Letter to the editor:

CURRENT RESULTS ON THE POTENTIAL HEALTH BENEFITS OF LUTEIN

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Dear Editor,

Lutein is a nutritionally beneficial organic tetraterpenoid pigment; its molecular formula and weight are $C_{40}H_{56}O_2$ and 568.87144 g/mol, respectively. It is responsible for the yellow color of fruits and vegetables and is found in high levels in parsley, spinach, kale, egg yolk, and lutein-fortified foods (Shegokar and Mitri, 2012).

Lutein has a wide range of beneficial health effects including antioxidant, antiinflammatory, antiatherogenic, antihypertensive, antidiabetic, antiulcer, and anticancer effects (Miyazawa et al., 2013; Johnson, 2014; Erdman et al., 2015; Manayi et al., 2015). Furthermore, it is used to prevent eye diseases including age-related macular degeneration (AMD), cataract, and retinitis pigmentosa (Koushan et al., 2013; Sulich et al., 2015).

The commercial value of lutein is growing with the customary age-related macular degeneration applications. The lutein market is segmented into pharmaceutical, nutraceutical, food, pet foods, cosmetics, and animal and fish feed. Lutein shows a range of biological activities and health benefits in animals; therefore, herein, we have reviewed the most recent studies on lutein and its biological and pharmacological activities (Table 1).

Table 1: Recent studies on lutein and its biological and pharmacological activities

Key findings	Reference
Interestingly, the combination of lutein with vitamin C which is responsible to improve the total antioxidant defense system properties in Sprague-Dawley (SD) rats is found by Song et al. (2015)	Song et al., 2015
The intestinal absorption of both micellar and dietary lutein has been en- hanced by phosphatidylcholine content. This implies that lutein deficiency in aged rats can be improved by phosphatidylcholine. On the other hand lutein bioavailability also enriched in lutein deficiency rats by phosphatidyl- choline which is either in free or bound form with food matrices.	Sheshappa et al., 2015

Key findings	Reference
Higher intakes of lutein-containing foods, including green leafy vegetables, were associated with higher levels of physical activity. Increasing the consumption of lutein-rich foods may have a positive effect on levels of physical activity.	Crichton et al., 2015
In order to identify the role of lutein in human brain, study of relationship between lutein and metabolic pathways is an important and useful criterion. Fundamental understanding of the relationships between lutein correlation with lipid pathway metabolites, energy pathway metabolites, brain osmo- lytes, amino acid neurotransmitters, and the antioxidant homocarnosine plays an important role for further analysis specifically in brain develop- ment.	Lieblein-Boff et al., 2015
Lutein treatment exerted potent antioxidant and anti-inflammatory effects and offered significant cytoprotection against alcohol-induced liver injury.	Du et al., 2015
Lutein protects against skeletal ischemia/reperfusion injury by downregu- lating oxidative stress and inflammatory mechanisms.	Cheng et al., 2015
Lutein has positive effects on non-alcoholic fatty liver disease via the modu- lation of hepatic lipid accumulation and insulin resistance.	Qiu et al., 2015
Lutein has potential beneficial effects in diabetes-induced testicular dam- age, probably through its antioxidant and anti-inflammatory properties.	Fatani et al., 2015
Lutein attenuates neuroinflammation in lipopolysaccharide-activated BV-2 microglia, partly through the inhibition of p38-, c-Jun N-terminal kinase (JNK)-, and Akt-stimulated NF-κB activation and promotion of extracellular signal-regulated kinase-induced NF-E2-related factor 2 activation, suggesting that it has great potential as a nutritional preventive strategy in inflammation-related neurodegenerative disorders.	Wu et al., 2015
Long-term lutein supplementation could increase serum lutein concentra- tion, macular pigment optical density (MPOD), and visual sensitivity in early age-related macular degeneration (AMD) patients. The advisable long-term lutein dosage for early AMD treatment is 10 mg daily.	Huang et al., 2015
Lutein has antioxidant properties and can thus prevent hepatotoxicity. This finding also suggests that dietary lutein may be a potential treatment for liver diseases, especially arsenicosis.	Li et al., 2015
New evidence supports the antiatherogenic properties of lutein and the mechanism of action underlying its atherosclerosis-preventive effect involves improvements in oxidative stress and lipid metabolism.	Han et al., 2015
Lutein modulates the expression of growth- and survival-associated genes in prostate cancer cells.	Rafi et al., 2015
In the case of lutein supplementation it inhibits the systemic activation of the complement system. This finding is the strong evidence for the reported beneficial effects about the management of AMD.	Tian et al., 2015
It is important to mention here that lutein/zeaxanthin-based dye solutions accomplished a safe profile for <i>in vitro</i> and <i>in vivo</i> studies. This result has been shown as a better choice for staining intraocular structures.	Casaroli-Marano et al., 2015
Even though lutein supplementation is useful for enhancing visual acuity based on improving MPOD done by Wang et al. (2014), but still more research work is still needed to give appropriate conclusive evidence. In the case of dosage per day analysis it is found that milder dose is much effective compared to higher dose.	Wang et al., 2014
The intestinal absorption of lutein and zeaxanthin may be improved by physiological and pharmacological interventions affecting high-density lipoprotein (HDL) metabolism.	Niesor et al., 2014

Table 1 (cont.): Recent studies on lutein and its biological and pharmacological activities

Key findings	Reference
Lutein can inhibit platelet-derived growth factor-BB induced migration of ret- inal pigment epithelium cells through the inhibition of both cytoplasmic and mitochondrial Akt activation.	Su et al., 2014
It is well known that lutein has antioxidant properties. That administration of lutein affords strong neuroprotective effect against transient cerebral ische- mic injury is the strong evidence for its exclusive antioxidant properties.	Sun et al., 2014
Lutein-fortified formula was safe and well-tolerated and supported the physical growth of evaluated infants.	Kon et al., 2014
Silk lutein extract enhanced both innate and adaptive immune functions, and may prove to be an effective supplement to strengthen immunity.	Promphet et al., 2014
Lutein and zeaxanthin alone or in association with brilliant blue showed a good safety profile in this experimental model.	Furlani et al., 2014
Lutein might scavenge reactive species and induce the expression of genes related to a better antioxidant response, thereby improving oxygen transport. The improvement in the redox state of cells through lutein treatment could be related to the antigenotoxic and antioxidant effects of lutein.	Serpeloni et al., 2014
It is important to mention here that the voluntary running of rats is the very good choice to enhance effective utilization of lipids. Interestingly the lutein level in the blood of rats significantly decreased with exercise. Therefore voluntary running and lutein fortified milk both are the combined source for utilization of lipids.	Matsumoto et al., 2014
Lutein is a promising content in medical field especially neural development in preterm infants. Regarding the preferential accumulation and mainte- nance of lutein have been studied and reported by Vishwanathan et al. (2014). This study is a pathway for further investigations regarding preterm infants.	Vishwanathan et al., 2014
Higher lutein, zeaxanthin, and vitamin C concentrations in plasma are in- corporated with prolonged leukocyte telomere length in common elderly humans and indicate a defensive role of these vitamins in telomere mainte- nance.	Sen et al., 2014
Nowadays Alzheimer's disease (AD) mortality in adults becomes global concern. Lycopene, lutein and zeaxanthin are the important factors in serum which are responsible to induce AD mortality in adults. From the results it is evident that above mentioned three factors should be high in serum level. Therefore it is concluded that from the findings high intake of lycopene, lutein and zeaxanthin enriched foods only can meet out the requirements to reduce the risk of AD mortality.	Min and Min, 2014
Nowadays age-related cataract (ARC) has paramount of importance among aged people. Lutein and zeaxanthin contents are suitable candi- dates to reduce the risk of age-related cataract (ARC). Hence the proper in- take of lutein and zeaxanthin plays key source for ARC prevention espe- cially for nuclear cataract.	Ma et al., 2014
The novel powerful agents named lutein and zeaxanthin which are having great importance in AMD therapy successfully extracted from <i>Fructus lycii</i> . <i>In vitro</i> and <i>in vivo</i> studies clearly explains beneficial role of active components lutein and zeaxanthin in AMD therapy.	Xu et al., 2013a
Lutein is a promising material extensively used for body weight and neuro- behavioral alterations, attenuated oxidative stress, and improved the activi- ty of the mitochondrial enzymes complex in rat brain. The performance of lutein against the Huntington's disease is also studied and reported.	Binawade et al., 2013

Table 1 (cont.): Recent studies on lutein and its biological and pharmacological activities

Key findings	Reference
Intestinal damage during conventional chemotherapy is a major challenge in rats for researches. Interestingly, lutein pre-treatment is a best choice to prevent intestinal damage. Form this study the methotrexate-induced apop- tosis of IEC-6 cells originating from rat jejunum crypt was studied and ex- plained in proper way.	Chang et al., 2013
In order to control the inflammatory pathway of the innate immune system lutein is an appropriate choice for researches. It possesses simple method to control the circulating levels of complement factors includes C5a and C3d.	Tian et al., 2013
Constant light conditions during the perinatal period may induce some neuronal abnormalities in both offspring and mother that may be partially ameliorated by the antioxidant effects of dietary lutein.	Yajima et al., 2013
Lutein has significant antihypertensive and antioxidant effects against hypertension induced by N(G)-nitro-L-arginine methyl ester hydrochloride in rats.	Sung et al., 2013
Usage of lutein has been extensively applied in medical field especially for preterm infants due to its excellent biological antioxidant property. Many researches are going on to understand the excellent biological activity of lute- in for preterm infants. But this research area is still required novel and in- novative pathways and solutions in developing new drugs for preterm in- fants.	Costa et al., 2013
Lutein supplementation reduced the levels of biomarkers of cardiovascular diseases by decreasing the lipid peroxidation and inflammatory response by increasing plasma lutein concentration and antioxidant capacity.	Wang et al., 2013
Daily supplementation with 20 mg of lutein increases macular pigment opti- cal density. Lutein may improve the ability to drive at night and to perform other spatial discrimination tasks under low illumination.	Yao et al., 2013
Atherosclerosis is a well-known vascular disease. It is reported that high lu- tein level in serum can regulate serum lipids and cytokines which are re- sponsible for early atherosclerosis. From this study it is evident that lutein level in serum plays a key role to control vascular diseases.	Xu et al., 2013b
Lutein has protective effects against B(a)P-induced oxidative stress, possibly by combating oxidative stress by its free radical scavenging activity.	Vijayapadma et al., 2014
Fundamental understanding of lutein exhibits rich and fascinating proper- ties of lutein in biomedical field. It is a potent neuroprotective agent that can salvage photoreceptors in rats. From the observations it is concluded that lutein is a milestone of drug designing process for various diseases.	Woo et al., 2013
The antiulcer activity of lutein may be attributable to the inhibition of oxida- tive stress produced by alcohol. These findings suggest the potential thera- peutic use of lutein as an effective antiulcer agent.	Sindhu et al., 2012

Table 1 (cont.): Recent studies on lutein and its biological and pharmacological activities

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

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.

Casaroli-Marano RP, Sousa-Martins D, Martínez-Conesa EM, Badaró E, Nunes RP, Lima-Filho AA, et al. Dye solutions based on lutein and zeaxanthin: in vitro and in vivo analysis of ocular toxicity profiles. Curr Eye Res. 2015;40:707-18.

Chang CJ, Lin JF, Chang HH, Lee GA, Hung CF. Lutein protects against methotrexate-induced and reactive oxygen species-mediated apoptotic cell injury of IEC-6 cells. PLoS One. 2013;8:e72553.

Cheng F, Zhang Q, Yan FF, Wan JF, Lin CS. Lutein protects against ischemia/reperfusion injury in rat skeletal muscle by modulating oxidative stress and inflammation. Immunopharmacol Immunotoxicol. 2015;37:329-34.

Costa S, Giannantonio C, Romagnoli C, Vento G, Gervasoni J, Persichilli S, et al. Effects of lutein supplementation on biological antioxidant status in preterm infants: a randomized clinical trial. J Matern Fe-tal Neonatal Med. 2013;26:1311-5.

Crichton G, Elias M, Alkerwi A, Buckley J. Intake of Lutein-rich vegetables is associated with higher levels of physical activity. Nutrients. 2015;7:8058-71.

Du SY, Zhang YL, Bai RX, Ai ZL, Xie BS, Yang HY. Lutein prevents alcohol-induced liver disease in rats by modulating oxidative stress and inflammation. Int J Clin Exp Med. 2015;8:8785-93.

Erdman JW Jr, Smith JW, Kuchan MJ, Mohn ES, Johnson EJ, Rubakhin SS, et al. Lutein and brain function. Foods. 2015;4:547-64.

Fatani AJ, Al-Rejaie SS, Abuohashish HM, Al-Assaf A, Parmar MY, Ahmed MM. Lutein dietary supplementation attenuates streptozotocin-induced testicular damage and oxidative stress in diabetic rats. BMC Complement Altern Med. 2015;15:204.

Furlani BA, Barroso L, Sousa-Martins D, Maia M, Moraes-Filho MN, Badaro E, et al. Lutein and zeaxanthin toxicity with and without brilliant blue in rabbits. J Ocul Pharmacol Ther. 2014;30:559-66.

Han H, Cui W, Wang L, Xiong Y, Liu L, Sun X, et al. Lutein prevents high fat diet-induced atherosclerosis in ApoE-deficient mice by inhibiting NADPH oxidase and increasing PPAR expression. Lipids. 2015;50: 261-73. Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. Biomed Res Int. 2015;2015:564738.

Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev. 2014;72:605-12.

Kon IY, Gmoshinskaya MV, Safronova AI, Alarcon P, Vandenplas Y. Growth and tolerance assessment of a lutein-fortified infant formula. Pediatr Gastroenterol Hepatol Nutr. 2014;17:104-11.

Koushan K, Rusovici R, Li W, Ferguson LR, Chalam KV. The role of lutein in eye-related disease. Nutrients. 2013;5:1823-39.

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.

Lieblein-Boff JC, Johnson EJ, Kennedy AD, Lai CS, Kuchan MJ. Exploratory metabolomic analyses reveal compounds correlated with lutein concentration in frontal cortex, hippocampus, and occipital cortex of human infant brain. PLoS One. 2015;10:e0136904.

Ma L, Hao ZX, Liu RR, Yu RB, Shi Q, Pan JP. A dose-response meta-analysis of dietary lutein and ze-axanthin intake in relation to risk of age-related cata-ract. Graefes Arch Clin Exp Ophthalmol. 2014;252: 63-70.

Manayi A, Abdollahi M, Raman T, Nabavi SF, Habtemariam S, Daglia M, et al. Lutein and cataract: from bench to bedside. Crit Rev Biotechnol. 2015;8:1-11.

Matsumoto M, Hagio M, Inoue R, Mitani T, Yajima M, Hara H, et al. Long-term oral feeding of luteinfortified milk increases voluntary running distance in rats. PLoS One. 2014;9:e93529.

Min JY, Min KB. Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults. Dement Geriatr Cogn Disord. 2014;37: 246-56.

Miyazawa T, Nakagawa K, Kimura F, Nakashima Y, Maruyama I, Higuchi O, et al. Chlorella is an effective dietary source of lutein for human erythrocytes. J Oleo Sci. 2013;62:773-9.

Niesor EJ, Chaput E, Mary JL, Staempfli A, Topp A, Stauffer A, et al. Effect of compounds affecting ABCA1 expression and CETP activity on the HDL pathway involved in intestinal absorption of lutein and zeaxanthin. Lipids. 2014;49:1233-43. Promphet P, Bunarsa S, Sutheerawattananonda M, Kunthalert D. Immune enhancement activities of silk lutein extract from Bombyx mori cocoons. Biol Res. 2014;47:15.

Qiu X, Gao DH, Xiang X, Xiong YF, Zhu TS, Liu LG, et al. Ameliorative effects of lutein on nonalcoholic fatty liver disease in rats. World J Gastroenterol. 2015;21:8061-72.

Rafi MM, Kanakasabai S, Gokarn SV, Krueger EG, Bright JJ. Dietary lutein modulates growth and survival genes in prostate cancer cells. J Med Food. 2015;18:173-81.

Sen A, Marsche G, Freudenberger P, Schallert M, Toeglhofer AM, Nagl C, et al. Association between higher plasma lutein, zeaxanthin, and vitamin C concentrations and longer telomere length: results of the Austrian Stroke Prevention Study. J Am Geriatr Soc. 2014;62:222-9.

Serpeloni JM, Cólus IM, de Oliveira FS, Aissa AF, Mercadante AZ, Bianchi ML, et al. Diet carotenoid lutein modulates the expression of genes related to oxygen transporters and decreases DNA damage and oxidative stress in mice. Food Chem Toxicol. 2014; 70:205-13.

Shegokar R, Mitri K. Carotenoid lutein: a promising candidate for pharmaceutical and nutraceutical applications. J Diet Suppl. 2012;9:183-210.

Sheshappa MB, Ranganathan A, Bhatiwada N, Talahalli RR, Vallikannan B. Dietary components affect the plasma and tissue levels of lutein in aged rats with lutein deficiency-a repeated gavage and dietary study. J Food Sci. 2015;80:H2322-30.

Sindhu ER, Kuttan R. Carotenoid lutein protects rats from gastric ulcer induced by ethanol. J Basic Clin Physiol Pharmacol. 2012;23:33-7.

Song MH, Shin EC, Hwang DY, Jang IS. Effects of lutein or lutein in combination with vitamin C on mRNA expression and activity of antioxidant enzymes and status of the antioxidant system in SD rats. Lab Anim Res. 2015;31:117-24.

Su CC, Chan CM, Chen HM, Wu CC, Hsiao CY, Lee PL, et al. Lutein inhibits the migration of retinal pigment epithelial cells via cytosolic and mitochondrial Akt pathways (lutein inhibits RPE cells migration). Int J Mol Sci. 2014;15:13755-67.

Sulich A, Hamułka J, Nogal D. Dietary sources of lutein in adults suffering eye disease (AMD/cataracts). Rocz Panstw Zakl Hig. 2015;66:55-60. Sun YX, Liu T, Dai XL, Zheng QS, Hui BD, Jiang ZF. Treatment with lutein provides neuroprotection in mice subjected to transient cerebral ischemia. J Asian Nat Prod Res. 2014;16:1084-93.

Sung JH, Jo YS, Kim SJ, Ryu JS, Kim MC, Ko HJ, et al. Effect of lutein on L-NAME-induced hypertensive rats. Korean J Physiol Pharmacol. 2013;17:339-45.

Tian Y, Kijlstra A, van der Veen RL, Makridaki M, Murray IJ, Berendschot TT. The effect of lutein supplementation on blood plasma levels of complement factor D, C5a and C3d. PLoS One. 2013;8:e73387.

Tian Y, Kijlstra A, van der Veen RL, Makridaki M, Murray IJ, Berendschot TT. Lutein supplementation leads to decreased soluble complement membrane attack complex sC5b-9 plasma levels. Acta Ophthalmol. 2015;93:141-5.

Vijayapadma V, Ramyaa P, Pavithra D, Krishnasamy R. Protective effect of lutein against benzo(a)pyreneinduced oxidative stress in human erythrocytes. Toxicol Ind Health. 2014;30:284-93.

Vishwanathan R, Kuchan MJ, Sen S, Johnson EJ. Lutein and preterm infants with decreased concentrations of brain carotenoids. J Pediatr Gastroenterol Nutr. 2014;59:659-65.

Wang MX, Jiao JH, Li ZY, Liu RR, Shi Q, Ma L. Lutein supplementation reduces plasma lipid peroxidation and C-reactive protein in healthy nonsmokers. Atherosclerosis. 2013;227:380-5.

Wang X, Jiang C, Zhang Y, Gong Y, Chen X, Zhang M. Role of lutein supplementation in the management of age-related macular degeneration: meta-analysis of randomized controlled trials. Ophthalmic Res. 2014; 52:198-205.

Woo TT, Li SY, Lai WW, Wong D, Lo AC. Neuroprotective effects of lutein in a rat model of retinal detachment. Graefes Arch Clin Exp Ophthalmol. 2013; 251:41-51.

Wu W, Li Y, Wu Y, Zhang Y, Wang Z, Liu X. Lutein suppresses inflammatory responses through Nrf2 activation and NF- κ B inactivation in lipopolysaccharidestimulated BV-2 microglia. Mol Nutr Food Res. 2015;59:1663-73.

Xu X, Hang L, Huang B, Wei Y, Zheng S, Li W. Efficacy of ethanol extract of *Fructus lycii* and its constituents Lutein/Zeaxanthin in protecting retinal pigment epithelium cells against oxidative stress: in vivo and in vitro models of age-related macular degeneration. J Ophthalmol. 2013a;2013:862806. Xu XR, Zou ZY, Xiao X, Huang YM, Wang X, Lin XM. Effects of lutein supplement on serum inflammatory cytokines, ApoE and lipid profiles in early atherosclerosis population. J Atheroscler Thromb. 2013b; 20:170-7.

Yajima M, Matsumoto M, Harada M, Hara H, Yajima T. Effects of constant light during perinatal periods on the behavioral and neuronal development of mice with or without dietary lutein. Biomed Res. 2013; 34:197-204.

Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition. 2013;29:958-64.