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Review Article

Lutein: A Comprehensive Review on its Chemical, Biological Activities and Therapeutic Potentials

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ABSTRACT

Background: Lutein is a naturally occurring carotenoid found in high amounts in flowers, grains, fruits and green vegetables with green leaves include spinach, kale and carrots. The market for lutein encompasses pharmaceutical, dietary supplement, food, animal and fish feed industries. **Objective:** The present review aimed to provide an updated and comprehensive analysis of lutein, including its chemistry, biological properties and therapeutic potentials. **Methods:** Relevant literatures were collected from several scientific databases, include Google Scholar, Pubmed and ScienceDirect between 2000 to till date. Following a detailed inclusion and exclusion screening process, the information obtained was summarized. **Results:** Information on the sources, chemistry and biological properties including antioxidant, anti-arthrisits, anti-inflammatory, hepatoprotective, cardioprotective, anti-cataract, antidiabetic, anticancer and bone remodelling activities, as well as food industry processing for lutein were tabled. Lutein can be considered powerful antioxidants along with multifaceted molecular targets, such as NF-κB, PI3K/Akt, Nrf-2, HO-1 and SIRT-1 signaling pathways in various pathological conditions. **Conclusion:** The present review observe the chemical, pharmacological properties, in addition to the therapeutic potentials of lutein. It is hoped that the information can provide a good reference to aid in the development and utilization of lutein in phytopharmaceuticals and food industries.

Key words: Lutein, Pharmacology, Molecular targets, Transcription factors, Inflammatory cytokines, Antioxidant.

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INTRODUCTION

Lutein is found in high quantity in some foods especially in egg yolk and corn as well as in some coloured fruits and vegetables including kiwi, grapes, spinach, orange juice and zucchini.[1] Lutein has been a subject of interest by researchers around the world due to its promising nutrient. The previous study has reported that lutein is mostly accrued in retina of human, thus shielding these from short-wavelength visible light. It is reported that the oxidized lutein and zeaxanthin act as antioxidants, thus protecting the retina.[2,3] Besides, lutein is also found in other parts of the human body including the skin, breast, brain and cervix, as confirmed by higher fasting plasma carotenoids concentration and increased in skin yellowness following its consumption.[4] It is believed that the protective effects of lutein on the human body are primarily contributed by its antioxidant potentials.

It has been suggested that 0.6-1.05 mmol/l of the resulting plasma concentration of lutein is deemed to be safe for human while exerting the expected beneficial effects.[5] Apart from that, the use of lutein in the animal and fish feed industries is restricted due to their instability as well as chemical changes that may have occurred during food processing.[6] Nevertheless, the application of lutein in pharmaceuticals as well as in the health supplements remain relevant due to their magnificent benefits to the human body. Since lutein can only be obtained from the diet, its supplementation is helpful to ensure adequate supply.

Lutein is considered as an effective functional compound with many biological properties that benefits for human health. Its market is segmented into pharmaceutical, dietary supplement, food and animal as well as the fish feed industries. However, there is no in-depth available to support its dearth of health benefits. Therefore, we aimed to provide an updated and comprehensive review of lutein, including its chemistry and biological properties to uncover its potential, accelerate its development and utilization in phytopharmaceuticals and the food industries.

METHODS

To complete this review, relevant literatures were collected from several scientific databases, include Google Scholar, Pubmed and ScienceDirect between 2000 to till date. The categories of keywords used were "Lutein" and "Sources" or "Pharmacological Studies" or "Molecular Mechanism" or "Biological Properties" or "Chemistry" or "Food Industry" or "Food Products" or "Formulations" or "Health Benefits". Studies which are not written in English and have no abstracts have been excluded from initial screening. There was no restriction to be followed for collecting the lutein-related studies, particularly in animal and human studies. After applying the inclusion and exclusion criteria and removing duplicates from the

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databases, the articles were chosen for final analysis. The information included in the review was divided into two main categories, which are lutein's phytochemical and pharmacological properties. They were additionally categorised according to the key findings of the study. Following a complete screening, the information obtained were summarized and were included in this present review.

CHEMISTRY

Lutein, known as a fat-soluble carotenoid pigment, consisting of 40 carbons with sequence of dominant, conjugated double bonds.[7] It is believed that the presence of double bonds in their structure has led to their prominent red color and ability supply free radicals. Besides, the distinctive carotenoids structure is believed to have contributed to their chemical and physical properties. Depending on their chemical structures, carotenoids are generally differentiated into two main groups, the xanthophylls and the carotenes. Lutein and its structural isomer zeaxanthin are known as xanthophylls, which are polar compounds and contain oxygen atoms in their structures (Figure 1). On the other hand, carotenes such as β-carotene and lycopene are hydrocarbons. When compared with other carotenoids, xanthophylls which consist of carbon, hydrogen, oxygen as well as the oxygen-containing hydroxyl group, contributed to their polarity during its absorption, metabolism, distribution and uptake into body tissues. There are two hydroxyl groups of lutein and zeaxanthin; one on either side of the molecule, which makes it distinguishable between other carotenoids and it is the one that controls the biological function of these two xanthophylls. On the other hand, zeaxanthin is a lutein stereoisomer in which one of its hydroxyl groups has different locations of its double bond.[8]

Lutein and zeaxanthin are distinct from other carotenoids, for example carotene and cryptoxanthin; since they are not a vitamin A precursors.[9] A study by Johnson[10] revealed that unlike other pro-vitamin A carotenoids, lutein that is a carotenoid pro-vitamin A cannot be converted to vitamin A. This fact explains why the source of lutein should only come from dietary sources or lutein supplementation. Structurally, lutein spans the cell membrane with a hydrophobic aliphatic chain and hydrophilic hydroxyl groups.[11] In general, lutein composed of 40-carbons (tetraterpenoids) with an interchange between single and double bonds linked to methyl group at each side. Lutein and zeaxanthin are differed with other types of carotenoids as seen in the occupancy of the –OH group at each of the molecule's side. The hydroxyl group is involved in their chemical reactivity with singlet oxygen.[1]

Spectral Data of Lutein[8]

Ultraviolet (UV): λmax (nm): (ε): In dioxane 429, 453 and 482, in methanol 330, 422, 443 and 470.

^{1}H-NMR ($CDCl_3$): Lutein has a symmetric structure, so the assignment of the peaks on ^{1}HNMR spectra is also symmetric. Peaks around 1 to 2 ppm were assigned to the protons on saturated carbons [C (2, 2'), C (4, 4'), C (16, 16'), C (17, 17'), C (18, 18'), C (19, 19'), C (20, 20')]. The singlet's at δ 0.85 and 0.99 (6H, s, 1'-gem-Me, H-16, H-17,) each integrated for three protons and the singlet at δ 1.07 (6H, s, 1-gem-Me H-16', H-17',) for six protons are attributed to the gem dimethyl groups at C-1 and C-1' respectively. Singlet's at δ 1.62 (3H, s, H-18), 1.73 (3H, s, H-18'), 1.91 (3H, s, H-19), 1.97 (9H, s, H-19', H-20 and H-20' are consistent with the methyl groups attached to unsaturated carbon atoms. The spectrum displayed three doublet of doublets at δ 1.84 (2H, dd, H-2, H-2'eq), 1.37 (1H, dd, H-2'ax) and 1.48 (1H, t, H-2ax) which correspond to the chemical shifts of the protons on carbon C-2. In addition, spectrum displayed a doublet of doublets at δ 2.04 (1H, dd, H-4ax) and a triplet at δ 2.33-2.45 (2H, m, H-6'-, H-4eq) for the H-4 and H-6' protons. The protons under the hydroxyl group H-3 and H-3' appeared as a pair of doublet of doublet at 4.0 (1H, m, H-3) and 4.25 (1H, H-3'). Those around 6 ppm were contributed by the olefinic protons on the carbon-carbon double bonds, at δ 5.43 (1H, dd, H-7'), 5.55 (1H, s, H-4'), 6.12 (2H, s, H-7-, H-8), 6.15 (3H, m, H-8', H-10, H-10'), 6.26 (2H, m, H-14,H-14'), 6.36 (2H, d, H-12-, H-12'), and at δ 6.55-6.71 (4H, m, H-11, H-11', H-15, H-15').

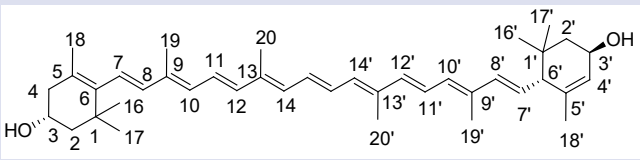

Figure 1: Chemical structure of lutein.

^{13}C-NMR ($CDCl_3$): Lutein displayed signals accounting for 40 carbon atoms in ^{13}C NMR spectrum. Out of these signals, the signals at δ 24.3, 28.7, 29.5 and 30.2 belongs to the gem dimethyl carbons, the signals at δ 21.6 (C-18) and 22.8 (C-18) belongs to the carbon atoms attached to C-5 and C-5' and the signals at δ 12.7 for a three carbon intensity and at 13.2 are due to C-19, C-19', C-20 and C-20' respectively. The remaining signals in the up-field region at δ 37.1, 34.0 are due to C-1 and C-1', at δ 48.4 and 44.7 are due to C-2 and C-2' and the signal at δ 55.0 belongs to C-6'. The C-4 carbon atom resonates at δ 42.5. The carbon atom under hydroxyl groups C-3 and C-3' appeared at δ 65.1 and 65.9. All the other signals at δ 124.5 (C-11'), 124.9 (C-11),126.2 (C-5), 125.6 (C-7), 128.6 (C-7'), 130.0 (C-15), 130.0 (C-15'),130.8 (C-10'), 131.3 (C-10), 132.6 (C-14), 132.6 (C-14'), 135.6 (C-9), 135.0 (C-9'), 136.5 (C-13), 137.6 (C-6), 137.6 (C-12), 138.5 (C-8), 125.6 (C-4'), 136.5 (C-13'), 137.8 (C-5'), 137.6 (C-12'), 137.8 (C-8') are due to unsaturated carbon atoms.

Mass spectrum (ECNI, methane): Lutein, molecular formula: $C_{40}H_{56}O_2$, melting point: 183-185 °C. In the mass spectrum, m/z peak appeared at 568 and M - H_2O peak appeared at m/z 550.[2]

DISTRIBUTION AND MEDICINAL BENEFITS OF LUTEIN

In general, the fat-soluble carotenoids pigment encompasses about 700 members in nature, where lutein belongs to the carotenoids family xanthophyll. Previous studies have reported that lutein is most likely to distributed in the dietary sources from fruits and vegetables which are regularly consumed.[12] Lutein is particularly found in dark green vegetables as well as in foods that are yellow-orange in color like egg yolk and corn and is solely biosynthesized by plants, algae, bacteria and some fungi.[13]

The biological activities of lutein have been categorized as functions, actions and associations. It refers to nutrient's fundamental function in biological applications, reflect the essential value as well as in preventing deficiency states. To date, there is no human defined clinical condition that is directly linked with lutein insufficiency or toxicity, other than reversible hypercarotenaemia that may be associated with or without carotenodermia. Hypercarotenaemia is manifested by carotenodermia indicated by the presence of yellowish discoloration of the skin, especially on the palms and soles. Hypercarotenaemia develops over a period of several months in individuals who consumed high carotenoid-rich foods of more than 30 mg/day. Carotenoid consumption very rarely results in metabolic carotenaemia owing to the presence of 15-15′-carotenoid dioxygenase unless in the presence of genetic defects. Besides, in people with the underlying condition of hypothyroidism, anorexia nervosa and diabetes mellitus are frequently associated with hypercarotenaemia even with a regular consumption of carotenoid-rich foods.

Secondly, actions describe the effects exerted by the molecules (usually at pharmacological doses) with beneficial or harmful consequences.

The parameter is usually tested in non-physiological conditions. Lutein has been investigated under various conditions including cell transformation, inhibition, monocyte-mediated inflammatory response inhibition, immune enhancement, *in-vitro* antioxidant activity, inhibition of low density lipoprotein (LDL) oxidation resistance, as well as, as macula defence. Nevertheless, most aspects of carotenoid metabolism remain largely unknown to human. Albert *et al.*[14] was identified a potential metabolic pathway of lutein. According to the study, they have identified two diastereomers [(3*R*,6'*R*)-3'-dehydro-lutein and (3*R*,6'*S*)-3'-dehydro-lutein] by using chiral-phase High performance liquid chromatography (HPLC) method, and revealed to be present in nearly equimolar amounts (Figure 2). The prediction of lutein's biological mechanism is generally difficult to be observed from *in-vivo* studies, although their relevance was demonstrable *in-vivo* physiological conditions as shown in human subjects. The word "association" is therefore applied to epidemiological evidence between the nutrient intake and the outcomes of health or diseases. The studies involving the epidemiological associations between lutein and other highly prevalent diseases including cancer and cardiovascular diseases have been a subject of interest by many researchers worldwide. Although lutein was associated with lack of pro-vitamin A, its biological activities, together with epidemiological evidence of numerous chronic and degenerative diseases, sparked interest in lutein being a potentially valuable natural compound which is essential to human health.[5]

BIOLOGICAL PROPERTIES AND THERAPEUTIC POTENTIALS OF LUTEIN

Lutein has been reported for many useful biological activities and therapeutic potentials and the underlying molecular mechanism of actions to the associated activities have been identified (Figures 3 and 4) and summarized in Table 1.

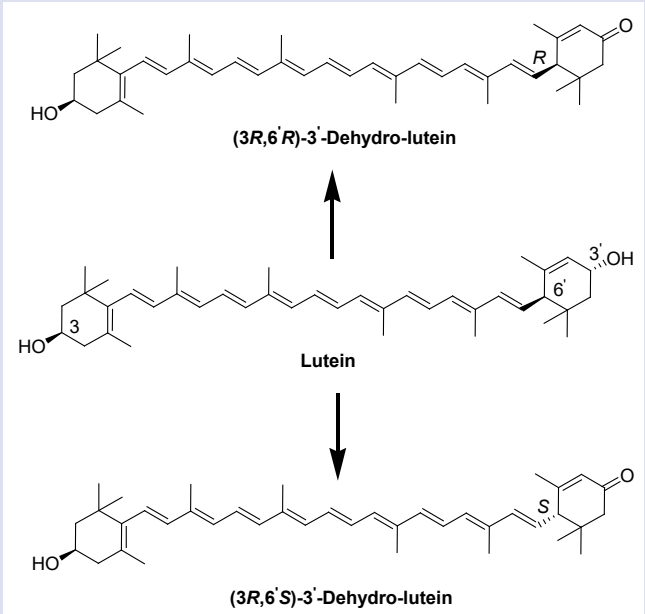

Figure 2: Metabolic pathways of lutein.

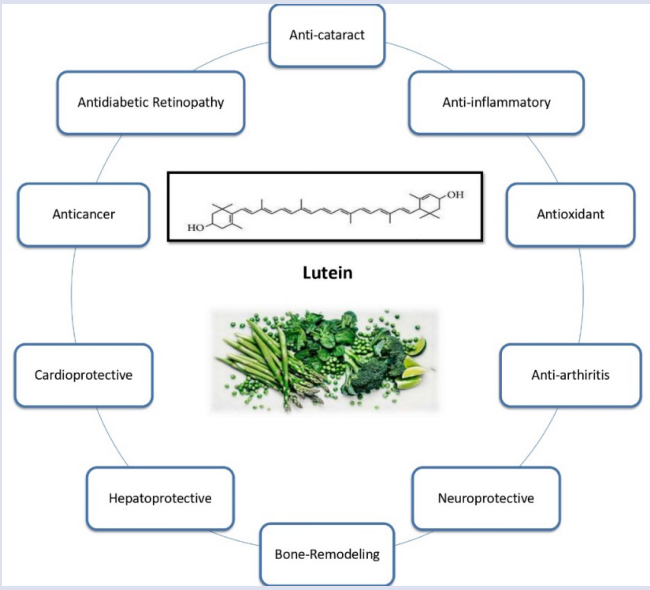

Figure 3: Biological activities and therapeutic potentials of lutein.

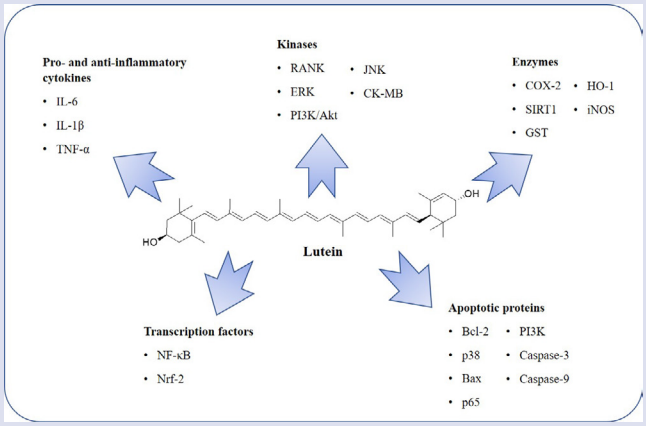

Figure 4: Multiple molecular targets of lutein. It could regulate the kinase, pro- and anti-inflammatory cytokines, enzymes, apoptotic proteins and transcriptional factors. The detailed information has been summarized in Table 1. All the abbreviations are available in the main text.

Table 1: An overview of some important underlying molecular mechanisms for different biological properties of lutein.

Biological Property	Mechanism	Reference
Antioxidant	• ↑ mRNA • ↓ Oxidative stress (OS) • ↓ ROS • ↓ NIK/IKK • ↓ PI3K/PTEN/Akt	Kim *et al.*[21]; Sindhu *et al.*[20]
Hepatoprotection	• ↑ mRNA • ↑ Protein expressions of Nrf-2 (NQO1, HO-1 and GST)	Li *et al.*[23]
Treatment for osteoarthritis	• ↓ NF-κB and COX-2 • ↓ IL-6, TNF-α and IL-1β • ↓ Cleavage of caspase-3	Qiao *et al.*[26]
Neuroprotection	• ↑ Endogenous oxidative system • ↓ TNF-α, IL-1β and NO formation • ↑ Phosphorylation of ERK1/2 • ↓ p3, JNK- and Akt-stimulated NF-κB activation • ↓ ROS	Wu *et al.*[36]; Binawade and Jagtap[30]; Nataraj *et al.*[31]
Anti-inflammatory	• ↓ TNF-α and IL-1β • ↓ iNOS and COX-2	Kim *et al.*[21]
Cardioprotection	• ↓ CK-MB • ↓ cTn T • ↓ IL-1β, IL-6, TNF-α • ↓ NF-κB p65 • ↓ Caspase-3 and -9 • Regulates Nrf-2/HO-1	Ouyang *et al.*[38]
Antidibetic retinopathy	• ↑ SIRT1 mRNA	Hwang *et al.*[48]
Anticancer	• Regulates 3-kinase (PI3K)/Akt phosphoinositide	Zhang *et al.*[53]
Bone Remodeling	• ↓ mRNA RANKL	Takeda *et al.*[54]
Treatment for burn-induced multiple organ injury	• ↓ TNF-α and caspase-3 • ↓ ROS	AbuBakr *et al.*[57]
Treatment for optic nerve injury	• ↓ MDA, IL-1β and TNF-α	Karakurt *et al.*[58]
Treatment for severe traumatic brain injury	• ↓ IL-1β, IL-6 and MCP-1 • Regulates NF-κB p65/ICAM-1/Nrf-2	Tan *et al.*[59]

Note: *↑ indicates increased response and ↓ indicates decreased response. All the abbreviations are available in the main text.

Antioxidant activity

Lutein was reported as potent antioxidant compound against hydroxyl (HO•), peroxyl (ROO•), superoxide anion (O2•-) and hypochlorous acid (HOCl) than other carotene and lycopene.[15-17] Interestingly, its antioxidant function has been due to the beneficial effects of lutein. The effect of lutein (1 mg/kg, p.o., for five days) on methotrexate (MTX)-induced (20 mg/kg, i.p.) pulmonary toxicity in rats was investigated by Mammadov *et al.*[18]. A significant restoration of malondialdehyde (MDA), myeloperoxidase (MPO), total glutathione (GSH), interleukin (IL)-1β (IL-1β) and tumor necrosis alfa (TNF-α) levels in the lung tissues to normalcy was observed in lutein-treated groups. Additionally, the histopathological findings supported the above findings and indicated that lutein may be useful in the treatment of MTX-induced oxidative lung damage. He *et al.*[19] has investigated the protective effects and mechanisms of lutein on lipopolysaccharide (LPS)-induced uveitis in mice. The nitric oxide (NO) levels were substantially decreased after the administration of lutein (125 and 500 mg/kg , p.o., for five days).

In addition, lutein lowered MDA content, increased radical absorbance potential of oxygen, glutathione (GSH), vitamin C levels, total activity of superoxide dismutase (SOD) and GSH peroxidase (GPx). In addition, copper-zinc SOD, manganese SOD, and GPx mRNA expressions were increased, further supporting the protective effects of lutein against oxidative damages. Lutein scavenges superoxide radicals, hydroxyl radicals, and inhibited *in-vitro* lipid peroxidation.[20] The researchers also reported that lutein-treated mice (50, 100 and 250 mg/kg, p.o., for one month) inhibited superoxide generation in macrophages and significantly increased the activity of catalase, SOD, GSH reductase and GSH levels in the blood and the liver while GSH peroxidase and GSH-S-transferase activity have also been found to increase in liver tissue.[20] According to Kim *et al.*[21], other than antioxidant activity, lutein has an anti-inflammatory effects where a reduction in intracellular hydrogen peroxide (H_2O_2) was seen. Moreover, exogenous H_2O_2 also induced the phosphorylated activations of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-inducing kinase (NIK), phosphatidylinositol 3-kinase (PI3K) and the oxidative inactivation of phosphatase and tensin homolog (PTEN), an early stage of the modulators of NF-κB activation. The overall effect was the regulation of the reactive oxygen species (ROS)-mediated redox of the NIK/inhibitory κB kinase (IKK) and PI3K/PTEN/Akt signaling pathways essential for NF-κB stimulation and the consequent expression of the inflammatory genes regulated by NF-κB.

Hepatoprotective activity

Kim *et al.*[22] found that lutein in the liver and the eyes of guinea pigs fed a hypercholesterolemic diet reduced inflammation and oxidative stress (OS). Another study indicated that supplementation with lutein could protect against accumulation of hepatic lipids and insulin resistance caused by a high-fat diet.[23] In a hypercholesterolemic diet given to guinea pigs, Murillo *et al.*[24] used lutein nanoemulsion (3.5 mg/day, for six weeks) and reported a rise in plasma and liver concentrations of this carotenoid, in addition to a point decrease in plasma alanine aminotransferase (ALT), total liver cholesterol and hepatic steatosis. All these results designate that lutein's nanoemulsion has protective effects on hepatic steatosis. The protective mechanism of lutein (40 mg/kg, intragastrically for five weeks) against arsenic trioxide-induced hepatotoxicity (4 mg/kg, also administered intragastrically for five weeks) in a mice model has been reported by Li *et al.*[23]. Lutein treatment reversed all changes in liver morphology and indices, resulting in a significant improvement in the liver function compared with the group treated with arsenic(III)-oxide. In addition, treatment with lutein increased the antioxidant enzyme activity and attenuated the rise in ROS and MDA as induced by arsenic(III)-oxide. In addition, lutein increases mRNA and protein expressions of NF-E2-related factor 2 (Nrf-2) signaling related genes [NADPH quinone dehydrogenase 1 (NQO1), heme oxygenase-1 (HO-1) and glutathione S-transferase (GST)] thus confirming that lutein can reduce OS-induced reproductive injury by triggering Nrf-2 signals. This result also suggests a possible antioxidant mechanism for lutein to prevent hepatotoxicity, indicating that lutein can mitigate liver damage, particularly as an arsenicosis therapy.[23]

Osteoarthritis

The anti-inflammatory effects of lutein in the inflammation caused by LPS in macrophages and skin inflammation were mediated by down-regulating inflammatory proteins and cytokine expression.[21,25] By reducing the OS and inflammation, lutein suppresses arthrosclerosis.[21] Qiao *et al.*[26] investigated the protective influence of lutein on the osteoarthritis caused by monosodium iodoacetate (MIA) in primary chondrocyte cells. Lutein treatment significantly improved chondrocyte cell viability, and provided substantial cytoprotection effects by enhancing antioxidant defense mechanisms and decreasing OS (both ROS and lipid peroxidation). In addition, lutein exhibited some anti-inflammatory effects by down-regulating the inflammatory proteins [NF-κB and cyclooxygenase (COX)-2] and pro-inflammatory cytokines including IL-6, tumor necrosis factor alpha (TNF-α) and IL-1β. Through maintaining the mitochondrial membrane potential and raising cysteine-aspartic proteases (Caspase)-3 activity, lutein reduced MIA-induced apoptosis. A significant cytoprotection was conferred by lutein against MIA-induced OS, inflammation, and apoptosis as a result of the modulatory effect of activations of NF-κB and Nrf-2.[26]

Neuroprotective activity

Several studies have demonstrated neuroprotective activity of the lutein against retinal ischemic damage.[27-29] Nevertheless, some researchers have found that lutein has protected neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 3-nitropropionic acid (3-NP) damage caused by Parkinson's and Huntington's disease models, respectively[30,31], and also enhances declarative memory for mice.[32] In addition, Wang *et al.*[33] and Milaneschi *et al.*[34] found low plasma lutein levels associated with depressive symptoms in patients with Alzheimer's disease, and predicted the emergence of a new depressive frame from older people. Quite recently, Zeni *et al.*[35] demonstrated that treatment with lutein has had an antidepressant-like impact involving OS and reducing neurochemical abnormalities. Wu *et al.*[36] investigated the impact of lutein on neuroinflammation of BV-2 microglia triggered by LPS. Before LPS administration (1 μg/ml at 12 h), pretreatment with lutein (50 μM) resulted in a significant inhibition of the functions of inducible NO synthase and COX-2, as well as TNF-α, IL-1β and NO formation. In addition, the analysis showed that lutein suppressed LPS-induced NF-κB activation by inhibiting phosphorylated p38 kinase, c-Jun N-terminal kinase (JNK), and Akt kinase. In addition, lutein significantly quenched ROS and enhanced HO-1 and NQO1 by enhancing phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) mediated Nrf-2 activation. Overall, the findings indicated that while promoting ERK-induced Nrf-2, lutein mitigates neuroinflammation in LPS-activated BV-2 microglia by inhibiting p3, JNK- and Akt-stimulated NF-κB activation, it indicates that lutein is a potential dietary preventive agent in inflammation-related neurodegenerative disorders.[36]

Anti-inflammatory activity

The effects of lutein on endotoxin-induced uveitis in rats was investigated by Jin *et al.*[37]. Lutein at two doses (10 and 100 mg/kg) caused reduction in the number of inflammatory cells although the dose of 1 mg/kg of lutein, was insufficient. Additionally, lutein had similar inhibition of inflammatory mediators as dexamethasone (1 mg/kg) when administered at 100 mg/kg. In the study, lutein reduced NO production of the aqueous humour. Furthermore, lutein has also inhibited the expression of inducible NO synthase (iNOS) in LPS-stimulated RAW cells. Thus, it appears that by blocking the protein expression of iNOS, lutein can ameliorate NO production. The data also indicated that lutein increases the expression of LPS-induced COX-2 in RAW264.7 cells, as well as the production of prostaglandin E2 (PGE2) in aqueous humour. Overall, the findings indicated that lutein has potential anti-inflammatory effects on endotoxin-induced uveitis by inhibiting the signalling pathway based on NF-κB and subsequently producing pro-inflammatory mediators. Kim *et al.*[21] confirmed lutein's inhibitory activity on LPS-induction which causes an increase in NO and PGE2 productions as well as suppression of LPS-induced secretion of TNF-α and IL-1β. Moreover, based on Western blot analysis, peritoneal macrophages stimulated LPS elevation of protein levels (iNOS, COX-2, TNF-α and IL-1β proteins and mRNA) which can be suppressed in a dose-dependent manner by co-treatment with lutein. Lutein with strong anti-inflammatory activity has been shown to be a long-lasting anti-inflammatory agent. Thus, lutein can also be used as a therapy for inflammation for different forms of inflammatory diseases.

Lutein can exert its anti-inflammatory activity by inhibiting various molecules that play a role in inflammation.

Cardioprotective activity

The biochemical and histopathological changes of lutein (40 mg/kg, p.o., for 28 days) against isoproterenol (ISO)-induced (85 mg/kg, s.c., for two consecutive days) myocardial infarction (MI) rat model was evaluated by Ouyang *et al.*[38]. Their results suggested that pretreatment with lutein "significantly reduced infarction size, lipid peroxidation product, cardiac markers [(lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB) and cardiac troponin T (cTn T)], inflammatory markers (IL-1β, IL-6, TNF-α and NF-κB p65), and apoptotic markers (caspase-3 and -9)".[38] In addition, lutein significantly increased antioxidant levels [catalase (CAT) and SOD] as well as dramatically upregulated HO-1 and Nrf-2 protein expressions. In addition, lutein significantly reversed all the histopathological changes and thus confirmed its cardioprotection.[38]

Anti-cataract activity

Results indicate that lutein has a potential role to play in reducing cataract risk.[39] The antioxidant function of lutein, along with its ability to suppress the blue light reaching the photoreceptors, can be due to its properties preventing cataracts.[40] Lutein plays a key antioxidant role in the retina and thus protects the eye from inflammation and OS.[41,42] To date, most data have been obtained on the protective function of lutein in the health of the eye in relation to age-related macular degeneration.[43] According to Manayi *et al.*[44], generation of ROS and reactive nitrogen species (NOS) in the eyes pose as risk factors in the initiation and progression of cataracts which may be ameliorated by the intake of antioxidants from the diet. Lutein which have high antioxidants activities may play a substantial role in this regards. Padmanabha and Vallikannan[45] investigated the effects of lutein-fatty acid combination on cataract formation in laboratory rats. From the study, it is reported that the risk of cataract development is reduced with the administration of dietary antioxidants particularly lutein and zeaxanthin. Lutein's anti-cataract activity is believed to be contributed by its high presence of eicosapentaenoic and docosahexaenoic acids, relative to linoleic or oleic acids. The antioxidant activity of lutein is combined with the inflammatory mediators of eicosanoids of fatty acids, resulting in the protective effects seen against the development of cataracts. The results suggest that the combined use of lutein and omega-3 fatty acid to prevent cataracts can effectively regulate both OS and inflammation.

Antidiabetic retinopathy

Latest findings have demonstrated that lutein administration inhibits high glucose-caused OS and reduces retinopathy in diabetic rats.[46,47]. According to the capability of lutein to moderate retinal inflammation and OS[41-43,46,47], it is particularly important to evaluate if this dietary carotenoid has anti-aging effects in retinal cells. Hwang *et al.*[48] researched the impact of lutein on premature senescence caused by hyperglycemia in a human retinal pigment epithelium (ARPE-19) cells. In ARPE-19 cells, a spontaneously immortalised cell line derived from human RPE, lutein inhibited significantly the premature senescence caused by high development of glucose and ROS. Lutein significantly increased the SIRT1 mRNA and protein levels, suggesting that by upregulating the expression of SIRT1, lutein exercised its encouraging special effects in those cells.[48] Resveratrol, another SIRT1 activator, mimicked lutein's inhibitory effects on both highly glucose-induced premature senescence and development of ROS. Sirtinol, a common SIRT1 inhibitor, blocked the effects of lutein, by contrast. These findings collectively suggest that by modulating SIRT1 signaling, lutein affects with the RPE senescence induced by hyperglycemia.[48] According to Nentwich and Ulbig[49], blindness tend to occur in the working-age group of individuals mostly as a result of microvascular complications of diabetes, also known as diabetic retinopathy. Oxidative damage is widely recognized as one of the root causes for diabetic retinopathy. The macular pigments found at the man central retina composed of three hydroxycarotenoids 1) lutein 2) zeaxanthin and 3) meso-zeaxanthin. These hydroxycarotenoids help to neutralize ROS by preventing oxidative damage to the retina, which is also known as biological antioxidants. In addition to their primary antioxidant roles, the carotenoids have also been shown to confer neuroprotective and anti-inflammatory activities on the retina. Neelam *et al.*[50] reported that the studies conducted using experimental animal models provides good evidence on the role of carotenoid in ameliorating oxidative damage as a result of diabetic retinopathy aetiopathogenesis. Additionally, macular carotenoids of lutein and zeaxanthin can prevent the development and/or progression of diabetic retinopathy by 1) improving OS [decreased in ROS with a concomitant increase in antioxidants] 2) increasing neuroprotection and 3) attenuating inflammation.

Anticancer activity

In-vitro studies have shown that lutein (10 μM) inhibited significantly the proliferation of human cervical carcinoma (HeLa) cells. Additionally, lutein inhibited the proliferation of HeLa cells by dose-dependent induction of apoptosis.[51] HeLa cells treated with lutein also showed enhanced accumulation of ROS associated with significant downregulation of Bcl-2 (anti-apoptotic) expression and upregulation of Bax (pro-apoptotic). Moreover, lutein mediated caspase-3 activation and inconsistency between the Bax and Bcl-2 sequences, resulting in a substantial loss of the HeLa cells' mitochondrial membrane potential.[51] In addition, terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assays showed substantial nuclei damage to DNA in lutein-treated HeLa cells, demonstrating the important role of lutein in the final apoptosis process.[51] Lutein is also potentially chemopreventive biomolecule and/or chemotherapeutic against HeLa.[51] The results are supported by research carried out by Grudzinski *et al.*[52], which investigated the cytotoxic effect of lutein on normal human epithelial colon cells (CCD 841 CoTr) and adenocarcinoma cells (HT-29), in which lutein showed some cytotoxic activity towards cancer cells but not against normal cells.

Zhang *et al.*[53] investigated the anticancer activity of lutein against A549, a lung cancer cell lines. Apoptosis induction by lutein in A549 was investigated using TUNEL and 4',6-diamidino-2-phenylindole (DAPI) staining assays to validate the molecular mechanism that is expected to occur through the regulation of 3-kinase (PI3K)/Akt phosphoinositide signaling molecules that are often affected by cancer. Results suggested that lutein inhibits the signaling pathway for PI3K/Akt and induces apoptosis in A549. Consequently, it has been proposed that lutein is a potent natural anticancer compound treating lung cancer without conferring major effects.[53] Previous *in-vitro* and *in-vivo* studies have reported that carotenoids are protective against certain types of cancer.[54] This statement is supported by a study by Gong *et al.*[55] in which, when several carotenoids were evaluated on breast cancer cell lines, lutein was found to significantly inhibit breast cancer cell growth by causing cell cycle arrest as well as increased apoptosis, thus resulting in increased ROS production that sequentially mediate inhibition of breast cancer cells growth. It is therefore suggested lutein's selective cytotoxic effects in breast tumours. The findings are further confirmed in another study where El-Raey *et al.*[8] indicated that the inhibitory effect of lutein is exerted by anti-tumour promotion (Epstein-Barr virus) and anti-tumour support (aberrant crypt foci). Besides, lutein also prevents skin tumorigenesis and promotes the dual-stage skin carcinogenesis, thus lessening the number of aberrant crypt foci in the rat colon. Sathasivam and Ki[56] also reported that dietary intake of carotenoids including lutein can decrease the risk of developing colon cancer. Lutein is one of the potential candidate, and this review supports its therapeutic

activity against cancer cell lines and some of the challenges related to its development as an adjuvant chemotherapeutic agent.

Bone remodelling activity

Takeda *et al.*[54] reported that the administration of lutein (1% w/w) in experimental mice enhanced bone mass in the growing mice occurring due to suppression of bone resorption and stimulation of bone formation. It was also reported that lutein can exert bone remodelling activity by the osteoblast cultures. In general, lutein stimulates bone formation while preventing bone resorption *in-vitro. In-vivo,* lutein administration increased femoral bone mass in male mice. The osteocalcin mRNA expressions, considered a standard mature osteoblast marker, were clearly induced by bone-inducing factors but lutein did not affect the expression.[54] Overall, based on the *in-vivo* study, lutein elevates the bone mass of growing male and female mice. Therefore, lutein clearly ameliorates bone-resorption as confirmed in cultured mouse calvaria by pit formation as well as due to the formation of osteoclasts from precursor cells. Additionally, lutein acts on 1) macrophages and osteoclast precursor cells, thus suppressing osteoclast formation depending on receptor activator of nuclear factor kappa-B ligand (RANKL) and 2) osteoblasts while suppressing osteoclast differentiation by inhibiting mRNA RANKL expression as induced by the osteoblast bone resorbing factor.[54] Thus, it has been concluded that lutein facilitates bone turnover and can be helpful to human bone health.

BENEFICIAL EFFECTS OF LUTEIN IN HUMAN WELL BEING

Burn-induced multiple organ injury

Thermal injury may lead to multiple organ dysfunctions resulting from the release of pro-inflammatory mediators and ROS. AbuBakr *et al.*[57] studied the protective effect of lutein on the remote organs in rats from thermal injury. Lutein administration (250 mg/kg , p.o., for three days) resulted in amelioration of the burn-induced biochemical and molecular changes as well as histopathological improvements. Rat-induced scald injury triggered the lutein enhanced apoptosis, oxidative damage, liver and kidney dysfunctions. Overall, lutein ameliorated serum activity aspartate amino transferase (AST), ALT and lactate dehydrogenase (LDH), serum BUN (Blood urea nitrogen), creatinine levels, tissue MDA and 8-Oxo-2'-deoxyguanosine (8-OHdG) levels with tissue GSH elevation, as well as CAT and SOD movements, thereby protecting against thermal trauma. In addition, due to its anti-apoptosis and anti-inflammatory activity, the tissue levels of TNF-α and caspase-3 have decreased.[57]

Optic nerve injury

Ethambutol and isoniazid are considered as first-line treatment in tuberculosis although they are associated with serious adverse effects, which is the optic nerve injury. A recent study conducted by Karakurt *et al.*[58] reported lutein administration (0.5 mg/kg, p.o., 14 days) was significantly effective in preventing isoniazid-(50 mg/kg, p.o., 14 days) and ethambutol-(50 mg/kg, p.o., 14 days) induced toxic optic neuropathy. Moreover, MDA, IL-1β and TNF-α levels in the lutein-administered group were significantly decreased in the blood samples and tissues obtained from rats. On the other hand, total GSH levels in serum and tissue of the group administered with lutein were significantly higher indicating that lutein has a significant effect in protecting from optic nerve injury.[58]

Severe Traumatic Brain Injury (STBI)

Tan *et al.*[59] investigated the mechanistic protective effect of lutein (40, 80 and 160 mg/kg, p.o., 5 weeks) against severe traumatic brain injury (STBI) in rats. They reported a significant protective effects against STBI by reducing IL-1β, IL-6 and monocyte chemoattractant protein-1 (MCP-1) expressions, serum ROS levels, SOD and GPx activities. The findings indicated that lutein protects against STBI, has anti-inflammatory and antioxidant effects and alters the expression of intracellular adhesion molecule (ICAM)-1/Nrf-2. Moreover, lutein rescued the inhibition of skilled motor functions caused by STBI and reduced the contusion volume in STBI rats.[59] Additionally, lutein altered the expression of anti-oxidative and inflammation-associated protein. The protective effect of lutein in the STBI model is purported to be mediated via its effects on an NF-κB p65/ICAM-1/Nrf-2 signalling pathway, thus suggesting that lutein may be developed as a drug for the treatment of STBI.[59]

IMPROVED FORMULATIONS OF LUTEIN

Lutein has low bioavailability due to its lipophilic nature, resulting in poor aqueous solubility before it reaches the circulatory system and targeted organs. Therefore, its improved oral formulation should be investigated. In a recent study, Bodoki *et al.*[60] has successfully developed a medium in enhancing the bioavailability of lutein, which is lutein Poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs). The release profile of lutein from PLGA NPs suspended in phosphate buffered saline showed that the majority of lutein (~70%) trapped in PLGA NPs were released within the first 48 h. Additionally, the diffusion assessments confirmed the movement of the embodied nano-trapped lutein across semi-permeable membranes into the bio-adhesive, thermosensitive hydrogel. However, lutein permeation is significantly restricted by the low water solubility of the antioxidant, which reaches a stable state within 24 h. The dependence of lutein's transfer rate on the cellulose membrane pore size suggests a bioactive permeation that is assisted by micelles.[60] It was anticipated that the inclusion of different types of nano-trapped lutein in thermosensitive bio-adhesive hydrogel may increase permeation into the eyes by extending the residence period at the administration site while retaining the bioactive form of the antioxidant.[60] Huang *et al.*[61] prepared microspheres of lutein-alginate using a calcium chloride gelation process to boost the antioxidant capabilities of lutein. Experiments on *in-vitro* release found that under acidic conditions, the microspheres presented slower releases than under neutralintestinal conditions. In the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, the antioxidant activity of microencapsulated lutein was greater than free lutein. Lutein stability in microspheres has been substantially improved compared to free lutein at different temperatures, indicating feasibility of microspheres filled with lutein as functional antioxidant ingredient in food products.[61]

APPLICATIONS OF LUTEIN IN THE FOOD PRODUCT INDUSTRIES

In general, lutein polyene is backbone and susceptible to extreme conditions in food processing which results in molecular degradation. The energy in the form of light, heat and mechanical stress can disrupt molecular conjugation, causing colour loss and the loss of biological activity.[12] Nowadays, commercial lutein production involves a four step process; cultivation, pre-treatment, processing and fine processing. Currently, fresh tagetes flowers (marigolds) are the raw material utilised in lutein extraction in which they are collected and sent to processing plants. Their hydrophobic nature is almost entirely confined to carotenoids in the lipid systems (emulsions) with significant quantities present in very fine dispersions capable of colouring aqueous matrices, making carotenoids useful as colouring dietary matrices in lipid phases. Carotenoids are the main contributor to the colour of food products including oils, lards, dressings, margarine and butter. The colour instilled in cookies, cake frosting and doughnuts or in any bakery items are dependent on the temperature. Therefore, high-temperature

exposed during the processing process, including the use of deep-frying oils, may affect carotenoid stability. A continuous research in the field of carotenoid chemistry and formulations will improve and facilitate the development of new production methods that may increase its application in food matrices and expand the market with wider applications.[62] Although carotenoids are mostly stored inside the chloroplast in plant cells, protecting them from the outside contact with other cell components, they remain prone to degradation due to environmental stress following the lost of cell integrity.

New developments are currently under study to improve carotenoid's stability. Microencapsulation method introduced by Rigon and Noreña[63] can lessen the oxidation of bioactive compounds in foods and allow better powder dispersal in water. Other techniques suggested by Brum *et al.*[64] used to stabilize lutein include nanoemulsion and nanocapsules, where a particle size of smaller than 1 µm can significantly facilitate lutein's solubility, thus improving its bioavailability and stability. The previous study conducted by Boon *et al.*[7], reported that chitosan nanoparticles can improve lutein's solubility and stability (by 58%) when compared to polyethylene glycol nanocapsules. Nanoencapsulation is an efficient technique to incorporate lipophilic carrier molecules such as carotenoids. Depending on the membrane thickness of the multilayer emulsions around the droplets, carotenoids can be protected against light, resulting in reduction of degradation. Besides, the use of opaque and airtight containers also helps to avoid direct contact with oxygen and light. Additionally, freezing or cooling, as well as the inclusion of antioxidants and a nitrogen-rich environment can reduce pigment losses.[7]

DISCUSSION

Lutein which is a naturally occurring carotenoids synthesized only by plants, but not in animals and humans, have been commercialized as health supplements. Miedema *et al.*[65] indicated a significant correlation between the consumption of fruits and vegetables intake during young adulthood and the prevalence of coronary artery calcium later in life. Young adults in the top tertile who consumed an average of 7-9 servings of fruits and vegetables per day have approximately 25% lower risk of getting coronary artery calcium after 20 years of follow up, as compared to young adults who consumed only 2-4 servings of fruits and vegetable per day. Besides, an adequate level of lutein intake was also associated with a protective effect against burn-injury, severe traumatic brain injury, as well as reducing the adverse effect induced by certain medications including optic neuropathy, lung and liver injuries. Many biological mechanisms have been suggested on the possible beneficial influence of lutein on cardiometabolic health. Overall, the combinational mechanisms suggest that lutein is beneficial to the overall health, as well as for specific organ systems. Nevertheless, since lutein is a fat-soluble pigment in nature, its bioavailability is considerably low to an extent that it impeded sufficient exertion of its beneficial effects. Thus, a current study successfully formulated poly lactic-co-glycolic acid (PLGA) nanoparticles of lutein which can improve lutein's bioavailability.[60]

In this review, we highlighted the comprehensive literature reports on chemical and biological properties of lutein. However, for determining the causality of these associations, additional research and randomised, controlled trials are needed. Furthermore, there is a need for more studies on the effects of lutein during foetal development, infancy and childhood to investigate the effects of lutein over lifetime. Numerous studies have shown that large doses of lutein, either by diet or a dietary supplement, have beneficial effects on eye disorders, preventing or even improving both age-related macular and cataract degeneration. However, inadequate consumption of lutein do not cause any harm to the human body. Yet the presence of lutein somehow can preserve the quality of life of human due to its various protective activities, especially as antioxidants. Since humans cannot synthesize lutein, it should be consumed from dietary sources or supplementation. Nevertheless, available evidence indicates that serum lutein concentrations ranging from 0.6 –1.05 mmol/l (350–600 mg/l) can be reached through dietary means and could be considered a possible 'goal' to promote health and prevent disease.

Promising stabilization techniques such as nanoemulsions and microencapsulation should be more widely explored. They have shown to increase the lutein stability and bioavailability without compromising its biological activity and pigmentation capacity. However, the lack of information based on *in-vivo* models requires further investigations to know the absorption, metabolic pathways and mechanism of action of lutein in humans. Additionally, the intrinsic properties of the food matrix (ripening state), processing (thermal or mechanical) and the existence of other dietary components such as fats, fiber or phyto-sterols influence lutein's bio-accessibility and bioavailability from the same matrix differently. Nevertheless, all these factors do not act singly, but interact with one another in ways that should be further investigated. More mechanistic oriented basic research is needed in the future to elucidate the mechanism of actions.

CONCLUSION AND FUTURE PERSPECTIVES

This review provided extensive details about chemical, pharmacological and therapeutic potentials of lutein, that is found in many green vegetables. Lutein has gained worldwide recognition for its many health benefits that mainly appear to function through its antioxidant and anti-inflammatory mechanisms. Evidence shows lutein can help to treat multiple diseases including cataracts, arthritis, diabetic retinopathy and cancer. Lutein also act as an cardioprotecive and neuroprotective compound as well. The studies also revealed that it can also help in managing multiple organ injury, optic nerve injury and severe traumatic brain injury. In addition, a relatively small dose will offer health benefits for people not diagnosed with health conditions. The underlying mechanisms of these pharmacological effects are diverse and seem to involve regulation of different molecular targets, including inflammatory cytokines (IL-6, IL-1β, and TNF-α), protein kinases (RANK, ERK, PI3K/Akt, JNK, and CK-MB), apoptotic-related proteins (Bcl-2, p38, Bax, p65, PI3K, caspase-3 and caspase-9), and enzymes (COX-2, SIRT1, GST, HO-1 and iNOS). Lutein also modulates the activity of NF-κB, Nrf-2 and its signaling pathways in various pathological conditions. In the future, further clinical trials are warranted to confirm its therapeutic efficacy and utilization in phytopharmaceuticals as well as food supplement in humans.

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CONFLICTS OF INTEREST

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ABBREVIATIONS

3-NP, 3-Nitropropionic Acid; 8-OHdG, 8-Oxo-2'-Deoxyguanosine; ALT, Alanine Transaminase; ARPE-19, Human Retinal Pigment Epithelium ; AST, Aspartate Transaminase; BUN, Blood Urea Nitrogen; CAC, Coronary Atherosclerosis Calcium; CAT, Catalase; CK-MB, Creatine Kinase-MB; COX-2, Cyclooxygenase-2; cTnT, Cardiac Troponin T; DAPI, 6-Diamidino-2-Phenylindole; DPPH, 2,2-Diphenyl-1-Picrylhydrazyl; GPx, GSH Peroxidase; GSH, Glutathione; GST,

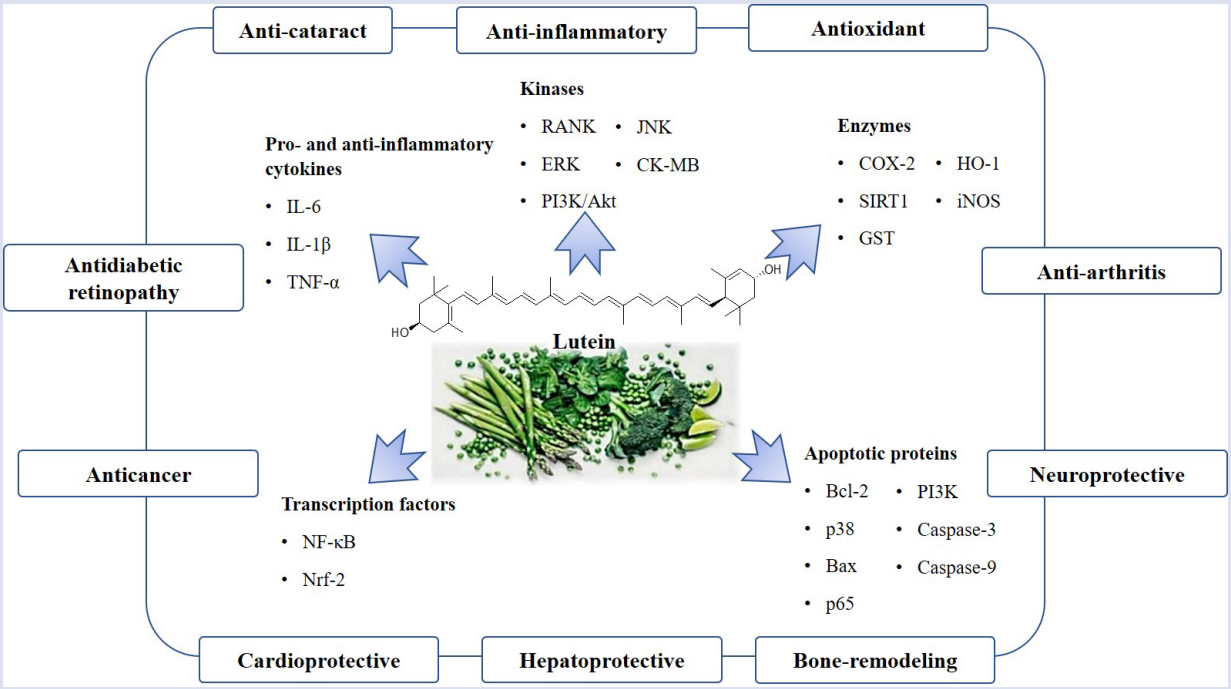
Glutathione S-Transferase; H_2O_2, Hydrogen Peroxide; HeLa, Human Cervical Carcinoma; HO•, Hydroxyl; HO-1, Heme Oxygenase-1; HPLC, High Performance Liquid Chromatography; HOCl, Hypochlorous Acid; ICAM, Intercellular Adhesion Molecule; IL, Interleukin; IKK, Inhibitory Kb Kinase; iNOS, Inducible Nitric Oxide Synthase; ISO, Isoproterenol; JNK, C-Jun N-Terminal Kinase ; LDH, Lactate Dehydrogenase; LDL, Low-density Lipoprotein; LPS, Lipopolysaccharide; MCP-1, Monocyte Chemoattractant Protein 1; MDA, Malondialdehyde; MI, Myocardial Infarction; MIA, Monosodium Iodoacetate; MPO, Myeloperoxidase; MPTP, Tetrahydropyridine; mRNA, Messenger RNA; MTX, Methotrexate; MZ, Meso-Zeaxanthin; NF-κB, Nuclear Factor NF-Kappa-B; NIK, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-Kb)-Inducing Kinase; NMR, Nuclear Magnetic Resonance; NO, Nitric Oxide; NOS, Nitrogen Species; NPs, Nanoparticles; NQO1, NADPH Quinone Dehydrogenase 1; Nrf-2, Nuclear Factor Erythroid 2-Related Factor 2; O2•-, Superoxide Anion; OS, Oxidative Stress; PGE2, Prostaglandin E2; PI3K, Phosphatidylinositol 3-Kinase; PLGA, Poly(Lactic-Co-Glycolic Acid); PTEN, Phosphatase and Tensin Homolog; RANKL, Receptor Activator of Nuclear Factor Kappa-B Ligand; ROO•, Peroxyl; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; STBI, Severe Traumatic Brain Injury; TNF-α, Tumour Necrosis Factor-Alpha; TUNEL, Terminal Deoxynucleotidyl Transferase-Mediated Dutp Nick End-Labeling; UV, Ultraviolet.

REFERENCES

1. Perrone S, Tei M, Longini M, Buonocore G. The multiple facets of lutein: a call for further investigation in the perinatal period. Oxid Med Cell Longev. 2016;2016:5381540.
2. Khachik F, Bernstein PS, Garland DL. Identification of lutein and zeaxanthin oxidation products in human and monkey retinas. Investig Ophthalmol Vis Sci. 1997;38:1802-11.
3. Roberts JE, Dennison J. The photobiology of lutein and zeaxanthin in the eye. J Ophthalmol. 2015;2015:687173.
4. Pezdirc K, Hutchesson MJ, Williams RL, Rollo ME, Burrows TL, Wood LG, *et al.* Consuming high-carotenoid fruit and vegetables influences skin yellowness and plasma carotenoids in young women: a single-blind randomized crossover trial. J Acad Nutr Diet. 2016;116:1257-65.
5. Granado F, Olmedilla B, Blanco I. Nutritional and clinical relevance of lutein in human health. Br J Nutr. 2003;90:487-502.
6. Qv XY, Zeng ZP, Jiang JG. Preparation of lutein microencapsulation by complex coacervation method and its physicochemical properties and stability. Food Hydrocoll. 2011;25:1596-1603.
7. Boon CS, McClements DJ, Weiss J, Decker EA. Factors influencing the chemical stability of carotenoids in foods. Crit Rev Food Sci Nutr. 2010;50:515-32.
8. El-Raey MA, Ibrahim GE, Eldahshan OA. Lycopene and lutein; A review for their chemistry and medicinal uses. J Pharmacogn Phytochem. 2013;2:245-54.
9. Ribaya-Mercado JD, Blumberg JB. Lutein and zeaxanthin and their potential roles in disease prevention. J Am Coll Nutr. 2004;23:567S-87S.
10. Johnson EJ. A biological role of lutein. Food Rev Int. 2004;20:1-16.
11. Gabrielska J, Gruszecki WI. Zeaxanthin (dihydroxy-β-carotene) but not β-carotene rigidifies lipid membranes: a 1H-NMR study of carotenoid-egg phosphatidylcholine liposomes. BBA-Biomembranes. 1996;1285:167-74.
12. Becerra MO, Contreras LM, Lo MH, Díaz JM, Herrera GC. Lutein as a functional food ingredient: Stability and bioavailability. J Funct Foods. 2020;66:103771.
13. Abdel-Aal ESM, Akhtar H, Zaheer K, Ali R. Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health. Nutrients. 2013;5:1169-85.
14. Albert GI, Hoeller U, Schierle J, Neuringer M, Johnson EJ, Schalch W. Metabolism of lutein and zeaxanthin in rhesus monkeys: identification of (3R, 6′ R)-and (3R, 6′ S)-3′ -dehydro-lutein as common metabolites and comparison to humans. Comp Biochem Physiol B Biochem Mol Biol. 2008;151:70-8.
15. Li H, Deng Z, Liu R, Loewen S, Tsao R. Carotenoid compositions of coloured tomato cultivars and contribution to antioxidant activities and protection against H_2O_2-induced cell death in H9c2. Food Chem. 2013;136:878-88.
16. Sun Z, Li T, Zhou ZG, Jiang Y. Microalgae as a source of lutein: chemistry, biosynthesis, and carotenogenesis. Adv Biochem Eng Biotechnol. 2015:331.
17. Wang M, Tsao R, Zhang S, Dong Z, Yang R, Gong J, *et al.* Antioxidant activity, mutagenicity/anti-mutagenicity, and clastogenicity/anti-clastogenicity of lutein from marigold flowers. Food Chem Toxicol. 2006;44:1522-9.
18. Mammadov R, Suleyman B, Akturan S, Cimen FK, Kurt N, Suleyman Z, *et al.* Effect of lutein on methotrexate-induced oxidative lung damage in rats: a biochemical and histopathological assessment. Korean J Intern Med. 2019;34:1279.
19. He RR, Tsoi B, Lan F, Yao N, Yao XS, Kurihara H. Antioxidant properties of lutein contribute to the protection against lipopolysaccharide-induced uveitis in mice. Chin Med 2011;6:1-8.
20. Sindhu ER, Preethi KC, Kuttan R. Antioxidant activity of carotenoid lutein *in vitro* and *in vivo*. Indian J Exp Biol. 2010;48:843-8.
21. Kim JH, Na HJ, Kim CK, Kim JY, Ha KS, Lee H, *et al.* The non-provitamin A carotenoid, lutein, inhibits NF-κB-dependent gene expression through redox-based regulation of the phosphatidylinositol 3-kinase/PTEN/Akt and NF-κB-inducing kinase pathways: role of H_2O_2 in NF-κB activation. Free Radic Biol Med. 2008;45:885-96.
22. Kim JE, Clark RM, Park Y, Lee J, Fernandez ML. Lutein decreases oxidative stress and inflammation in liver and eyes of guinea pigs fed a hypercholesterolemic diet. Nutr Res Pract. 2012;6:113-9.
23. Li S, Ding Y, Niu Q, Xu S, Pang L, Ma R, *et al.* Lutein has a protective effect on hepatotoxicity induced by arsenic via Nrf2 signaling. Biomed Res Int. 2015;2015:315205.
24. Murillo AG, Aguilar D, Norris GH, DiMarco DM, Missimer A, Hu S, *et al.* Compared with powdered lutein, a lutein nanoemulsion increases plasma and liver lutein, protects against hepatic steatosis, and affects lipoprotein metabolism in guinea pigs. J Nutr. 2016;146:1961-9.
25. Oh J, Kim JH, Park JG, Yi Y-S, Park KW, Rho HS, *et al.* Radical scavenging activity-based and AP-1-targeted anti-inflammatory effects of lutein in macrophage-like and skin keratinocytic cells. Mediators Inflamm. 2013;2013:787042.
26. Qiao YQ, Jiang PF, Gao YZ. Lutein prevents osteoarthritis through Nrf2 activation and downregulation of inflammation. Archives Med Sci. 2018;14:617-24.
27. Choi J-S, Kim D, Hong Y-M, Mizuno S, Joo C-K. Inhibition of nNOS and COX-2 expression by lutein in acute retinal ischemia. Nutrition. 2006;22:668-71.
28. Li SY, Fu ZJ, Ma H, Jang WC, So KF, Wong D, *et al.* Effect of lutein on retinal neurons and oxidative stress in a model of acute retinal ischemia/reperfusion. Investig. Investig Ophthalmol Vis Sci. 2009;50:836-43.
29. Sasaki M, Yuki K, Kurihara T, Miyake S, Noda K, Kobayashi S, *et al.* Biological role of lutein in the light-induced retinal degeneration. J Nutr Biochem. 2012;23:423-9.
30. Binawade Y, Jagtap A. Neuroprotective effect of lutein against 3-Nitropropionic acid-induced Huntington's disease-like symptoms: Possible behavioral, biochemical, and cellular alterations. J Med Food. 2013;16:934-43.
31. Nataraj J, Manivasagam T, Thenmozhi AJ, Essa MM. Lutein protects dopaminergic neurons against MPTP-induced apoptotic death and motor dysfunction by ameliorating mitochondrial disruption and oxidative stress. Nutr Neurosci. 2016;19:237-46.
32. Do Prado Silva JT, Geiss JMT, Oliveira SM, da Silva Brum E, Sagae SC, Becker D, *et al.* Nanoencapsulation of lutein and its effect on mice's declarative memory. Mater Sci Eng C. 2017;76:1005-11.
33. Wang W, Shinto L, Connor WE, Quinn JF. Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity. J Alzheimers Dis. 2008;13:31-8.
34. Milaneschi Y, Bandinelli S, Penninx BW, Corsi AM, Lauretani F, Vazzana R, *et al.* The relationship between plasma carotenoids and depressive symptoms in older persons. World J Biol Psychiatry. 2012;13:588-98.
35. 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.
36. Wu W, Li Y, Wu Y, Zhang Y, Wang Z, Liu X. Lutein suppresses inflammatory responses through Nrf2 activation and NF-κB inactivation in lipopolysaccharide-stimulated BV-2 microglia. Mol Nutr Food Res. 2015;59:1663-73.
37. Jin XH, Ohgami K, Shiratori K, Suzuki Y, Hirano T, Koyama Y, *et al.* Inhibitory effects of lutein on endotoxin-induced uveitis in Lewis rats. Investig Ophthalmol Vis Sci. 2006;47:2562-68.
38. 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;57:529-35.
39. Koushan K, Rusovici R, Li W, Ferguson LR, Chalam KV. The role of lutein in eye-related disease. Nutrients. 2013;5:1823-39.
40. Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, *et al.* Lutein, zeaxanthin, and meso-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. Prog Retin Eye Res. 2016;50:34-66.
41. Eisenhauer B, Natoli S, Liew G, Flood VM. Lutein and zeaxanthin-food sources, bioavailability and dietary variety in age-related macular degeneration protection. Nutrients. 2017;9:120.

42. Jia YP, Sun L, Yu HS, Liang LP, Li W, Ding H, *et al.* The pharmacological effects of lutein and zeaxanthin on visual disorders and cognition diseases. Molecules. 2017;22:610.
43. Liu R, Wang T, Zhang B, Qin L, Wu C, Li Q, *et al.* Lutein and zeaxanthin supplementation and association with visual function in age-related macular degeneration. Investig Ophthalmol Vis Sci. 2015;56:252-8.
44. Manayi A, Abdollahi M, Raman T, Nabavi SF, Habtemariam S, Daglia M, *et al.* Lutein and cataract: from bench to bedside. Crit Rev Biotechnol. 2016;36:829-39.
45. Padmanabha S, Vallikannan B. Fatty acids modulate the efficacy of lutein in cataract prevention: Assessment of oxidative and inflammatory parameters in rats. Biochem Biophys Res Commun. 2018;500:435-42.
46. Kowluru RA, Zhong Q, Santos JM, Thandampallayam M, Putt D, Gierhart DL. Beneficial effects of the nutritional supplements on the development of diabetic retinopathy. Nutr Metab. 2014;11:1-10.
47. Sasaki M, Ozawa Y, Kurihara T, Kubota S, Yuki K, Noda K, *et al.* Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia. 2010;53:971-9.
48. Hwang JS, Han SG, Lee CH, Seo HG. Lutein suppresses hyperglycemia-induced premature senescence of retinal pigment epithelial cells by upregulating SIRT1. J Food Biochem. 2018;42:e12495.
49. Nentwich MM, Ulbig MW. Diabetic retinopathy-ocular complications of diabetes mellitus. World J Diabetes. 2015;6:489.
50. Neelam K, Goenadi CJ, Lun K, Yip CC, Eong KGA. Putative protective role of lutein and zeaxanthin in diabetic retinopathy. Br J Ophthalmol. 2017;101:551-8.
51. Gansukh E, Mya KK, Jung M, Keum YS, Kim DH, Saini RK. Lutein derived from marigold (Tagetes erecta) petals triggers ROS generation and activates Bax and caspase-3 mediated apoptosis of human cervical carcinoma (HeLa) cells. Food Chem Toxicol. 2019;127:11-8.
52. Grudzinski W, Piet M, Luchowski R, Reszczynska E, Welc R, Paduch R, *et al.* Different molecular organization of two carotenoids, lutein and zeaxanthin, in human colon epithelial cells and colon adenocarcinoma cells. Spectrochim Acta A Mol Biomol Spectrosc. 2018;188:57-63.
53. Zhang WL, Zhao YN, Shi ZZ, Cong D, Bai YS. 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. 2018;37;341-50.
54. Takeda H, Tominari T, Hirata M, Watanabe K, Matsumoto C, Grundler FM, *et al.* Lutein enhances bone mass by stimulating bone formation and suppressing bone resorption in growing mice. Biol Pharm Bull. 2017;40:716-21.
55. Gong X, Smith JR, Swanson HM, Rubin LP. Carotenoid lutein selectively inhibits breast cancer cell growth and potentiates the effect of chemotherapeutic agents through ROS-mediated mechanisms. Molecules. 2018;23:905.
56. Sathasivam R, Ki JS. A review of the biological activities of microalgal carotenoids and their potential use in healthcare and cosmetic industries. Mar Drugs. 2018;16:26.
57. AbuBakr HO, Aljuaydi SH, Abou-Zeid SM, El-Bahrawy A. Burn-induced multiple organ injury and protective effect of lutein in rats. Inflammation. 2018;41:760-72.
58. Karakurt Y, Süleyman H, Keskin Cimen F, Tasli G, Ucak T, Icel E, *et al.* The effects of lutein on optic nerve injury induced by ethambutol and isoniazid: an experimental study. Cutan Ocul Toxicol. 2019;38:136-40.
59. 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. 2017;16:4235-40.
60. Bodoki E, Vostinaru O, Samoila O, Dinte E, Bodoki AE, Swetledge S, *et al.* Topical nanodelivery system of lutein for the prevention of selenite-induced cataract. Nanomed Nanotechnol Biol Med. 2019;15:188-97.
61. Huang J, Bai F, Wu Y, Ye Q, Liang D, Shi C, *et al.* Development and evaluation of lutein-loaded alginate microspheres with improved stability and antioxidant. J Sci Food Agric. 2019;99:5195-201.
62. Rodriguez-Amaya DB. Natural food pigments and colorants. Curr Opin Food Sci. 2016;7:20-6.
63. Rigon RT, Noreña CPZ. Microencapsulation by spray-drying of bioactive compounds extracted from blackberry (*Rubus fruticosus*). J Food Sci Technol. 2016;53:1515-24.
64. Brum AAS, dos Santos PP, da Silva MM, Paese K, Guterres SS, Costa TMH, *et al.* Lutein-loaded lipid-core nanocapsules: Physicochemical characterization and stability evaluation. Colloids Surf A Physicochem Eng Asp. 2017;522:477-84.
65. Miedema MD, Petrone A, Shikany JM, Greenland P, Lewis CE, Pletcher MJ, *et al.* Association of fruit and vegetable consumption during early adulthood with the prevalence of coronary artery calcium after 20 years of follow-up: The coronary artery risk development in young adults (CARDIA) study. Circulation. 2015;132:1990-8.

GRAPHICAL ABSTRACT



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