Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION |38 (1): 47-56 (2024) Rcpp

Received: 16 January 2024 | **Reviewed**: 19 March 2024 | **Accepted**: 19 March 2024 | **Published**: 25 March 2024

Open Access | **Review**

Lutein in chronic diseases: A mini review

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Abstract
Lutein is a xanthophyll carotenoid that can be found in a divergency of fruits and plants. Its main action is to protect eye health and vision. Its antioxidant properties play a crucial role in eye agitations, in decreasing inflammation, in protecting the neural tissues from chemical analyzed hypoxia and cell apoptosis. Lutein supplementation in association with low-calorie diet had a notable abatement in fat-free mass, visceral fat and serum levels of total cholesterol and LDL (low-density lipoprotein)-cholesterol. Lutein may also have a natural anti-cancer effect. This is because foods rich in lutein have antioxidant activity and oppose inflammation and oxidative stress. The aim of this mini-review was to provide an up-to-date overview of the main effects of lutein in health and disease.

KEYWORDS
lutein, eye health, diabetes, cancer, brain, heart

How to cite this article: Trapali M. Lutein in chronic diseases: A mini review. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (1): 47-56 (2024).
https://doi.org/10.61873/ybcs9028

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1. INTRODUCTION

Carotenoids are yellow, orange and red coloring matters. They exist in all photosynthetic cells, but their color is covered by that of chlorophyll. In autumn, when the chlorophyll decomposes, their color becomes visible. They are linear molecules that contain conjugated systems of double bonds, which is why their color is also due. These are hydrocarbons in carotenes and oxygenated hydrocarbons in xanthophylls with chains of 40 carbon atoms. Carotenoids are usually found in close contact with chlorophylls. The energy they absorb can be transferred to chlorophyll. Also, in bright light situations, carotenoids protect chlorophyll. Carotenoids absorb the extra energy from chlorophyll and give it off as heat, instead of this energy being given to oxygen, resulting in photooxidation and destruction of the photosynthetic mechanism. In humans, carotenoids (mainly β-carotene, the most abundant carotene in foods) have an action similar to vitamin A, i.e. they can be converted to retinal, and they also have an antioxidant effect. Phytoene synthase and carotene desaturase are the responsible enzymes for carotenoids synthesis in alive creatures [1].

Its biosynthesis takes place through the isoprenoid pathway, which starts with acetyl-coenzyme A. The first major terpenoid in the pathway is 15-cis-phytoene, which after a series of oxidations

forms lycopene. After 15-cis-phytoene the pathway branches and the two molecules from which the rest are synthesized are γ and δ carotene. Carotenoids are primarily yielded in plants, algae and photosynthetic bacteria and some species of fungi. Animals cannot biosynthesize them, so they must receive them through food. It is believed that eating foods full in carotenoids could lower the danger of colon, lung, and breast malignancies. Among carotenoids, phycoxanthin and astaxanthin are known for their antioxidant activity, which could help control cancer progression. Phycoxanthin, a major carotenoid, has been shown to impede colon cancer cell generation. Astaxanthin is abundant in algae, and has been reported to exhibit various biological activities including preventive effects against bladder cancer, an action that may be due in part to suppressing the accumulation of cancer cells [2].

More than 600 carotenoids exist in nature, of which only about 20 are found in human blood and tissues. The main carotenoids in human beings are d-carotene, p-carotene, cryptoxanthin, lutein, lycopene and zeaxanthin. They are incapable of dissolving in water but dispersible in fat and lipid solvent [3].

The aim of this mini-review is to describe the involvement of lutein in different pathological situations such as eye disturbances, obesity, diabetes, heart health.

2. CHARACTERISTICS OF LUTEIN

Lutein and zeaxanthin are two principal carotenoids commonly found in fruits and vegetables. They belong to the xanthophyll carotenoids, known for their yellow to red pigments. These compounds play vital roles in various biological processes. Both lutein and zeaxanthin are naturally occurring compounds that the body cannot synthesize. The body selectively accumulates these carotenoids in different tissues, with lutein predominating in the eye and zeaxanthin being highest in the central macula.

Lutein (Figure 1) has the molecular formula $C_{40}H_{56}O_2$ while zeaxanthin has the molecular formula $C_{40}H_{56}O$. Structurally, both compounds consist of a 40-carbon backbone with oxygen atoms. However, lutein contains two hydroxyl groups (OH), while zeaxanthin contains one hydroxyl and one keto group (C=O). These subtle differences in their structures lead to differences in their physical and chemical effects. One of the main differences between lutein and zeaxanthin is their absorption and localization in the body. In the human diet, lutein is most commonly found in green vegetables such as spinach, and fruits such as avocados and oranges. Lutein is best absorbed when eaten with a food that is high in fat. This is because low-density lipoproteins are the main means by which lutein is transported in the body. Therefore, the combination of foods high in lutein and fat is considered ideal.

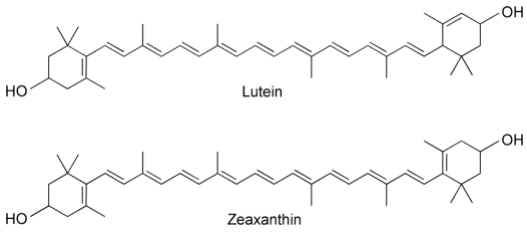

Figure 1: Chemical structures of lutein and zeaxanthin.

On the other hand, zeaxanthin is found in higher amounts in foods such as corn, orange bell peppers, and egg yolks. The carotenoids present in these special foods give them their characteristic color. Compared to zeaxanthin, lutein is more easily absorbed by the body. This is partly due to the existence of extra hydroxyl groups in the lutein structure. In addition, lutein is preferentially absorbed by the macula of the eye, helping to shelter the retina from oxidative harm generated by exposure to blue light.

Summarizing all of the above, Lutein has the features of "uncultivated", "nourishing" and can be extensively accustomed in food, health products, cosmetics, medicine, feed additives, papermaking, printing and dyeing industries:

1. In the food field, marigold extract is mostly utilized as food additives for colorant and nutrient. Lutein mainly comes from marigold flowers, has extremely high content of marigold and other carotenoid-like elements, less impurities, easy to separate and purify, and can be used as a good source for industrial production. The plant itself only synthesizes lutein, xanthophylls are generally sustained in green vegetables such as spinach and marigold. Lutein acts as a regulator of light energy and serves as a non-photochemical quencher to counteract triple chlorophyll in plants, which is made at elevated light amounts, during photosynthesis. Lutein is also used as a dominant impulsive yellow coloring matter. The median daily lutein input of human beings following a Mediterranean diet is among 1.07 and 2.9 mg/day [4, 5,6].
2. In the pharmaceutical field as a raw material, marigold extract is commonly handled in vision care items to soften optical tiredness, lessen the

occurrence of Age-related macular degeneration (AMD), retinitis pigmentosa, cataract, retinopathy, short sighting and of retinoblastoma.
3. In cosmetics, xanthophyll is mostly handled as a raw material for whitening, anti-wrinkle protection and UV protection.

Known for its antioxidant properties, lutein helps abrogate dangerous free radicals and keep safe cells from oxidative destruction. Especially, a number of studies have noticed that Lutein impedes both the pro-inflammatory cytokine cascade [7] and the transcription factor nuclear factor-kB (NF-kB) [8,9,10]. There is also conclusive proof that it lessens reactive oxygen species (ROS) production [11,12], the formulation of inferential nitric oxide synthase (iNOS) and the stimulation of the complement system [13].

3. LUTEIN AND EYE DISTURBANCES

3.1. Age-related macular degeneration

Age-related macular degeneration is a condition that results in progressive loss of central eyesight and is one of the main sources of reduced optical acuity. Advanced macular degeneration can lead to blindness in the legal sense of the term (visual acuity less than 1/10), but it never results in total blindness since peripheral vision remains intact. Macular degeneration usually occurs in people over the age of 50, but some forms of the disease can also affect younger people. The condition can be due to hereditary causes, however, age, diet, smoking and exposure to the sun are factors that can lead to its appearance. People with a family history are advised to get checked more often because the risk of developing the disease is greater. Symptoms experienced by affected patients include blurred vision, distortion of straight lines (they appear wavy), difficulty reading (missing letters or syllables from words), reduced perception of color contrasts, and the presence of dark spots in central vision [14].

There are two types of macular degeneration. The dry type (non-exudative or atrophic) which is more widespread and usually develops slowly and the wet type (exudative or neovascular) which is less common but develops faster and is the most severe form of the disease. Fluid type degeneration is qualified for acute eye sighting deficit and may cause a significant reduction in visual acuity within a few months.

Dry type: Vision loss in dry macular degeneration is due to long-term deposition of proteins and lipids in the area beneath a protective film of cells called the neuro epithelium pigment that splits the retina from the choroid. Protein and lipid deposits form nodules that look like yellow dots and are called drusen. Small amounts of drusen do not usually cause vision loss, but as they increase in number and expand, they lead to destruction of photosensitive cells. This results in the retina showing atrophy in the macular area often referred to as geographic atrophy. These lesions cause a dark spot in the center of vision that can become more extensive over time.

Liquid type: Wet macular degeneration occurs when the retinal pigment epithelium cannot prevent the development of new, fragile, abnormal blood vessels under the macula (choroidal neovascularization). Vascular endothelial growth factor (VEGF) is responsible for the growth of abnormal new blood vessels resulting in leakage of fluid and blood. This leakage creates swelling and lesions that destroy the light-sensitive cells of the macula causing a gradual loss of central vision. VEGF is in charge of the augmentation of pathological new vessels resulting in fluid and blood leakage. This leakage creates swelling and lesions that destroy the light-sensitive cells of the macula causing a gradual loss of central vision [14,15,16].

Lutein [50] is the most important nutrient of the human retina. There is a high concentration of lutein in the area of the macula (the base of faculty of sight) and in the lens of the retina of the eye, and the human body cannot synthesize it on its own. Antioxidant action neutralizes harmful free radicals, filters blue light that is damaging to the eyes and avoids oxidative injury to the eyes generated by light. Lutein has strong antioxidant properties, so it protects the eyes in many ways. Research evidence has shown that lutein can promote eye health in the following ways:

1. Suppression of inflammation in the eyes
2. Eye protection from free radicals and oxidative stress
3. Improvement of visual acuity
4. Improve visual contrast sensitivity
5. Protection of eye tissue from damage caused by sunlight
6. Reduction of loss and death of eye cells, associated with eye diseases
7. Eye protection from harmful blue light
8. Converting light signals into electrical signals in the retina and facilitating their transmission to the visual cortex of the brain
9. Protection against the development of myopia
10. Protection of preterm infants from the effects of retinopathy of prematurity

3.2. Cataract

Cataract is one of the most usual eye disorders,

which manifests with normal aging (senile cataract). Cataracts are actually the clouding of the natural, crystalline lens of the eye that is behind the iris. Through this lens, which under normal conditions is transparent, the light rays pass to finally be guided to the retina (back lining of the eye). Over the years, the crystalline lens loses its original consistency – clarity and becomes cloudy, which inevitably results in blurred vision. The average age at which cataracts significantly affect vision is 65 to 70 years, but this does not mean that it is not possible to appear earlier or later. In rare cases there may be clouding of the natural, crystalline lens from a young age (juvenile cataract).

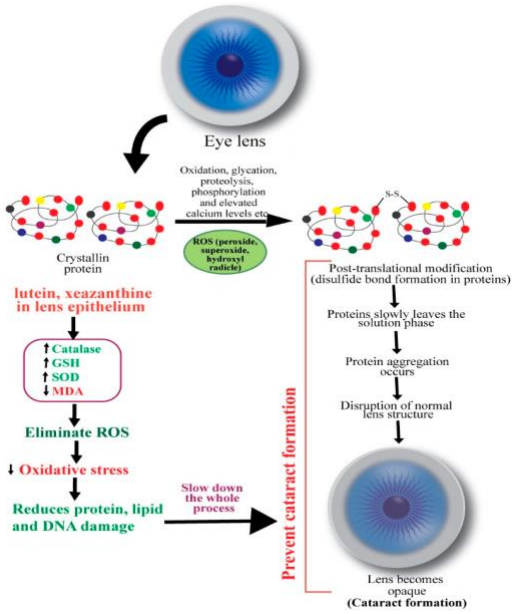

Figure 2. Schematic diagram showing the mechanisms of action of carotenoids to prevent cataract. ROS: reactive oxygen species [14]

Human lens comprises lutein and zeaxanthin [19]. Lutein and zeaxanthin are deposited constantly from the body to the epithelial/cortical layer of the lens, where they pick through discarded things like ROS by overexpressing glutathione (GSH), catalase and superoxide dismutase (SOD) actions (Figure 2). Lutein and zeaxanthin could also lower the possibility for cataract by shielding from oxidative damage lens protein, lipid, and DNA [20]. Intriguingly, a person with cataract displayed elevated serum concentration of pro-oxidants and decreased levels of antioxidants. Serum levels of malondialdehyde (MDA) were remarkably higher, while the levels of superoxide dismutase (SOD) and glutathione peroxidase (GPX) were considerably lower in cataract patients compared to age-matched healthy individuals [21,22].

Studies have demonstrated a significant correlation between high lutein plasma concentrations and a low risk for growing cataract while daily lutein intake (15 mg/d) for at least two years, lowered cataract appearance. Two different cohort studies proved that lutein intake had protective influence on the development of nuclear cataracts. However other studies claim that lutein administration does not affect cataract [23,24,25]. More benefits might be seen when it's combined with other carotenoid vitamins. But it's not clear if taking lutein supplements by mouth helps people who already have cataracts. However, in rats, lutein potentiates the beneficial effects when administered with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) via lowering the inflammation caused by oxidative stress [54]. Intake of up to 20 mg/day for lutein was found to be safe for humans [27].

An in vitro study indicates that lutein is able to block cataract in bovine cells by impeding the accumulation and relocation of lens cells [28].

4. DISEASES OF THE NERVOUS SYSTEM

Lutein can protect the neural tissues from chemical analyzed hypoxia and cell apoptosis, hydrogen peroxide and streptozotocin-induced ROS, ischemia-reperfusion injury [29,30,31]. ROS and infection are strongly associated pathophysiological events. Moreover, lutein protection on dopaminergic neurons is by reducing mitochondrial dysfunction in mice. When 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin mimics the symptoms of Parkinson's disease, was granted in mice with lutein the MPTP-induced neuronal damage/apoptosis by constraining the actuation of pro-apoptotic markers (Bax, caspases-3, 8 and 9) and increasing anti-apoptotic marker (Bcl-2) expressions was calmed [32].

The brain is especially at risk to free radical storming due to its high concentration of polyunsaturated fatty acid and high metabolic occupation. Lutein is irreconcilably limited to membrane domains rich in DHA, and therefore is well located to obstruct oxidation of these lipids [33].

Raised DHA oxidation has been noticed in the brain of patients with Alzheimer disease, a fact that probably explains the connection among lutein and cognition via inhibition of DHA oxidation [34]. However, lutein may result through specific independent mechanisms affecting brain function. Lutein has been suggested to regulate functional properties of photoreceptor, synaptic membranes

along with altering their physiochemical and structural characteristics [33,35].
The polarity of the lutein and zeaxanthin molecules enables them to be oriented perpendicular to the lipid bilayer of cell membranes. This directly affects membrane properties, fluidity, ion exchange capacity, oxygen diffusion capacity [33] and may affect intraneuronal communication [36]. Lutein reduces ROS levels and inhibits NF-kB activation and the expression of inflammatory mediators (IL-1β, IL-6, MCP-1, TNF-α, COX-2, iNOS) [37]. In microglia activated by lipopolysaccharides, it induces the expression of antioxidant Nrf2 target genes (HO-1, NQO1) and consequently the reduction of the inflammatory response [38]. By this mechanism, lutein prevents the occurrence of neuroinflammation caused by oxidative stress. A four-month double-blinded, trial in older women displayed that those who were supplemented with lutein (12 mg/d), DHA (800 mg/d), or a combination had improved memory scores and rate of learning [39,40,41]. Also, another study showed that supplementation with lutein and zeaxanthin in young healthy adults improved cognitive function [42] by lowering brain-derived neurotrophic factor, the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β and anti-oxidant capacity [43.

5. DIABETES / OBESITY

Diabetes mellitus T2DM is one of the most common chronic diseases and is a serious health problem in the world population. According to the most recent international statistics, diabetes people worldwide is more than 400 million, and it is anticipated to become 640 million in 2040. It is depending on several causes while the main characteristic is long term hyperglycemia [44,45,46,47]. Obesity is a main danger for chronic diseases such as T2DM, hypertension, cardiovascular diseases, and cancer [48]. The development and progression of T2DM and its complications are closely linked with oxidative stress and the inflammatory response.

Elevated concentration of carotenoids in the blood are associated with low blood glucose level, reducing though the danger of diabetes or its aggravations. Supplements with lutein and DHA help to balance all the changes caused by diabetes. Low concentration of lutein has been observed in the serum and retina of diabetics. Besides, a lutein-rich diet shields against the evolution of retinopathy in diabetic people [49].

The amount of adipose tissue positively affects the levels of inflammatory mediators and the oxidative stress of the cells [50]. Obesity is directly associated with insulin resistance and augmented levels of inflammatory mediators IL-6, TNF-α and C-reactive protein. A double-blind, randomized controlled trial showed that lutein supplementation in association with low-calorie diet had a notable abatement in fat-free mass, visceral fat and serum levels of total cholesterol and LDL-cholesterol [51,52,53]. Serum lutein and zeaxanthin levels were observed to be conversely associated to serum CRP concentrations [54].

One of the complications of diabetes is diabetic kidney disease. Lutein levels were significantly lower in those patients, negatively correlated with body mass index, glycosylated hemoglobin, fasting blood glucose, triglyceride and positively correlated with high-density lipoprotein cholesterol [55]. Besides, long-term lutein administration in the Ins2Akita/+ mouse retina, provoked abolishment of retinal inflammation and shielding of retinal vasculature [56].

6. CANCER

Although the mechanism linking lutein to cancer cell formation is not clear, studies show that elevated levels of lutein in the blood are related with a lower risk of certain types of cancer. Lutein may have a natural anti-cancer effect. This is because foods rich in lutein have antioxidant activity and oppose inflammation and oxidative stress. The important role of lutein involvement as an inhibitor in MCF-7 and MDA-MB-231 cells of the growth of human breast cancer cells through the enhancement of survival signaling markers associated with the antioxidant defense response has been studied [57].

In vitro culture of PC-3 cells with lutein persuaded small reduction in proliferation that ameliorated in associated processing with peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Lutein enhanced drug-induced cell cycle interruption and apoptosis in prostate cancer, changing the expression of development and apoptosis-associated biomarker genes in PC-3 cells [58].

Administration of lutein in animal models decreases K-ras, which plays a primary role in the regulation of cell division, differentiation and apoptosis, and AKT, a serine/threonine-specific protein kinase that has an important role in controlling the balance between survival and death pathways in cells [59]. Mice received lutein lowered cellular proliferation in colon [60,61,62]. Moreover, lutein participates in reducing ROS and DNA damage [63]. The growth inhibitory prospective of lutein in MCF-7 and MDA-MB-231 cells and in in A549 Human Non-Small-Cell Lung Cancer Cells was studied. Lutein was an effective inhibitor of human

breast cancer cell growth suppressing protein expression of superoxide dismutase-2 and heme oxygenase-1, and its transcription factor nuclear factor erythroid 2-related factor-2 and inhibiting the PI3K/AKT signaling pathway [64,65].

7. CARDIOVASCULAR DISEASES

Carotenoids such as lutein assist lowering the possibility of cardiovascular disease and stroke. Because lutein has anti-inflammatory and antioxidant properties, it benefits the heart by fighting inflammation, the main cause of coronary heart disease. Less levels of lutein in the blood come up with thickening of the artery walls. This increases the risk of developing atherosclerosis and the blockage of the carotid arteries that contribute to heart attacks. People with high concentration of lutein in the blood have less plaque build-up in the walls of arteries. The lower the levels of lutein in the blood, the greater is the accumulation of plaque in the artery walls. Lutein may be a strong preventive agent opposed to atherosclerosis development in humans and animals. Moreover, the citations from mouse models attest that the antiatherogenic result was attained with lowering lipoproteins and chylomicron levels via pathways that involve reduced inflammation and oxidative stress in the artery wall [7,66].

Besides, serum levels of lutein and zeaxanthin were decreased in patients with coronary artery disease, associated with low level of lipoproteins, expanding the risk of coronary artery disease [7]. Humans with atherosclerosis exposed higher blood levels of complement factors C3 and C3a.Complement component 3, has a key role in the complement system and natural immunity. C3 creates a pore in the membrane killing pathogens or host cells. Lutein reduced the levels of plasma C3 and C3a, guiding to cardiometabolic health [67]. Treatment dose of lutein 100 μg/kg in hypertensive patients and in rats 0.5 and 2 mg/kg, p.o. for 3 weeks, decreased blood pressure suppressing ROS production, inhibiting angiotensin-II, endothelin-1, and oxidized low-density lipoprotein [68].

8. SKIN HEALTH

Lutein and zeaxanthin have been shown to have protective effects on skin health. By absorbing harmful UV radiation and neutralizing free radicals, these carotenoids can help prevent sunburn, premature aging, and skin damage from overexposure to the sun. They are often found in topical skin care products and are included for their photoprotective potential.

Lutein reduces skin UV-induced inflammation and immunosuppression by impeding neutrophils aggregation [69] and decreasing ROS generation following UV radiation display in mice. Lutein also inhibits transient receptor potential ankyrin 1 activation-induced neutrophil accession, guiding to abolishment of skin inflammation [70]. It also inhibits molecular markers of oxidative stress such as intercellular adhesion molecule 1, heme oxygenase-1, and matrix metalloproteinases 1 and 9 [71].

9. CONCLUSION

Known for its antioxidant properties, lutein helps abrogate dangerous free radicals and keep safe cells from oxidative destruction. Especially, a number of studies have noticed that Lutein impedes both the pro-inflammatory cytokine cascade and the transcription factor nuclear factor-kB (NF-kB). There is also conclusive proof that it lessens ROS production, the formulation of inferential nitric oxide synthase (iNOS) and the stimulation of the complement system. Lutein has strong antioxidant properties, so it protects the eyes in many ways. Research evidence has shown that lutein can promote eye health. Lutein can also protect the neural tissues from chemical analyzed hypoxia and cell apoptosis, high levels of carotenoids and lutein in the blood are related with low blood glucose concentration, while it regulates functional properties of photoreceptor, synaptic and other membranes in brain. Finally, lutein is involved in the treatment of various types of cancer, atheroprotection and cardiometabolic health and skin inflammation suppression. All the above are the promising key-messages for the use of the lutein in clinical practice as it is resulting that lutein-deficiency is a real issue in clinical reality. Lutein is categorized as Generally Regarded as Safe with minimal side effects upon long term using up. So, the priorities of the research community are to elucidate the modes of action of lutein further and place it in vivo studies.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

ACKNOWLEDGEMENTS

The publication of this article was financially supported by the Special Accounts for Research Grants, University of West Attica.

REFERENCES

1. Swapnil P., Meena, M., Singh S.K., Dhuldhaj U.P., Harish Marwal, A. Vital roles of carotenoids in plants and humans to deteriorate stress with its structure, biosyn-

thesis, metabolic engineering and functional aspects. *Curr. Plant Biol*. 26: 100203 (2021).
DOI:**10.1016/j.cpb.2021.100203**
[**Scopus**] [**Google Scholar**]

2. Mrowicka M., Mrowicki J., Kucharska E., Majsterek I. Lutein and Zeaxanthin and Their Roles in Age-Related Macular Degeneration-Neurodegenerative Disease. *Nutrients.* 14(4): 827 (2022).
DOI: **10.3390/nu14040827**
[**PubMed**] [**Scopus**] [**Google Scholar**]

3. Fiedor, J., Burda K. Potential role of carotenoids as antioxidants in human health and disease. *Nutrients.* 6 (2): 466-488 (2014).
DOI: **10.3390/nu6020466**
[**PubMed**] [**Scopus**] [**Google Scholar**]

4. Lee H.S., Cho Y.H., Park J., Shin H.R., Sung M.K. Dietary intake of phytonutrients in relation to fruit and vegetable consumption in Korea. *J. Acad. Nutr. Diet*. 113 (9): 1194-1199 (2013).
DOI: **10.1016/j.jand.2013.04.022**
[**PubMed**] [**Scopus**] [**Google Scholar**]

5. Olmedilla-Alonso B., Beltrán-de-Miguel B., Estévez-Santiago R., Cuadrado-Vives C. Markers of lutein and zeaxanthin status in two age groups of men and women: Dietary intake, serum concentrations, lipid profile and macular pigment optical density. *Nutr. J*. 13: 52 (2014).
DOI: **10.1186/1475-2891-13-52**
[PubMed] [**Scopus**] [**Google Scholar**]

6. O'Neill, M.E., Carroll Y., Corridan B., Olmedilla B., Granado F., Blanco I., Van den Berg H., Hininger I., Rousell A.M., Chopra M., et al. A European carotenoid database to assess carotenoid intakes and its use in a five-country comparative study. *Br. J. Nutr*. 85(4): 499-507 (2001).
DOI: **10.1079/bjn2000284**
[**PubMed**] [**Scopus**] [**Google Scholar**]

7. Chung R.W.S., Leanderson P., Lundberg A.K., Jonasson L. Lutein exerts anti-inflammatory effects in patients with coronary artery disease. *Atherosclerosis*. 262: 87-93 (2017).
DOI: **10.1016/j.atherosclerosis.2017.05.008**
[**PubMed**] [**Scopus**] [**Google Scholar**]

8. Chang, J., Zhang, Y., Li, Y., Lu, K., Shen, Y., Guo, Y., Qi, Q., Wang, M., Zhang, S. NrF2/ARE and NF-B -pathway regulation may be the mechanism for lutein inhibition of human breast cancer cell. *Future Oncol*. 14(8): 719-726 (2018).
DOI: **10.2217/fon-2017-0584**
[**PubMed**] [**Scopus**] [**Google Scholar**]

9. Liu T., Liu W.H., Zhao J.S., Meng F.Z., Wang H. Lutein protects against-amyloid peptide-induced oxidative stress in cerebrovascular endothelial cells through modulation of Nrf-2 and NF-b. *Cell. Biol. Toxicol*. 33(1): 57-67 (2017).
DOI: **10.1007/s10565-016-9360-y**
[**PubMed**] [**Scopus**] [**Google Scholar**]

10. Muriach M., Bosch-Morell F., Arnal E., Alexander G., Blomhoff R., Romero F.J. Lutein prevents the effect of high glucose levels on immune system cells in vivo and *in vitro. J. Physiol. Biochem*. 64(2): 149-157 (2008).
DOI: **10.1007/BF03168243**
[**PubMed**] [**Scopus**] [**Google Scholar**]

11. Li S., Ding Y., Niu Q., Xu S., Pang L., Ma R., Jing M., Feng G., Tang J.X., Zhang Q., et al. Lutein has a protective effect on hepatotoxicity induced by arsenic via Nrf2 signaling. *BioMed Res. Int*. 2015:2015:315205.
DOI: **10.1155/2015/315205**
[**PubMed**] [**Scopus**] [**Google Scholar**]

12. Rafi M.M., Shafaie Y. Dietary lutein modulates inducible nitric oxide synthase (iNOS) gene and protein expression in mouse macrophage cells (RAW 264.7). *Mol. Nutr. Food Res*. 51(3): 333–340 (2007).
DOI: **10.1002/mnfr.200600170**
[**PubMed**] [**Scopus**] [**Google Scholar**]

13. Tian Y., Kijlstra, A., van der Veen R.L., Makridaki M., Murray I.J., Berendschot T.T. Lutein supplementation leads to decreased soluble complement membrane attack complex sC5b-9 plasma levels. *Acta Ophthalmol*. 93 (2): 141-145 (2015).
DOI: **10.1111/aos.12535**
[**PubMed**] [**Scopus**] [**Google Scholar**]

14. Guymer R.,Campbell T. Age-related macular degeneration. *Lancet* 401(10386):1459-1472 (2023).
DOI: **10.1016/S0140-6736(22)02609-5**
[**PubMed**] [**Scopus**] [**Google Scholar**]

15. Flores R., Carneiro A., Vieira M., Tenreiro S., Seabra M.Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives. *Ophthalmologica* 244(6):495-511 (2021).
DOI: **10.1159/000517520**
[**PubMed**] [**Scopus**] [**Google Scholar**]

16. Thomas C., Mirza R., Gill M. Age-Related Macular Degeneration. *Med Clin North Am* 105(3): 473-491 (2021)
DOI: **10.1016/j.mcna.2021.01.003**
[**PubMed**] [**Scopus**] [**Google Scholar**]

17. Buscemi S., Corleo D., Di Pace F., Petroni M., Satriano A., Marchesini G. The Effect of Lutein on Eye and Extra-Eye Health *Nutrients* 10(9): 1321(2018).
DOI: **10.3390/nu10091321**
[**PubMed**] [**Scopus**] [**Google Scholar**]

18. Johra F., Bepari A., Bristy A., Reza H. A Mechanistic Review of β-Carotene, Lutein, and Zeaxanthin in Eye Health and Disease. *Antioxidants*/. 9 (11): 1046 (2020).
DOI: **10.3390/antiox9111046**
[**PubMed**] [**Scopus**] [**Google Scholar**]

19. Yeum K.J., Shang F., Schalch W., Russell R.M., Taylor, A. Fat-soluble nutrient concentrations in different layers of human cataractous lens. *Curr. Eye Res*. 19 (6): 502-505 (1999).
DOI: **10.1076/ceyr.19.6.502.5282**
[**PubMed**] [**Scopus**] [**Google Scholar**]

20. Gao S., Qin T., Liu Z., Caceres M.A., Ronchi C.F., Chen O., Yeum K., Taylor A., Blumberg J.B., Liu Y. Lutein and zeaxanthin supplementation reduces H2O2 induced oxidative damage in human lens epithelial cells. Mol. Vis. 17: 3180-3190 (2011).
[PubMed] [Google Scholar]

21. Chang D., Zhang X., Rong S., Sha Q., Liu P., Han T., Pan H. Serum antioxidative enzymes levels and oxidative stress products in age-related cataract patients. *Oxid. Med. Cell*. Longev. 2013:2013:587826.
DOI: 10.1155/2013/587826
[PubMed] [Scopus] [Google Scholar]

22. Kaur, J., Kukreja S., Kaur A., Malhotra N., Kaur R. The oxidative stress in cataract patients. *J. Clin. Diagn. Res*. 6 (10): 1629-1632 (2012).
DOI: 10.7860/JCDR/2012/4856.2626
[PubMed] [Scopus] [Google Scholar]

23. Karppi J., Laukkanen J.A., Kurl S. Plasma lutein and zeaxanthin and the risk of age-related nuclear cataract among the elderly Finnish population. *Br. J. Nutr.* 108: 148–154 (2012).
DOI: 10.1017/S0007114511005332
[PubMed] [Scopus] [Google Scholar]

24. Olmedilla B., Granado F., Blanco I., Vaquero M. Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: A 2-y double-blind, placebo-controlled pilot study. *Nutrition.*19: 21–24 (2003).
DOI: 10.1016/S0899-9007(02)00861-4
[PubMed] [Scopus] [Google Scholar]

25. Jobra F.Bepari A., Bristy A., Reza H. A Mechanistic Review of Carotene, Lutein, and Zeaxanthin in Eye Health and Disease. *Antioxidants* 9.1046(2020).
DOI: 10.3390/antiox9111046
[PubMed] [Scopus] [Google Scholar]

26. Padmanabha S., Vallikannan B. Fatty acids modulate the efficacy of lutein in cataract prevention: Assessment of oxidative and inflammatory parameters in rats. *Bioch. Biophys. Res. Comm.*500:435-442 (2018)
DOI: 10.1016/j.bbrc.2018.04.098
[PubMed] [Scopus] [Google Scholar]

27. Shao, A., Hathcock, J.N. Risk assessment for the carotenoid's lutein and lycopene. *Regul. Toxicol. Pharm.* 45, 289–298 (2006).
DOI: 10.1016/j.yrtph.2006.05.007
[PubMed] [Scopus] [Google Scholar]

28. Hu Y., Xu Z.J. Effects of lutein on the growth and migration of bovine lens epithelial cells in vitro. *Huazhong Univ. Sci. Technol. Med. Sci.* 28:360–363 (2008).
DOI: 10.1007/s11596-008-0331-2
[PubMed] [Scopus] [Google Scholar]

29. Dilsiz, N., Sahaboglu A., Yıldız M.Z., Reichenbach, A. Protective Effects of Various Antioxidants during Ischemia-Reperfusion in the Rat Retina. Graefe's Arch. *Clin. Exp. Ophthalmol*. 244 (5): 627–633 (2006).
DOI: 10.1007/s00417-005-0084-6
[PubMed] [Scopus] [Google Scholar]

30. Li S.Y., Lo A.C.Y. Lutein Protects RGC-5 Cells against Hypoxia and Oxidative Stress. *Int. J. Mol. Sci*. 11 (5): 2109-2117(2010).
DOI: 10.3390/ijms11052109
[PubMed] [Scopus] [Google Scholar]

31. Nataraj J., Manivasagam T., Justin Thenmozhi A., Essa M.M. Lutein Protects Dopaminergic Neurons against MPTP-Induced Apoptotic Death and Motor Dysfunction by Ameliorating Mitochondrial Disruption and Oxidative Stress. *Nutr. Neurosci.*19(6): 237-246 (2016).
DOI: 10.1179/1476830515Y.0000000010
[PubMed] [Scopus] [Google Scholar]

32. Nataraj J., Manivasagam T., Thenmozhi A., Essa M. Lutein protects dopaminergic neurons against MPTP-induced apoptotic death and motor dysfunction by ameliorating mitochondrial disruption and oxidative stress. *Nutr Neurosci* 19(6): 237-46 (2016).
DOI: 10.1179/1476830515Y.0000000010
[PubMed] [Scopus] [Google Scholar]

33. Widomska, J., Subczynski, W.K. Why has nature chosen lutein and zeaxanthin to protect the retina? *J. Clin. Exp. Ophthamol.* 5(1): 326 (2014)
DOI: 10.4172/2155-9570.1000326
[PubMed] [Google] [Scholar]

34. Miller E., Morel A., Saso, L., Saluk J. Isoprostanes and neuroprostanes as biomarkers of oxidative stress in neurodegenerative diseases. *Oxid. Med. Cell. Longev*. 2014:2014:572491.
DOI: 10.1155/2014/572491
[PubMed] [Scopus] [Google Scholar]

35. Gruszecki W.I. Carotenoid orientation: Role in membrane stabilization. In Carotenoids in Health and Disease. *Krinsky, N.I., Mayne, S.T., Sies, H., Eds., Marcel Dekker, Inc.: New York, NY, USA*, pp. 151-164 (2004).

36. Stahl W., Sies H. Effects of carotenoids and retinoids on gap junctional communication. *BioFactors*. 15(2-4): 95–98 (2001).
DOI: 10.1002/biof.5520150209
[PubMed] [Scopus] [Google Scholar]

37. Tan D., Yu X., Chen M., Chen J., Xu J. Lutein protects against severe traumatic brain injury through anti-inflammation and antioxidative effects via ICAM-1/Nrf-2. *Mol. Med. Rep*. 16(4): 4235-4240 (2017).
DOI: 10.3892/mmr.2017.7040
[PubMed] [Scopus] [Google Scholar]

38. Wu W., Li Y., Wu Y., Zhang Y., Wang Z., Liu X. Lutein suppresses inflammatory responses through Nrf2 activation and NF-kB inactivation in lipopolysaccharide-stimulated BV-2 microglia. *Mol. Nutr. Food. Res*. 59(9): 1663-1673 (2015).

DOI: 10.1002/mnfr.201500109
[PubMed] [Scopus] [Google Scholar]

39. Erdman, J.J.W., Smith, J.W., Kuchan, M.J., Mohn, E.S., Johnson, E.J., Rubakhin, S.S., Wang, L., Sweedler, J.V. Neuringer, M. Lutein and Brain Function. *Foods* 4, 547–564 (2015).
DOI: 10.3390/foods4040547
[PubMed] [Scopus] [Google Scholar]

40. Johnson, E.J., McDonald, K.; Caldarella, S.M., Chung, H.-Y., Troen, A.M., Snodderly, D.M. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. *Nutr. Neurosci*. 11, 75–83 (2008).
DOI: 10.1179/147683008X301450
[PubMed] [Scopus] [Google Scholar]

41. Bovier, E.R., Renzi, L.M., Hammond, B.R. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency. *PLoS ONE* 9, e108178 (2014).
DOI: 10.1371/journal.pone.0108178
[PubMed] [Scopus] [Google Scholar]

42. Renzi-Hammond, L.M., Bovier, E.R., Fletcher, L.M., Miller, L.S., Mew born, C.M., Lindbergh, C.A., Baxter, J.H., Hammond, B.R. Effects of a Lutein and Zeaxanthin Intervention on Cognitive Function: A Randomized, Double-Masked, Placebo-Controlled Trial of Younger Healthy Adults. *Nutrients* 9, 1246 (2017).
DOI: 10.3390/nu9111246
[PubMed] [Scopus] [Google Scholar]

43. Stringham, N.T., Holmes, P.V., Stringham, J.M. Lutein Supplementation Increases Serum Brain-Derived Neurotrophic Factor (BDNF) in Humans. *FASEB J*. 30, 689-3 (2016).
DOI: 10.1096/fasebj.30.1_supplement.689.3
[Google Scholar]

44. Trapali M. Oxidic degradation of lipids in patients with type II Diabetes. *Rev. Clin. Pharmacol. Pharmacokinet., Int. Ed.* 35(2): 75-77 (2021).
DOI: 10.5281/zenodo.10030548
[Scopus] [Google Scholar]

45. Trapali, M., Houhoula, D., Batrinou, A., Kanellou, A., Strati, I., Siatelis, A., Halvatsiotis, P. Association of TNF-α- 308G/A and LEPR Gln223Arg Polymorphisms with the Risk of Type 2 Diabetes. Mellitus. *Genes*. 13 (1): 59. (2022).
DOI: 10.3390/genes13010059
[PubMed] [Scopus] [Google Scholar]

46. Trapali M. Antioxidant Activity in Patients with Type II Diabetes. *Rev. Clin. Pharmacol. Pharmacokinet., Int. Ed*. 36(1): 23-26 (2022).
DOI: 10.5281/zenodo.8436470
[Scopus]

47. Trapali M., Papadopoulou A. Genetic polymorphisms possibly implicated in Diabetes Mellitus. *Rev. Clin. Pharmacol. Pharmacokinet., Int. Ed*. 37 (1) 43-48 (2023).
DOI: 10.5281/zenodo.10029552
[Scopus]

48. Hinnouho G.M., Czernichow S., Dugravot A., Nabi H., Brunner E.J., Kivimaki M., Singh-Manoux A. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: The Whitehall II cohort study. *Eur. Heart J*., 36 (9): 551-559 (2015).
DOI: 10.1093/eurheartj/ehu123
[PubMed] [Scopus] [Google Scholar]

49. Sahli M.W., Mares J.A., Meyers K.J., Klein R., Brady W.E., Klein B.E.K., Ochs-Balcom H.M., Donahue, R.P., Millen A.E. Dietary Intake of Lutein and Diabetic Retinopathy in the Atherosclerosis Risk in Communities Study (ARIC). *Ophthalmic Epidemiol*. 23(2): 99-108 (2016).
DOI: 10.3109/09286586.2015.1129426
[PubMed] [Scopus] [Google Scholar]

50. Fernandez-Sanchez, A., Madrigal-Santillan E., Bautista M., Esquivel-Soto J., Morales-Gonzalez A., Esquivel-Chirino C., Durante-Montiel I., Sánchez-Rivera G., Valadez-Vega C., Morales-González J.A. Inflammation, oxidative stress, and obesity. *Int. J. Mol. Sci*. 12(5): 3117-3132 (2011).
DOI: 10.3390/ijms12053117
[PubMed] [Scopus] [Google Scholar]

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*.126, 1028–1039. (2021).
DOI: 10.1017/S0007114520004997
[PubMed] [Scopus] [Google Scholar]

52. 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* 12, 2342 (2020).
DOI: 10.3390/nu12082342
[PubMed] [Scopus] [Google Scholar]

53. Zheng, Z., Yin, Y., Lu, R., Jiang, Z. Lycopene Ameliorated Oxidative Stress and Inflammation in Type 2 Diabetic Rats. *J. Food Sci*. 84, 1194–1200 (2019).
DOI: 10.1111/1750-3841.14505
[PubMed] [Scopus] [Google Scholar]

54. Tuzcu M., Orhan C., Muz O.E., 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*. 17(1): 129 (2017).
DOI: 10.1186/s12886-017-0524-1
[PubMed] [Scopus] [Google Scholar]

55. 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*. 36: e24350 (2022).

DOI: 10.1002/jcla.24350
[PubMed] [Scopus] [Google Scholar]

56. Wang W, Tam KC, Ng TC, et al. Long-term lutein administration attenuates retinal inflammation and functional deficits in early diabetic retinopathy using the Ins2Akita/+ mice. *BMJ Open Diabetes Res Care.* 8(1): e1519 (2020).
DOI: 10.1136/bmjdrc-2020-001519
[PubMed] [Scopus] [Google Scholar]

57. Kavalappa Y., Gopal S., Ponessaki G. Lutein inhibits breast cancer cell growth by suppressing antioxidant and cell survival signals and induces apoptosis. *J Cell Physiol.* 236(3): 1798-1809 (2021).
DOI: 10.1002/jcp.29961
[PubMed] [Scopus] [Google Scholar]

58. Rafi M., Kanakasabai S., Gokarn S., Krueger E., Bright J. Dietary lutein modulates growth and survival genes in prostate cancer cells. *J Med Food*. 18(2): 173-81 (2015).
DOI: 10.1089/jmf.2014.0003
[PubMed] [Scopus] [Google Scholar]

59. Femia, A.P., Tarquini E., Salvadori M., Ferri S., Giannini A. K-ras mutations and mucin profile in preneoplastic lesions and colon tumors induced in rats by 1,2-dimethylhydrazine. *Int. J. Cancer*. 122(1): 117-123 (2008).
DOI: 10.1002/ijc.23065
[PubMed] [Scopus] [Google Scholar]

60. Gali-Muhtasib H.U., Younes I.H., Karchesy J.J., el-Sabban, M.E. Plant tannins inhibit the induction of aberrant crypt foci and colonic tumors by 1,2-dimethylhydrazine in mice. *Nutr. Cancer* 39(1): 108-116 (2001).
DOI: 10.1207/S15327914nc391_15
[PubMed] [Scopus] [Google Scholar]

61. Reynoso-Camacho R., González-Jasso E., Ferriz-Martínez R., Villalón-Corona B., Salgado L., Ramos-Gómez M. Dietary supplementation of lutein reduces colon carcinogenesis in DMH-treated rats by modulating K-ras, PKB, and β-catenin proteins. *Nutr. Cancer.* 63(1): 39-45 (2010).
DOI: 10.1080/01635581.2010.516477
[PubMed] [Scopus] [Google Scholar]

62. Satia-Abouta J., Galanko J.A., Martin C.F., Potter J.D., Ammerman A., Sandler R.S. Associations of micronutrients with colon cancer risk in African Americans and whites: Results from the North Carolina Colon Cancer Study. *Cancer Epidemiol. Biomark. Prev*. 12(8): 747–754 (2003).
[Scopus] [Google Scholar]

63. Santocono M., Zurria M., Berrettini M., Fedeli D., Falcioni G. Influence of astaxanthin, zeaxanthin and lutein on DNA damage and repair in UVA-irradiated cells. *J. Photochem. Photobiol B*. 2006, 85(3): 205-215.
DOI: 10.1016/j.jphotobiol.2006.07.009
[PubMed] [Scopus] [Google Scholar]

64. Kavalappa Y., Gopal S., Ponessaki G. Lutein inhibits breast cancer cell growth by suppressing antioxidant and cell survival signals and induces apoptosis. *J Cell Physiol* 236(3):1798-1809 (2021).
DOI: 10.1002/jcp.29961
[PubMed] [Scopus] [Google Scholar]

65. Zhang W., Zhao Y., Shi Z., Cong D., Bai Y. Lutein Inhibits Cell Growth and Activates Apoptosis via the PI3K/AKT/mTOR Signaling Pathway in A549 Human Non-Small-Cell Lung Cancer Cells *J Environ Pathol Toxicol Oncol* 37(4):341-350 (2018).
DOI:10.1615/JEnvironPatholToxicolOncol.2018027418
[PubMed] [Scopus] [Google Scholar]

66. Lidebjer C., Leanderson P., Ernerudh J., Jonasson L. Low plasma levels of oxygenated carotenoids in patients with coronary artery disease. *Nutr. Metab. Cardiovasc. Dis*. 17 (6): 448-456 (2007).
DOI: 10.1016/j.numecd.2006.02.006
[PubMed] [Scopus] [Google Scholar]

67. Howard A.N., Thurnham D.I. Lutein and atherosclerosis: Belfast versus Toulouse revisited. *Med. Hypotheses*. 98: 63-68 (2017).
DOI: 10.1016/j.mehy.2016.10.030
[PubMed] [Scopus] [Google Scholar]

68. Abbasian F., Alavi M., Roohbakhsh A. Dietary carotenoids to improve hypertension *Heliyon.* 9(9): e19399 (2023).
DOI: 10.1016/j.heliyon.2023.e19399
[PubMed] [Scopus] [Google Scholar]

69. Horváth G., Kemény Á., Barthó L., Molnár P., Deli J., Szente L., Bozó T., Pál S., Sándor K., Sz˝oke É., et al. Effects of some natural carotenoids on TRPA1- and TRPV1-induced neurogenic inflammatory processes in vivo in the mouse skin. J. *Mol. Neurosci*. 56 (1): 113-121 (2015).
DOI: 10.1007/s12031-014-0472-7
[PubMed] [Scopus] [Google Scholar]

70. Lee E.H., Faulhaber D., Hanson K.M., Ding W., Peters S., Kodali S., Granstein R.D. Dietary lutein reduces ultraviolet radiation-induced inflammation and immunosuppression. *J. Investig. Dermatol*. 122 (2): 510-517 (2004).
DOI: 10.1046/j.0022-202X.2004.22227.x
[PubMed] [Scopus] [Google Scholar]

71. Baswan S., Klosner A., Weir C., Salter-Venzon D., Gellenbeck K., Leverett J., Krutmann J. Role of ingestible carotenoids in skin protection: A review of clinical evidence. *Photodermatol Photoimmunol Photomed*. 37:490–504 (2021)
DOI: 10.1111/phpp.12690
[PubMed] [Scopus] [Google Scholar]