Nutraceuticals for infants with retinopathy of prematurity: perspective

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Abstract

Retinopathy of prematurity (ROP) is one of the most common causes of childhood blindness worldwide. Its prevalence is rising as more premature infants are surviving owing to advances in neonatal care. The current treatments for ROP are invasive and may increase the risk of future eye complications. Nutraceuticals (dietary oils, carotenoids, and vitamin supplements) are generally safe for use in children without detrimental adverse effects. Research has demonstrated nutraceuticals' anti-angiogenesis properties and their potential to protect against ROP. Dietary oils suppress inflammation and neovascularization in ROP models when administered intravenously. Carotenoids, such as lutein, promote retinal revascularization in mice. Vitamin A, C, and E supplements are unable to prevent ROP pathogenesis, despite well-documented antioxidative effects. The discrepancy between laboratory and clinical trial results may be due to differences in the dosage that can affect the eye, the outcome measurements used, and the presence of confounders in clinical trials. Future studies should investigate the short- and long-term effects of nutraceuticals on infants' vision.

Key words: Blindness; Child; Hyperoxia; Hypoxia; Retinal neovascularization

Introduction

Childhood blindness accounts for approximately 4% of all blindness cases; children with blindness, on average, live without vision 40 years longer than adults.[1] Retinopathy of prematurity (ROP) is a common cause of childhood blindness worldwide, responsible for 14% of all childhood blindness cases.[2,3] The number of ROP cases increases as supplemental oxygen therapy increases the survival rate of premature babies.[4] The relative hypoxia following oxygen therapy causes neovascularization and blindness in ROP. A Swedish study reported that up to 73% of premature infants have ROP.[5] In a Hong Kong hospital, 16.9% of premature infants are diagnosed with ROP in 2013.[6] ROP as a cause of blindness is expected to increase as neonatal care advances and more premature infants survive.[7]

The current mainstay treatments for ROP are cryotherapy, laser therapy, and intravitreal injection of anti-vascular endothelial growth factor (VEGF).[8] However, these treatments are associated with rare ocular and systemic adverse effects including cataracts, corneal burns, and delayed neurodevelopment.[9-13] A noninvasive, high-efficacy treatment for ROP has yet to be developed.

Nutraceuticals in ROP

Nutraceuticals are natural substances with health benefits in both in vivo and in vitro ROP models.[14] They are widely used in cardiovascular diseases for their antioxidative and anti-inflammatory responses.[15] Nutraceuticals may be less likely to trigger adverse effects in children and may promote

Table. Clinical effects of nutraceuticals on infants with retinopathy of prematurity

Study	Study design	Sample size	Compound used	Route	Dosage	Outcome
Pawlik et al,[26] 2011	Cohort study	68 (treatment group: 44)	20% clinoleic: 50% soybean and olive oil emulsion; 10% omegaven: 50% fish-oil emulsion	Intravenous	Birth weight <1000 g: omegaven 0.15 g + clinoleic 0.35 g Birth weight >1000 g: omegaven 0.35 g + clinoleic 0.65 g	Reduced ROP incidence Reduced risk of laser therapy for infants
Beken et al,[29] 2014	RCT	80 (treatment group: 40)	20% intralipid: soybean oil 200 g/dL 20% SMOFlipid: soybean oil 60 g/dL, MCT 60 g/dL, olive oil 50 g/dL, fish oil 30 g/dL	Intravenous	Birthweight <1000g: 0.5 g lipids per kg Birthweight >1000g: 1.0 g lipids per kg	Reduced ROP incidence
Najm et al,[25] 2017	RCT	78 (treatment group: 41)	Lipid solution (clinoleic or SMOFlipid)	Enteral	6-12 h after birth: 1 g/kg/d with daily increases up to 2 g/kg/d	No difference in ROP incidence
Bernabe-Garcia et al,[31] 2019	RCT	110 (treatment group: 55)	Docosahexaenoic acid	Enteral	75 mg/kg/d	No difference in ROP incidence Reduced risk of stage-3 ROP
Tu et al,[30] 2020	RCT	396 (treatment group: 193)	20% Lipovenoes medium-chain triglycerides: 50% soybean oil SMOFlipid: 30% soybean oil, 25% olive oil, and 15% fish oil	Intravenous	3 g/kg/d	Reduced ROP incidence Reduced the need for anti-VEGF treatment
Hellstrom et al,[32] 2021	RCT	206 (treatment group: 101)	Enteral oil	Enteral	Arachidonic acid 100 mg/kg/d, docosahexaenoic acid 50 mg/kg/d	No difference in ROP incidence Lowered the risk of severe ROP by 50%
Romagnoli et al,[44] 2011	RCT	63 (treatment group: 31)	Lutein + zeaxanthin	Enteral	Lutein 0.5 mg/kg/d Zeaxanthin 0.02 mg/kg/d	No difference in ROP incidence
Dani et al,[42] 2012	RCT	114 (treatment group: 58)	Lutein + zeaxanthin	Enteral	Lutein 0.14 mg daily Zeaxanthin 0.006 mg daily	No difference in ROP incidence
Rubin et al,[19] 2012	RCT	183 (treatment group: 92)	Lutein + zeaxanthin + lycopene + beta-carotene	Enteral	Lutein 211 µg Lycopene 143 µg Beta-carotene 219 µg	No difference in ROP incidence Fewer infants in treatment group developed ROP Significantly greater sensitivity response in rod photoreceptors
Manzoni et al,[43] 2013	RCT	229 (treatment group: 113)	Lutein + zeaxanthin	Enteral	Lutein 0.14 mg daily Zeaxanthin 0.006mg daily	No difference in ROP incidence
Mactier et al,[45] 2012	RCT	89 (treatment group: 42)	Vitamin A	Intramuscular	10000 IU 3 times a week from day 2 for a minimum of 2 weeks or the start of oral feeding	No difference in ROP incidence or severity Weak correlation between retinal sensitivity and total vitamin A intake per kg over the first 4 weeks of life
Sun et al,[49] 2020	RCT	262 (treatment group: 132)	Vitamin A	Enteric	1500 IU/day	Reduced incidence of ROP (mild, type I, and type II)
Darlow et al,[55] 2005	RCT	119 (low dose throughout: 40; low dose for 10 days then high dose: 40; high dose throughout: 39)	Vitamin C	Enteric	Additional 20 mg/kg/day	No difference in ROP incidence or severity
Romero-Maldonado et al,[48] 2021	RCT	90 (treatment group: 48)	Vitamin E	Enteric	12.5 IU every 12 h from 72 h after birth to 28 days	Reduced incidence of ROP Reduced severity of ROP

Abbreviations: RCT=randomized controlled trial, ROP=retinopathy of prematurity, and VEGF=vascular endothelial growth factor

long-term health.[16,17] For example, prolonged carotenoid consumption reduces the risks of atherosclerosis and macular degeneration.[18,19] We aim to review clinical studies of nutraceuticals (dietary oils, carotenoids, and vitamin supplements) for managing ROP (**Table**).

Dietary oils

Dietary oils are mainly found in fatty fish (salmon and trout) and plant-based oils (soybean oil).[20] They contain long-chain polyunsaturated fatty acids (LCPUFAs), including arachidonic acid (AA) and docosahexaenoic acid

(DHA), which are important for infants' neurological and visual development. Indeed, they are given to premature infants for nutrition and immunomodulation.[14] LCPUFAs downregulate tumor necrosis factor α and inhibit cell proliferation, suppressing inflammatory and oxidative responses and thus reducing neovascularization in ROP models.[21-23] Premature infants have lower serum AA levels,[24] so additional LCPUFAs might be therapeutic in ROP. However, not all clinical trials have observed a significant reduction in the incidence of ROP after treatment with enteral LCPUFAs.[25]

The main source of lipids for premature infants is fat emulsions that do not contain DHA.[26] Therefore, supplementary DHA in breast milk is recommended to prevent ROP.[27,28] However, LCPUFAs are effective to reduce both the incidence of ROP and the need for laser or anti-VEGF treatment only when administered intravenously. When LCPUFAs are given enterally, although the severity of ROP reduces, the incidence does not.[26,29-32] This discrepancy implies that premature infants with poor gut development cannot effectively digest LCPUFAs.[33] As the intravenous route is invasive and associated with risks of bruising, inflammation, and infection, different routes of administration for LCPUFA should be considered.

The type of LCPUFA given to premature infants affects the therapeutic effect on ROP. Interactions between different nutraceuticals may be disturbed by the supplementation of certain LCPUFAs.[34] Simple administration of DHA and AA has a limited effect on the incidence of ROP.[31,32] Further investigation into the optimum dosage, formulation, and route of administration is required before LCPUFAs can be used therapeutically.

Carotenoids

Carotenoids are pigments found mainly in dark green vegetables and egg yolk. They are obtained exclusively from diet and are essential to the formation of macular pigment.[35,36] Lutein, in particular, reduces inflammation by lowering the number of glial fibrillary acidic protein and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling-positive apoptotic cells after retinal hypoxia in both in vitro and in vivo mouse models.[37,38] In the human body, lutein is found mostly in the macula and the lens, with anti-oxidative effects. It protects against cataracts and age-related macular degeneration by blocking blue light.[8,39] It is 'generally regarded as safe' by the United States Food and Drug Administration.[40]

Lutein promotes retinal revascularization and reduces vascular leakage in oxygen-induced retinopathy mouse models,[41] but no such effects have been observed in clinical trials. Adding lutein to human milk has no significant protective effect against ROP development.[19,42-44] However, in one study, only 8% of mild ROP infants developed severe ROP after treatment with supplementary lutein, compared to 28% in controls; infants with supplementary lutein have significantly greater rod photoreceptor sensitivity responses.[19]

Discrepancy between laboratory and clinical data may be related to the absorption of lutein supplements. Lutein is lipophilic, so effective enteral absorption is difficult, especially in premature infants because the transfer of lipophilic nutrients occurs during the later weeks of pregnancy.[19] As a result of poor absorption, the plasma lutein levels are not high enough to exert a neuro-protective and revascularization effect on the retina. Dissolving lutein in olive oil to increase its absorption and bioavailability has been suggested.[14]

Vitamin supplements

Vitamins A, C, and E all have antioxidative effects. Vitamin A is found mainly in leafy green vegetables, fish oils, milk, and eggs; vitamin C in citrus fruits and bell peppers; and vitamin E in nuts and seeds. Vitamin A (retinol) increases the availability of rhodopsin for phototransduction, which reduces the demand for oxygen in photoreceptor development;[45] vitamin C exerts its antioxidant effect by electron donation and transfer;[46] and vitamin E inhibits the production of new oxygen radicals while neutralizing existing ones.[47] They potentially protect against oxidative damage in ROP.

Both vitamins A and E are used to reduce the risk of developing respiratory complications such as bronchopulmonary dysplasia and respiratory distress syndrome. Infants with better lung function have less need for high-concentration oxygen therapy and are therefore less exposed to the oxidative damage that causes ROP.[45,48,49] However, vitamin A's protective effect is only evident when it is administered orally.[49] Intramuscular injection of vitamin A did not reduce ROP incidence.[45] The plasma level of vitamin A does not correlate with body stores, making it difficult to establish an optimal dose.[50] Vitamin E protects polyunsaturated fatty acid from lipoperoxidation, which is involved in ROP pathogenesis.[51,52] Enteric supplementation of vitamin E reduces the risk of ROP in very low-birthweight infants by 60%.[48] However, using vitamin E for ROP prophylaxis may increase the risk of intraventricular hemorrhage during the early days of prematurity.[52]

Vitamin C (ascorbic acid) is an antioxidant and has pro-oxidative effect.[53,54] However, existing clinical studies have not demonstrated any significant reduction in either the incidence or severity of ROP after administration of supplementary ascorbic acid.[55] In fact, excessively high plasma levels of ascorbic acid may increase mortality in the first days of life.[56] Therefore, vitamin C supplementation is not suitable for the prevention of ROP.

Discrepancy between laboratory and clinical evidence

Laboratory studies have demonstrated the benefits of nutraceuticals including anti-angiogenesis, suppression of endothelial growth factor secretion, and reduction of neovascular areas. However, only a few clinical trials

have shown a reduction in the incidence of ROP after administering nutraceuticals.

The dose of nutraceuticals that can reach the eye may be different. Oral, intravitreal, and intraperitoneal administrations are typical in laboratory studies, but oral and intravenous routes are typically used in clinical trials. Different administration routes result in different metabolism and affect the amount of nutraceutical that reaches the retina. Moreover, premature infants' underdeveloped feeding and absorption may reduce the plasma level and efficacy of nutraceuticals. The dosage given in clinical trials is also limited by the unknown effects of nutraceuticals on the infant's overall health. Clinical trials start at a low dose, which may not be enough to be effective. Therefore, the level of nutraceuticals that can induce an effect in clinical trials is difficult to standardize and measure.

Parameters used to quantify outcomes are different. Laboratory studies usually measure the reduction in angiogenesis and inflammation, the suppression of VEGF and angiotensin II, and the reduction in neovascularization area, whereas clinical studies mainly measure ROP incidence and severity. The effects shown in laboratory studies are probably insufficient to reduce the incidence or severity of ROP in clinical studies.

There are confounders in clinical trials. Premature infants differ in birthweight, degree of prematurity, comorbidities, genetic predisposition, and/or quality of care. These factors, which are more standardized in laboratory studies, may affect the efficacy of nutraceuticals in reducing ROP incidence.

Future directions

There is sufficient laboratory-based evidence to confirm that the antioxidative and anti-inflammatory effects of nutraceuticals are effective in preventing ROP. However, clinical trials of nutraceuticals for premature infants to prevent ROP are limited. Most clinical trials investigate the effects of dietary oils, carotenoids, and vitamin supplements, but the effects of flavonoids and herbal formula are less studied. Flavonoids, found in green tea extracts, inhibit angiogenesis and suppress matrix metalloproteinase-2 activity in rats.[57] They are found in bilberries and have antioxidative properties, which help to reduce lipid peroxidation and prevent cell apoptosis.[58,59] Although the mechanisms of action behind most herbs are not well understood, a few standardized herbal formulae such as Guibi-tang and Samul-tang reportedly protect against retinal neovascularization in murine oxygen-induced retinopathy models.[60,61]

The long-term effects of nutraceuticals on visual acuity and neurological development of infants with ROP should be monitored. The interaction effects between nutraceuticals and existing treatments such as anti-VEGF are unclear. For example, vitamin E reduces LCPUFA lipoperoxidation and potentially demonstrates a synergistic effect when given adjunctively with anti-VEGF therapy. More basic and clinical studies on short- and long-term effects of nutraceuticals are warranted.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, CHYL and ACYL were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Acknowledgment

This research was funded by the Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (reference: 09201116).

References

1. *Gilbert C, Foster A. Childhood blindness in the context of VISION 2020--the right to sight. Bull World Health Organ 2001;79:227-32.*
2. *Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. J AAPOS 2012;16:501-7.* Crossref
3. *Gilbert C. Changing challenges in the control of blindness in children. Eye (Lond) 2007;21:1338-43.* Crossref
4. *Baker JP. The incubator and the medical discovery of the premature infant. J Perinatol 2000;5:321-8.* Crossref
5. *Austeng D, Källen KBM, Uwe W. Ewald M, Jakobsson PG,*

Holmström GE. incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. Arch Ophthalmol 2009;127:1315-9. Crossref

6. *Iu LP, Lai CH, Fan MC, Wong IY, Lai JS. Screening for retinopathy of prematurity and treatment outcome in a tertiary hospital in Hong Kong. Hong Kong Med J 2017;23:41-7.* Crossref
7. *Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7:e37-e46.* Crossref
8. *Tsang JKW, Liu J, Lo ACY. Vascular and neuronal protection in the developing retina: potential therapeutic targets for retinopathy of prematurity. Int J Mol Sci 2019;20:4321.* Crossref
9. *Clark D, Mandal K. Treatment of retinopathy of prematurity. Early Hum Dev 2008;84:95-9.* Crossref
10. *Lenis TL, Gunzenhauser RC, Fung SSM, et al. Myopia and anterior segment optical coherence tomography findings in laser-treated retinopathy of prematurity eyes. J AAPOS 2020;24:86.e1-e7.* Crossref
11. *Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol 2012;153:327-33.e1.* Crossref
12. *Hoerster R, Muether P, Dahlke C, et al. Serum concentrations of vascular endothelial growth factor in an infant treated with ranibizumab for retinopathy of prematurity. Acta Ophthalmol 2013;91:e74-5.* Crossref
13. *Morin J, Luu TM, Superstein R, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics 2016;137:e20153218.* Crossref
14. *Tsang JKW, Wolf SA, Pompoes IM, et al. Potential effects of nutraceuticals in retinopathy of prematurity. Life (Basel) 2021;11:79.* Crossref
15. *Shahidi F. Nutraceuticals, Functional foods and dietary supplements in health and disease. J Food Drug Anal 2012;20:226-30.* Crossref
16. *Kalra EK. Nutraceutical: definition and introduction. AAPS PharmSci 2003;5:E25.* Crossref
17. *Chauhan B, Kumar G, Kalam N, Ansari SH. Current concepts and prospects of herbal nutraceutical: a review. J Adv Pharm Technol Res 2013;4:4-8.* Crossref
18. *Riccioni G. Carotenoids and cardiovascular disease. Curr Atheroscler Rep 2009;11:434-9.* Crossref
19. *Rubin LP, Chan GM, Barrett-Reis BM, et al. Effect of carotenoid supplementation on plasma carotenoids, inflammation and visual development in preterm infants. J Perinatol 2012;32:418-24.* Crossref
20. *Kapoor B, Kapoor D, Gautam S, Singh R, Bhardwaj S. Dietary polyunsaturated fatty acids (PUFAs): uses and potential health benefits. Curr Nutr Rep 2021;10:232-42.* Crossref
21. *Shimazawa M, Nakajima Y, Mashima Y, Hara H. Docosahexaenoic acid (DHA) has neuroprotective effects against oxidative stress in retinal ganglion cells. Brain Res 2009;1251:269-75.* Crossref
22. *Fu Z, Lofqvist CA, Shao Z, et al. Dietary omega-3 polyunsaturated fatty acids decrease retinal neovascularization by adipose-endoplasmic reticulum stress reduction to increase adiponectin. Am J Clin Nutr 2015;101:879-88.* Crossref
23. *SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog Retin Eye Res 2005;24:87-138.* Crossref
24. *Lofqvist CA, Najm S, Hellgren G, et al. Association of retinopathy of prematurity with low levels of arachidonic acid: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol 2018;136:271-7.* Crossref
25. *Najm S, Lofqvist C, Hellgren G, et al. Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: a randomized controlled trial. Clin Nutr ESPEN 2017;20:17-23.* Crossref
26. *Pawlik D, Lauterbach R, Turyk E. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. Pediatrics 2011;127:223-8.* Crossref
27. *Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med 2008;36:5-14.* Crossref
28. *Makrides M, Gibson RA, McPhee AJ, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. JAMA 2009;301:175-82.* Crossref
29. *Beken S, Dilli D, Fettah ND, Kabatas EU, Zenciroglu A, Okumus N. The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: a randomized controlled trial. Early Hum Dev 2014;90:27-31.* Crossref
30. *Tu CF, Lee CH, Chen HN, Tsao LY, Chen JY, Hsiao CC. Effects of fish oil-containing lipid emulsions on retinopathy of prematurity in very low birth weight infants. Pediatr Neonatol 2020;61:224-30.* Crossref
31. *Bernabe-Garcia M, Villegas-Silva R, Villavicencio-Torres A, et al. Enteral docosahexaenoic acid and retinopathy of prematurity: a randomized clinical trial. JPEN J Parenter Enteral Nutr 2019;43:874-82.* Crossref
32. *Hellstrom A, Nilsson AK, Wackernagel D, et al. Effect of enteral lipid supplement on severe retinopathy of prematurity: a randomized clinical trial. JAMA Pediatr 2021;175:359-67.* Crossref
33. *Patel RM. Short- and long-term outcomes for extremely preterm infants. Am J Perinatol 2016;33:318-28.* Crossref
34. *Hartnett ME. The prematurity of recommending particular polyunsaturated fatty acid supplements for retinopathy of prematurity. JAMA Ophthalmol 2018;136:277-8.* Crossref
35. *Bernstein PS, Arunkumar R. The emerging roles of the macular pigment carotenoids throughout the lifespan and in prenatal supplementation. J Lipid Res 2021;62:100038.* Crossref
36. *Arunkumar R, Gorusupudi A, Bernstein PS. The macular carotenoids: a biochemical overview. Biochim Biophys Acta Mol Cell Biol Lipids 2020;1865:158617.* Crossref
37. *Li SY, Fung FK, Fu ZJ, Wong D, Chan HH, Lo AC. Anti-inflammatory effects of lutein in retinal ischemic/hypoxic injury: in vivo and in vitro studies. Invest Ophthalmol Vis Sci 2012;53:5976-84.* Crossref
38. *Li SY, Lo AC. Lutein protects RGC-5 cells against hypoxia and oxidative stress. Int J Mol Sci 2010;11:2109-17.* Crossref
39. *Alves-Rodrigues A, Shao A. The science behind lutein. Toxicol Lett 2004;150:57-83.* Crossref
40. *Ranard KM, Jeon S, Mohn ES, Griffiths JC, Johnson EJ, Erdman JW Jr. Dietary guidance for lutein: consideration for intake recommendations is scientifically supported. Eur J Nutr 2017;56(Suppl 3):37-42.* Crossref
41. *Fu Z, Meng SS, Burnim SB, Smith LE, Lo AC. Lutein facilitates physiological revascularization in a mouse model of retinopathy of prematurity. Clin Exp Ophthalmol 2017;45:529-38.* Crossref
42. *Dani C, Lori I, Favelli F, et al. Lutein and zeaxanthin supplementation in preterm infants to prevent retinopathy of*

prematurity: a randomized controlled study. J Matern Fetal Neonatal Med 2012;25:523-7. Crossref

43. *Manzoni P, Guardione R, Bonetti P, et al. Lutein and zeaxanthin supplementation in preterm very low-birth-weight neonates in neonatal intensive care units: a multicenter randomized controlled trial. Am J Perinatol 2013;30:25-32.* Crossref
44. *Romagnoli C, Giannantonio C, Cota F, et al. A prospective, randomized, double blind study comparing lutein to placebo for reducing occurrence and severity of retinopathy of prematurity. J Matern Fetal Neonatal Med 2011;24(Suppl 1):147-50.* Crossref
45. *Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. J Pediatr 2012;160:954-9.e1.* Crossref
46. *Caritá AC, Fonseca-Santos B, Shultz JD, Michniak-Kohn B, Chorilli M, Leonardi GR. Vitamin C: one compound, several uses. Advances for delivery, efficiency and stability. Nanomedicine 2020;24:102117.* Crossref
47. *Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. J Physiol Biochem 2001;57:43-56.* Crossref
48. *Romero-Maldonado S, Montoya-Estrada A, Reyes-Munoz E, et al. Efficacy of water-based vitamin E solution versus placebo in the prevention of retinopathy of prematurity in very low birth weight infants: a randomized clinical trial. Medicine 2021;100:e26765.* Crossref
49. *Sun H, Cheng R, Wang Z. Early vitamin A supplementation improves the outcome of retinopathy of prematurity in extremely preterm infants. Retina (Phila) 2020;40:1176-84.* Crossref
50. *Loerch JD, Underwood BA, Lewis KC. Response of plasma levels of vitamin A to a dose of vitamin A as an indicator of hepatic vitamin A reserves in rats. J Nutr 1979;109:778-86.* Crossref
51. *Perrone S, Negro S, Tataranno ML, Buonocore G. Oxidative stress and antioxidant strategies in newborns. J Matern Fetal Neonatal Med 2010;23(Suppl 3):63-5.* Crossref
52. *Phelps DL, Rosenbaum AL, Isenberg SJ, Leake RD, Dorey FJ. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. Pediatrics 1987;79:489-500.* Crossref
53. *Halliwell B. Vitamin C: antioxidant or pro-oxidant in vivo? Free Radic Res 1996;25:439-54.* Crossref
54. *Carr A, Frei B. Does vitamin C act as a pro-oxidant under physiological conditions? FASEB J 1999;13:1007-24.* Crossref
55. *Darlow BA, Buss H, McGill F, Fletcher L, Graham P, Winterbourn CC. Vitamin C supplementation in very preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2005;90:F117-22.* Crossref
56. *Silvers KM, Gibson AT, Powers HJ. High plasma vitamin C concentrations at birth associated with low antioxidant status and poor outcome in premature infants. Arch Dis Child Fetal Neonatal Ed 1994;71:F40-4.* Crossref
57. *Cao Y, Cao R. Angiogenesis inhibited by drinking tea. Nature 1999;398:381.* Crossref
58. *Tsuda T. Dietary anthocyanin-rich plants: biochemical basis and recent progress in health benefits studies. Mol Nutr Food Res 2012;56:159-70.* Crossref
59. *Wang Y, Zhao L, Lu F, et al. Retinoprotective effects of bilberry anthocyanins via antioxidant, anti-inflammatory, and anti-apoptotic mechanisms in a visible light-induced retinal degeneration model in pigmented rabbits. Molecules 2015;20:22395-410.* Crossref
60. *Lee YM, Kim CS, Jo K, Sohn EJ, Kim JS, Kim J. Inhibitory effect of Samul-tang on retinal neovascularization in oxygen-induced retinopathy. BMC Complement Altern Med 2015;15:271.* Crossref
61. *Lee YM, Lee YR, Kim CS, et al. Effect of Guibi-Tang, a traditional herbal formula, on retinal neovascularization in a mouse model of proliferative retinopathy. Int J Mol Sci 2015;16:29900-10.* Crossref