.1002/jcb.26097.
19. Maiuolo J, Bulotta RM, Oppedisano F, Bosco F, Scarano F, Nucera S, Guarnieri L, Ruga S, Macri R, Caminiti R, Musolino V, Gliozzi M, Carresi C, Cardamone A, Coppoletta A, Nicita M, Carnevali A, Scorcia V, Mollace V. Potential properties of natural nutraceuticals and antioxidants in age-related eye disorders. Life (Basel). 2022;13(1):77. https://doi.org/10.3390/life13010077.
20. Shivarudrappa AH, Ponesakki G. Lutein reverses hyperglycemia-mediated blockage of Nrf2 translocation by modulating the activation of intracellular protein kinases in retinal pigment epithelial (ARPE-19) cells. J Cell Commun Signal. 2020;14(2):207–21. https://doi.org/10.1007/s12079-019-00539-1.
21. Gopal SS, Sukhdeo SV, Vallikannan B, Ponesakki G. Lutein ameliorates high-fat diet-induced obesity, fatty liver, and glucose intolerance in C57BL/6J mice. Phytother Res. 2023;37(1):329–41. https://doi.org/10.1002/ptr.7615.
22. Li LH, Lee JC, Leung HH, Lam WC, Fu Z, Lo ACY. Lutein supplementation for eye diseases. Nutrients. 2020;12(6):1721. https://doi.org/10.3390/nu12061721.
23. Nanjaiah H, Vallikannan B. Lutein upregulates the PGC-1α, NRF1, and TFAM expression by AMPK activation and downregulates ROS to maintain mtDNA integrity and mitochondrial biogenesis in hyperglycemic ARPE-19 cells and rat retina. Biotechnol Appl Biochem. 2019;66(6):999–1009. https://doi.org/10.1002/bab.1821.
24. Anitha RE, Janani R, Peethambaran D, Baskaran V. Lactucaxanthin protects retinal pigment epithelium from hyperglycemia-regulated hypoxia/ER stress/VEGF pathway mediated angiogenesis in ARPE-19 cell and rat model. Eur J Pharmacol. 2021;899:174014. https://doi.org/10.1016/j.ejphar.2021.174014.
25. Rani EA, Janani R, Chonche MJ, Vallikannan B. Lactucaxanthin regulates the cascade of retinal oxidative stress, endoplasmic reticulum stress and inflammatory signaling in diabetic rats. Ocul Immunol Inflamm. 2023;31(2):320–8. https://doi.org/10.1080/09273948.2022.2027464.
26. Pan F, Cui W, Gao L, Shi X, Yang H, Hu Y, Li M. Serum lutein is a promising biomarker for type 2 diabetes mellitus and diabetic kidney disease in the elderly. J Clin Lab Anal. 2022;36(4):e24350. https://doi.org/10.1002/jcla.24350.
27. Gao H, Lv Y, Liu Y, Li J, Wang X, Zhou Z, Tipoe GL, Ouyang S, Guo Y, Zhang J, Hao X, Li W, Koike K, So KF, Xiao J. Wolfberry-derived zeaxanthin dipalmitate attenuates ethanol-induced hepatic damage. Mol Nutr Food Res. 2019;63(11):e1801339. https://doi.org/10.1002/mnfr.201801339.
28. Lai JS, Yuan WL, Ong CN, Tan KH, Yap F, Chong YS, Gluckman PD, Godfrey KM, Lee YS, Chan JKY, Chan SY, Chong MFF. Perinatal plasma carotenoid and vitamin E concentrations with maternal blood pressure during and after pregnancy. Nutr Metab Cardiovasc Dis. 2022;32(12):2811–21. https://doi.org/10.1016/j.numecd.2022.07.019.
29. Jiang YW, Sun ZH, Tong WW, Yang K, Guo KQ, Liu G, Pan A. Dietary intake and circulating concentrations of carotenoids and risk of type 2 diabetes: a dose-response meta-analysis of prospective observational studies. Adv Nutr. 2021;12(5):1723–33. https://doi.org/10.1093/advances/nmab048.
30. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol. 2019;74(20):2529–32. https://doi.org/10.1016/j.jacc.2019.10.009.
31. Hajizadeh-Sharafabad F, Ghoreishi Z, Maleki V, Tarighat-Esfanjani A. Mechanistic insights into the effect of lutein on atherosclerosis, vascular dysfunction, and related risk factors: a systematic review of in vivo, ex vivo and in vitro studies. Pharmacol Res. 2019;149:104477. https://doi.org/10.1016/j.phrs.2019.104477.
32. Ghasemi F, Navab F, Rouhani MH, Amini P, Shokri-Mashhadi N. The effect of lutein and zeaxanthine on dyslipidemia: a meta-analysis study. Prostaglandins Other Lipid Mediat. 2023;164:106691. https://doi.org/10.1016/j.prostaglandins.2022.106691.
33. Leermakers ET, Darweesh SK, Baena CP, Moreira EM, Melo van Lent D, Tielemans MJ, Muka T, Vitezova A, Chowdhury R, Bramer WM, Kiefte-de Jong JC, Felix JF, Franco OH. The effects of lutein on cardiometabolic health across the life course: a systematic review and meta-analysis. Am J Clin Nutr. 2016;103(2):481–494. https://doi.org/10.3945/ajcn.115.120931.
34. Li H, Huang C, Zhu J, Gao K, Fang J, Li H. Lutein suppresses oxidative stress and inflammation by Nrf2 activation in an osteoporosis rat model. Med Sci Monit. 2018;24:5071–5075. https://doi.org/10.12659/MSM.908699.
35. Tuzcu M, Orhan C, Muz OE, Sahin N, Juturu V, Sahin K. Lutein and zeaxanthin isomers modulates lipid metabolism and the inflammatory state of retina in obesity-induced high-fat diet rodent model. BMC Ophthalmol. 2017;17(1):129. https://doi.org/10.1186/s12886-017-0524-1.

36. Ouyang B, Li Z, Ji X, Huang J, Zhang H, Jiang C. The protective role of lutein on isoproterenol-induced cardiac failure rat model through improving cardiac morphology, antioxidant status via positively regulating Nrf2/HO-1 signalling pathway. Pharm Biol. 2019;57(1):529–35. https://doi.org/10.1080/13880209.2019.1649436.
37. Martell SG, Kim J, Cannavale CN, Mehta TD, Erdman JW Jr, Adamson B, Motl RW, Khan NA. Randomized, placebo-controlled, single-blind study of lutein supplementation on carotenoid status and cognition in persons with multiple sclerosis. J Nutr. 2023;153(8):2298–311. https://doi.org/10.1016/j.tjnut.2023.06.027.
38. Muke S, Kaikini A, Peshattiwar V, Bagle S, Dighe V, Sathaye S. Neuroprotective effect of coumarin nasal formulation: kindling model assessment of epilepsy. Front Pharmacol. 2018;9:992. https://doi.org/10.3389/fphar.2018.00992.
39. Al-Rafiah AR, Mehdar KM. Histopathological and biochemical assessment of neuroprotective effects of sodium valproate and lutein on the pilocarpine albino rat model of epilepsy. Behav Neurol. 2021;2021:5549638. https://doi.org/10.1155/2021/5549638.
40. Zhou Y, Murrough J, Yu Y, Roy N, Sayegh R, Asbell P, Maguire MG, Ying GS; DREAM Study Research Group. Association between depression and severity of dry eye symptoms, signs, and ınflammatory markers in the dream study. JAMA Ophthalmol. 2022;140(4):392–399. https://doi.org/10.1001/jamaophthalmol.2022.0140.
41. Zeni ALB, Camargo A, Dalmagro AP. Lutein prevents corticosterone-induced depressive-like behavior in mice with the involvement of antioxidant and neuroprotective activities. Pharmacol Biochem Behav. 2019;179:63–72. https://doi.org/10.1016/j.pbb.2019.02.004.
42. Fernandes EJ, Poetini MR, Barrientos MS, Bortolotto VC, Araujo SM, Santos Musachio EA, De Carvalho AS, Leimann FV, Gonçalves OH, Ramborger BP, Roehrs R, Prigol M, Guerra GP. Exposure to lutein-loaded nanoparticles attenuates Parkinson's model-induced damage in Drosophila melanogaster: restoration of dopaminergic and cholinergic system and oxidative stress indicators. Chem Biol Interact. 2021;340:109431. https://doi.org/10.1016/j.cbi.2021.109431.
43. Talebi S, Ghoreishy SM, Jayedi A, Travica N, Mohammadi H. Dietary antioxidants and risk of Parkinson's disease: a systematic review and dose-response meta-analysis of observational studies. Adv Nutr. 2022;13(5):1493–504. https://doi.org/10.1093/advances/nmac001.
44. Alfredsson L, Olsson T. Lifestyle and environmental factors in multiple sclerosis. Cold Spring Harb Perspect Med. 2019;9(4):a028944. https://doi.org/10.1101/cshperspect.a028944.
45. Beydoun MA, Beydoun HA, Fanelli-Kuczmarski MT, Weiss J, Hossain S, Canas JA, Evans MK, Zonderman AB. Association of serum antioxidant vitamins and carotenoids with incident Alzheimer disease and all-cause dementia among us adults. Neurology. 2022;98(21):e2150–62. https://doi.org/10.1212/WNL.0000000000200289.
46. Qu M, Shi H, Wang K, Wang X, Yu N, Guo B. The associations of plasma/serum carotenoids with Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2021;82(3):1055–66. https://doi.org/10.3233/JAD-210384.
47. Gunal MY, Sakul AA, Caglayan AB, Erten F, Kursun OED, Kilic E, Sahin K. Protective effect of lutein/zeaxanthin isomers in traumatic brain injury in mice. Neurotox Res. 2021;39(5):1543–50. https://doi.org/10.1007/s12640-021-00385-3.
48. Xin H, Cui Y, An Z, Yang Q, Zou X, Yu N. Attenuated glutamate induced ROS production by antioxidative compounds in neural cell lines. RSC Adv. 2019;9(60):34735–43. https://doi.org/10.1039/c9ra03848e.
49. Pap R, Pandur E, Jánosa G, Sipos K, Nagy T, Agócs A, Deli J. Lutein decreases inflammation and oxidative stress and prevents iron accumulation and lipid peroxidation at glutamate-ınduced neurotoxicity. Antioxidants (Basel). 2022;11(11):2269. https://doi.org/10.3390/antiox11112269.
50. Blüher M. Metabolically healthy obesity. Endocr Rev. 2020;41(3):bnaa004. https://doi.org/10.1210/endrev/bnaa004.
51. Hajizadeh-Sharafabad F, Tarighat-Esfanjani A, Ghoreishi Z, Sarreshtedari M. Lutein supplementation combined with a low-calorie diet in middle-aged obese individuals: effects on anthropometric indices, body composition and metabolic parameters. Br J Nutr. 2021;126(7):1028–39. https://doi.org/10.1017/S0007114520004997.
52. Mounien L, Tourniaire F, Landrier JF. Anti-Obesity effect of carotenoids: direct impact on adipose tissue and adipose tissue-driven ındirect effects. Nutrients. 2019;11(7):1562. https://doi.org/10.3390/nu11071562.
53. Yu X, Yuan C, Song X, Zhang H. Association of dietary carotenoids intakes with obesity in adults: NHANES 2007–2018. J Nutr Sci Vitaminol (Tokyo). 2023;69(6):402–11. https://doi.org/10.3177/jnsv.69.402.
54. Shamarao N, Chethankumar M. Antiobesity drug-likeness properties and pancreatic lipase inhibition of a novel low molecular weight lutein oxidized product, Lop6. Food Funct. 2022;13(11):6036–55. https://doi.org/10.1039/d1fo04064b.
55. Al-Thepyani M, Algarni S, Gashlan H, Elzubier M, Baz L. Evaluation of the anti-obesity effect of zeaxanthin and exercise in HFD-induced obese rats. Nutrients. 2022;14(23):4944. https://doi.org/10.3390/nu14234944.
56. Obana A, Gohto Y, Nakazawa R, Moriyama T, Gellermann W, Bernstein PS. Effect of an antioxidant supplement containing high dose lutein and zeaxanthin on macular pigment and skin carotenoid levels. Sci Rep. 2020;10(1):10262. https://doi.org/10.1038/s41598-020-66962-2.
57. Takagi T, Hayashi R, Nakai Y, Okada S, Miyashita R, Yamada M, Mihara Y, Mizushima K, Morita M, Uchiyama K, Naito Y, Itoh Y. Dietary intake of carotenoid-rich vegetables reduces visceral adiposity in obese japanese men-a randomized, double-blind trial. Nutrients. 2020;12(8):2342. https://doi.org/10.3390/nu12082342.
58. Keskinbora K, Güven F. Artificial intelligence and ophthalmology. Turk J Ophthalmol. 2020;50(1):37–43. https://doi.org/10.4274/tjo.galenos.2020.78989.
59. Johra FT, Bepari AK, Bristy AT, Reza HM. A mechanistic review of β-carotene, lutein, and zeaxanthin in eye health and disease. Antioxidants (Basel). 2020;9(11):1046. https://doi.org/10.3390/antiox9111046.
60. Chen Z, Yu L, Li W, Zhang H, Huang X, Chen W, Wang D. Association of vitamins with hearing loss, vision disorder and sleep problem in the US general population. Environ Sci Pollut Res Int. 2023;30(18):53876–86. https://doi.org/10.1007/s11356-023-26164-5.
61. Lem DW, Davey PG, Gierhart DL, Rosen RB. A systematic review of carotenoids in the management of age-related macular degeneration. Antioxidants (Basel). 2021;10(8):1255. https://doi.org/10.3390/antiox10081255.
62. McGwin G Jr, Kar D, Berlin A, Clark ME, Swain TA, Crosson JN, Sloan KR, Owsley C, Curcio CA. Macular and plasma xanthophylls are higher in age-related macular degeneration than in normal aging: alabama study on early age-related macular degeneration 2 baseline. Ophthalmol Sci. 2022;3(2):100263. https://doi.org/10.1016/j.xops.2022.100263.
63. Bernstein PS, Arunkumar R. The emerging roles of the macular pigment carotenoids throughout the lifespan and in prenatal supplementation. J Lipid Res. 2021;62:100038. https://doi.org/10.1194/jlr.TR120000956.

64. Lai JS, Veetil VO, Lanca C, Lee BL, Godfrey KM, Gluckman PD, Shek LP, Yap F, Tan KH, Chong YS, Ong CN, Ngo CS, Saw SM, Chong MFF. Maternal lutein and zeaxanthin concentrations in relation to offspring visual acuity at 3 years of age: the GUSTO study. Nutrients. 2020;12(2):274. https://doi.org/10.3390/nu12020274.
65. Richer S, Novil S, Gullett T, Dervishi A, Nassiri S, Duong C, Davis R, Davey PG. Night vision and carotenoids (NVC): a randomized placebo controlled clinical trial on effects of carotenoid supplementation on night vision in older adults. Nutrients. 2021;13(9):3191. https://doi.org/10.3390/nu13093191.
66. Loughman J, Loskutova E, Butler JS, Siah WF, O'Brien C. Macular pigment response to lutein, zeaxanthin, and meso-zeaxanthin supplementation in open-angle glaucoma: a randomized controlled trial. Ophthalmol Sci. 2021;1(3):100039. https://doi.org/10.1016/j.xops.2021.100039.
67. Fitzpatrick N, Chachay V, Bowtell J, Jackman S, Capra S, Shore A, Briskey D. An appraisal of trials investigating the effects on macular pigment optical density of lutein and zeaxanthin dietary interventions: a narrative review. Nutr Rev. 2022;80(3):513–24. https://doi.org/10.1093/nutrit/nuab038.
68. Yoshida K, Sakai O, Honda T, Kikuya T, Takeda R, Sawabe A, Inaba M, Koike C. Effects of astaxanthin, lutein, and zeaxanthin on eye-hand coordination and smooth-pursuit eye movement after visual display terminal operation in healthy subjects: a randomized, double-blind placebo-controlled ıntergroup trial. Nutrients. 2023;15(6):1459. https://doi.org/10.3390/nu15061459.
69. Lawler T, Korger J, Liu Y, Liu Z, Pak JW, Barrett N, Blodi B, Domalpally A, Johnson E, Wallace R, Mares JA; Carotenoids in Age-Related Eye Disease Study Investigators. Serum and macular carotenoids in relation to retinal vessel caliber fifteen years later, in the second carotenoids in age-related eye disease study. Invest Ophthalmol Vis Sci. 2021;62(9):20. https://doi.org/10.1167/iovs.62.9.20.
70. Li SS, Wang HH, Zhang D. Efficacy of different nutrients in age-related macular degeneration: a systematic review and network meta-analysis. Semin Ophthalmol. 2022;37(4):515–23. https://doi.org/10.1080/08820538.2021.2022165.
71. Feng L, Nie K, Jiang H, Fan W. Effects of lutein supplementation in age-related macular degeneration. PLoS ONE. 2019;14(12):e0227048. https://doi.org/10.1371/journal.pone.0227048.
72. Liu Y, Ni M, Wu R, Yang Z, Zhu X, Chen J. The level and efficacy of lutein in patients with age-related macular degeneration: a comprehensive systematic review and meta-analysis. Ann Transl Med. 2022;10(6):299. https://doi.org/10.21037/atm-22-173.
73. Merle BMJ, Cougnard-Grégoire A, Korobelnik JF, Schalch W, Etheve S, Rougier MB, Féart C, Samieri C, Delyfer MN, Delcourt C. Plasma lutein, a nutritional biomarker for development of advanced age-related macular degeneration: the alienor study. Nutrients. 2021;13(6):2047. https://doi.org/10.3390/nu13062047.
74. Jiang H, Wang L, Li J, Fan Y, Li Z, Ma M, Liu S, Li B, Shi J, Li C, Mi B, Chen F, Wang D, Pei C, Ma L. Dietary vitamins, carotenoids and their sources in relation to age-related macular degeneration risk in China: a population-based case-control study. Br J Nutr. 2023;129(10):1804–11. https://doi.org/10.1017/S0007114522002161.
75. Majeed M, Majeed S, Nagabhushanam K. An open-label pilot study on macumax supplementation for dry-type age-related macular degeneration. J Med Food. 2021;24(5):551–7. https://doi.org/10.1089/jmf.2020.0097.
76. Brown GC, Brown MM, Gierhart D, Olk RJ. Prevention surpasses treatment: 5-year follow-up, cost-utility, and cost-benefit of zeaxanthin therapy for neovascular age-related macular degeneration. Ophthalmol Ther. 2023;12(5):2583–608. https://doi.org/10.1007/s40123-023-00742-9.
77. Genç Y, Bardakci H, Yücel Ç, Karatoprak GŞ, Küpeli Akkol E, Hakan Barak T, Sobarzo-Sánchez E. Oxidative stress and marine carotenoids: application by using nanoformulations. Mar Drugs. 2020;18(8):423. https://doi.org/10.3390/md18080423.
78. Baraya YS, Yankuzo HM, Wong KK, Yaacob NS. Strobilanthes crispus bioactive subfraction inhibits tumor progression and improves hematological and morphological parameters in mouse mammary carcinoma model. J Ethnopharmacol. 2021;267:113522. https://doi.org/10.1016/j.jep.2020.113522.
79. Wu S, Liu Y, Michalek JE, Mesa RA, Parma DL, Rodriguez R, Mansour AM, Svatek R, Tucker TC, Ramirez AG. Carotenoid intake and circulating carotenoids are inversely associated with the risk of bladder cancer: a dose-response meta-analysis. Adv Nutr. 2020;11(3):630–43. https://doi.org/10.1093/advances/nmz120.
80. Kim J, Lee J, Oh JH, Chang HJ, Sohn DK, Kwon O, Shin A, Kim J. Dietary lutein plus zeaxanthin ıntake and DICER1 rs3742330 A > G polymorphism relative to colorectal cancer risk. Sci Rep. 2019;9(1):3406. https://doi.org/10.1038/s41598-019-39747-5.
81. Bock CH, Ruterbusch JJ, Holowatyj AN, Steck SE, Van Dyke AL, Ho WJ, Cote ML, Hofmann JN, Davis F, Graubard BI, Schwartz KL, Purdue MP. Renal cell carcinoma risk associated with lower intake of micronutrients. Cancer Med. 2018;7(8):4087–97. https://doi.org/10.1002/cam4.1639.
82. Terlikowska KM, Dobrzycka B, Kinalski M, Terlikowski SJ. Serum concentrations of carotenoids and fat-soluble vitamins in relation to nutritional status of patients with ovarian cancer. Nutr Cancer. 2021;73(8):1480–8. https://doi.org/10.1080/01635581.2020.1801779.
83. Murphy CH, Duggan E, Davis J, O'Halloran AM, Knight SP, Kenny RA, McCarthy SN, Romero-Ortuno R. Plasma lutein and zeaxanthin concentrations associated with musculoskeletal health and incident frailty in the Irish Longitudinal Study on ageing (TILDA). Exp Gerontol. 2023;171:112013. https://doi.org/10.1016/j.exger.2022.112013.
84. Kulczyński B, Sidor A, Brzozowska A, Gramza-Michałowska A. The role of carotenoids in bone health-a narrative review. Nutrition. 2024;119:112306. https://doi.org/10.1016/j.nut.2023.112306.
85. Tominari T, Matsumoto C, Watanabe K, Hirata M, Grundler FM, Inada M, Miyaura C. Lutein, a carotenoid, suppresses osteoclastic bone resorption and stimulates bone formation in cultures. Biosci Biotechnol Biochem. 2017;81(2):302–6. https://doi.org/10.1080/09168451.2016.1243983.
86. Takeda H, Tominari T, Hirata M, Watanabe K, Matsumoto C, Grundler FMW, Inada M, Miyaura C. Lutein enhances bone mass by stimulating bone formation and suppressing bone resorption in growing mice. Biol Pharm Bull. 2017;40(5):716–21. https://doi.org/10.1248/bpb.b16-00897.
87. Niu P, Liu Y, Zhang Y, Li L. Associations between blood antioxidant levels and femoral neck strength. BMC Musculoskelet Disord. 2023;24(1):252. https://doi.org/10.1186/s12891-023-06370-5.
88. Kan B, Guo D, Yuan B, Vuong AM, Jiang D, Zhang M, Cheng H, Zhao Q, Li B, Feng L, Huang F, Wang N, Shen X, Yang S. Dietary carotenoid intake and osteoporosis: the National Health and Nutrition Examination Survey, 2005–2018. Arch Osteoporos. 2021;17(1):2. https://doi.org/10.1007/s11657-021-01047-9.
89. Heo H, Madhavan J, Eun S, Jung H, Lee H. Pre-clinical evaluation of proprietary lutein, zeaxanthin, and rosemary formulation for its dermal protective activity in male Swiss Albino mice. Prev Nutr Food Sci. 2021;26(4):425–33. https://doi.org/10.3746/pnf.2021.26.4.425.

90. Hu Y, Cai X, Zhang N, Li Y, Mao Y, Ge S, Yao Y, Gao H. Relation between dietary carotenoid intake, serum concentration, and mortality risk of CKD patients among US adults: National Health and Nutrition Examination Survey 2001–2014. Front Med (Lausanne). 2022;9:871767. https://doi.org/10.3389/fmed.2022.871767.
91. Chen X, Chen Y, Chen Y, Wang X, He M. Protective effect of lutein on oxidative stress damage caused by acute PM2.5 exposure in rats. Ann Palliat Med. 2020;9(4):2028–2036. https://doi.org/10.21037/apm-20-1138.
92. Yang R, Cao Z, Liu X, Xiao M, Li M, Chen Y, Chen L, Sun C, Chu X, Ren Q, Wei W. Inverse correlations between serum carotenoids and respiratory morbidity and mortality: the Third National Health and Nutrition Examination Survey. Br J Nutr. 2023;130(11):1932–41. https://doi.org/10.1017/S0007114523000806.
93. Jin X, Jin W, Li G, Zheng J. Zeaxanthin attenuates OVA-induced allergic asthma in mice by regulating the p38 MAPK/β-catenin signaling pathway. Allergol Immunopathol (Madr). 2022;50(5):75–83. https://doi.org/10.15586/aei.v50i5.664.
94. Głąbska D, Guzek D, Zakrzewska P, Lech G. Intake of lutein and zeaxanthin as a possible factor influencing gastrointestinal symptoms in caucasian individuals with ulcerative colitis in remission phase. J Clin Med. 2019;8(1):77. https://doi.org/10.3390/jcm8010077.
95. Li L, Liu X, Tao N, Chen Q, Sun Z, Yang Q, Zhao X, Liu J. Dietary carotenoid intake and dental fluorosis in relation to SOD2 (RS 11968525) polymorphisms in Guizhou. China Asia Pac J Clin Nutr. 2022;31(2):320–30. https://doi.org/10.6133/apjcn.202206_31(2).0018.
96. Gong X, Draper CS, Allison GS, Marisiddaiah R, Rubin LP. Effects of the macular carotenoid lutein in human retinal pigment epithelial cells. Antioxidants (Basel). 2017;6(4):100. https://doi.org/10.3390/antiox6040100.
97. Chung RWS, Leanderson P, Lundberg AK, Jonasson L. Lutein exerts anti-inflammatory effects in patients with coronary artery disease. Atherosclerosis. 2017;262:87–93. https://doi.org/10.1016/j.atherosclerosis.2017.05.008.
98. Chang J, Zhang Y, Li Y, Lu K, Shen Y, Guo Y, Qi Q, Wang M, Zhang S. NrF2/ARE and NF-κB pathway regulation may be the mechanism for lutein inhibition of human breast cancer cell. Future Oncol. 2018;14(8):719–26. https://doi.org/10.2217/fon-2017-0584.
99. Wang N, Wang D, Luo G, Zhou J, Tan Z, Du Y, Xie H, Liu L, Yang X, Hao L. Lutein attenuates excessive lipid accumulation in differentiated 3T3-L1 cells and abdominal adipose tissue of rats by the SIRT1-mediated pathway. Int J Biochem Cell Biol. 2021;133:105932. https://doi.org/10.1016/j.biocel.2021.105932.
100. Sahin K, Gencoglu H, Akdemir F, Orhan C, Tuzcu M, Sahin N, Yilmaz I, Juturu V. Lutein and zeaxanthin isomers may attenuate photo-oxidative retinal damage via modulation of G protein-coupled receptors and growth factors in rats. Biochem Biophys Res Commun. 2019;516(1):163–70. https://doi.org/10.3390/ph16111543.
101. Madhavan J, Chandrasekharan S, Priya MK, Godavarthi A. Modulatory effect of carotenoid supplement constituting lutein and zeaxanthin (10:1) on anti-oxidant enzymes and macular pigments level in rats. Pharmacogn Mag. 2018;14(54):268–74. https://doi.org/10.4103/pm.pm_340_17.
102. Sharavana G, Joseph GS, Baskaran V. Lutein attenuates oxidative stress markers and ameliorates glucose homeostasis through polyol pathway in heart and kidney of STZ-induced hyperglycemic rat model. Eur J Nutr. 2017;56(8):2475–85. https://doi.org/10.1007/s00394-016-1283-0.
103. Kou L, Du M, Zhang C, Dai Z, Li X, Zhang B. The hypoglycemic, hypolipidemic, and anti-diabetic nephritic activities of zeaxanthin in diet-streptozotocin-induced diabetic sprague dawley rats. Appl Biochem Biotechnol. 2017;182(3):944–55. https://doi.org/10.1007/s12010-016-2372-5.
104. Liu M, Liu H, Xie J, Xu Q, Pan C, Wang J, Wu X, Sanabil, Zheng M, Liu J. Anti-obesity effects of zeaxanthin on 3T3-L1 preadipocyte and high fat induced obese mice. Food Funct. 2017;8(9):3327–3338. https://doi.org/10.1039/c7fo00486a.
105. Li X, Zhang P, Li H, Yu H, Xi Y. The protective effects of zeaxanthin on amyloid-β peptide 1–42-induced impairment of learning and memory ability in rats. Front Behav Neurosci. 2022;16:912896. https://doi.org/10.3389/fnbeh.2022.912896.
106. Mammadov R, Suleyman B, Akturan S, Cimen FK, Kurt N, Suleyman Z, Malkoc İ. Effect of lutein on methotrexate-induced oxidative lung damage in rats: a biochemical and histopathological assessment. Korean J Intern Med. 2019;34(6):1279–86. https://doi.org/10.3904/kjim.2018.145.
107. Cannavale CN, Hassevoort KM, Edwards CG, Thompson SV, Burd NA, Holscher HD, Erdman JW Jr, Cohen NJ, Khan NA. Serum lutein is related to relational memory performance. Nutrients. 2019;11(4):768. https://doi.org/10.3390/nu11040768.
108. Bovier ER, Hammond BR. The macular carotenoids lutein and zeaxanthin are related to increased bone density in young healthy adults. Foods. 2017;6(9):78. https://doi.org/10.3390/foods6090078.
109. Yan B, Lu MS, Wang L, Mo XF, Luo WP, Du YF, Zhang CX. Specific serum carotenoids are inversely associated with breast cancer risk among Chinese women: a case-control study. Br J Nutr. 2016;115(1):129–37. https://doi.org/10.1017/S000711451500416X.
110. Chen F, Hu J, Liu P, Li J, Wei Z, Liu P. Carotenoid intake and risk of non-Hodgkin lymphoma: a systematic review and dose-response meta-analysis of observational studies. Ann Hematol. 2017;96(6):957–65. https://doi.org/10.1007/s00277-016-2898-1.
111. Olmedilla-Alonso B, Estévez-Santiago R, Silván JM, Sánchez-Prieto M, de Pascual-Teresa S. Effect of long-term xanthophyll and anthocyanin supplementation on lutein and zeaxanthin serum concentrations and macular pigment optical density in postmenopausal women. Nutrients. 2018;10(8):959. https://doi.org/10.3390/nu10080959.
112. Cota F, Costa S, Giannantonio C, Purcaro V, Catenazzi P, Vento G. Lutein supplementation and retinopathy of prematurity: a meta-analysis. J Matern Fetal Neonatal Med. 2022;35(1):175–80. https://doi.org/10.1080/14767058.2020.1712700.
113. García-Layana A, Recalde S, Hernandez M, Abraldes MJ, Nascimento J, Hernández-Galilea E, Olmedilla-Alonso B, Escobar-Barranco JJ, Zapata MA, Silva R, Caballero Arredondo M, Lopez-Sabater MC, Mendez-Martínez S, Pardiñas-Barón N, Calvo P, Fernández-Robredo P. A randomized study of nutritional supplementation in patients with unilateral wet age-related macular degeneration. Nutrients. 2021;13(4):1253. https://doi.org/10.3390/nu13041253.
114. Olmedilla-Alonso B, Rodríguez-Rodríguez E, Beltrán-de-Miguel B, Sánchez-Prieto M, Estévez-Santiago R. Changes in lutein status markers (serum and faecal concentrations, macular pigment) in response to a lutein-rich fruit or vegetable (three pieces/day) dietary ıntervention in normolipemic subjects. Nutrients. 2021;13(10):3614. https://doi.org/10.3390/nu13103614.
115. Sueyasu T, Yasumoto K, Tokuda H, Kaneda Y, Obata H, Rogi T, Izumo T, Kondo S, Saito J, Tsukiura T, Nakai M. Effects of long-chain polyunsaturated fatty acids in combination with lutein and zeaxanthin on episodic memory in healthy older adults. Nutrients. 2023;15(13):2825. https://doi.org/10.3390/nu15132825.
116. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Bampidis V, Azimonti G, de Lourdes Bastos M, Christensen H, Dusemund B, Kouba M, Kos Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen

R, Bories G, Costa LG, Gropp J, Lundebye AK, Renshaw OH, Vettori MV, Aquilina G. Safety and efficacy of lutein and lutein/zeaxanthin extracts from Tagetes Erecta for poultry for fattening snd laying (Except Turkeys). EFSA J. 2019;17(5):e05698. https://doi.org/10.2903/j.efsa.2019.5698.

117. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Aguilar F, Dusemund B, Galtier P, Gilbert J, Gott DM, Grilli S, Gürtler R, Koenig J, Lambré C, Larsen JC, Leblanc A, Montensen A, Massin-Parent D, Pratt I, Rietjens IMCM, Stankovic I, Tobback P, Verguieva T, Woutersen RA. Scientific opinion on the re-evaluation of lutein (E 161b) as a food additive. EFSA J. 2010;8(7):1678. https://doi.org/10.2903/j.efsa.2010.1678.
118. Wierzejska RE. Dietary supplements-for whom? The current state of knowledge about the health effects of selected supplement use. Int J Environ Res Public Health. 2021;18(17):8897. https://doi.org/10.3390/ijerph18178897.
119. Jideani AIO, Silungwe H, Takalani T, Omolola AO, Udeh HO, Anyasi TA. Antioxidant-rich natural fruit and vegetable products and human health. Int J Food Prop. 2021;24(1):41–67. https://doi.org/10.1080/10942912.2020.1866597.