Review Article

Capsula Eburnea

# LUTEIN: RATIONALE AND ITS USE IN OPTICAL RETINOPATHY OF PREMATURITY

**Rossella Occhipinti**

## SUMMARY

Retinopathy of prematurity (ROP) is one of the most common causes of blindness in premature infants, and its incidence has been increasing markedly. This increase is due to the fact that the survival rates of very premature infants have also increased as a result of scientific progress and widespread availability of technological equipment in neonatal intensive care units. Such infants are exposed to a hyperoxic environment for prolonged periods, that can be hostile to the physiological development of the retina. Therefore, an extensive focus has been placed on the use of carotenoids, antioxidants for excellence, such as lutein and its isomer zeaxanthin, which are used in the prevention of retinal damage caused by oxygen free radicals. The aim of this article is to summarize the current literature on the effects and possible mechanisms of action of lutein and its isomer, and, in particular, to provide information on fundamental lutein sources to premature newborns.

## Introduction

Approximately 5-7 % of infants are born prematurely, with premature births occurring prior to the 37$^{th}$ gestational week being the principal cause of neonatal mortality, morbidity and long-term disability. The retina is the only body tissue that does not develop veins until the fourth gestational month; in fact, the veins reach the nasal periphery after the eight gestational month, not reaching the retinal periphery before the first month after birth. The avascular retina produces VEGF that stimulates vascular migration in the developing retina *in utero*. With a premature birth, VEGF production is down-regulated by the relative hyperoxia and vascular migration is halted, triggering an increase in Reactive Oxygen Species (ROS) that cause irreversible retinal damage [1]. Lutein and zeaxanthin have been shown to be effective in reducing ROS-induced retinal damage.

## Lutein: chemical and biological properties

Lutein is a natural antioxidant that belongs to the carotenoid family (Fig. 1a). Carotenoids are common pigments found in the chloroplast and chromoplasts of plants: these are the organelles responsible for the colours of flowers, fruits and leaves. The carotenoids known to be ingested, absorbed and metabolized by humans, also found in the serum, are five. Undoubtedly, lutein and its isomer zeaxanthin (Fig. 1b) are the most important ones; these two are found selectively concentrated in some human tissues [2]. Once ingested through food or dietary supplements, 50-90% of lutein is eliminated in faeces, while the remaining part is absorbed with the aid of bile and fats digested through diet; lutein is then incorporated into the chylomicrons and transported in the bloodstream to various parts of the body [3]: liver, breast, colon, uterine cervix, and, at

***Address of the author:***
Department of Biological Chemistry, Medical Chemistry and Molecular Biology, University of Catania, Italy.

***Send correspondence to**: Dr. Rossella Occhipinti, rossella6184@yahoo.it*

***Received**: April 1st, 2011 — **Revised**: April 21st, 2011 — **Accepted**: May 6th, 2011*

the ocular level, crystalline lens, iris and retina, where it selectively concentrates in the central region, known as the macula lutea (making up the main component of its pigment) [4].

The preventive action of lutein is due to two key properties: firstly, its antioxidant activity that contributes to the inhibition of free radical formation, and secondly, its scavenging activity that neutralizes free radicals already present in the retina. Numerous studies have demonstrated that a balanced intake of lutein and other essential nutrients, such as vitamins C and E [5], creates a valuable protective effect against photo-oxidative ocular damage; lutein filters light, mainly its blue wavelengths (440nm) that are particularly aggressive and damaging to the delicate macular structure especially in infants, who are certainly more susceptible to blue light-induced damage [6, 7].

## Development of visual function in infants

The development of the human eye involves a complex series of consecutive events that take place up to the first few years of life. At birth, the dioptric apparatus (cornea, aqueous humour, crystalline lens and vitreous body) of mature newborns is well developed, and all structures are transparent to allow the passage of light and focusing of images on the retina. However, the visual capacities of the infant are not yet fully developed, since the visual cortex is still immature at birth; in fact, during the first months of life, an anatomical reorganization of the retinal connections takes place, associated with the development and maturation of the geniculate visual pathway.

Foveal development is completed between the fourth and fifth month of life. Between the 12$^{th}$ and 18$^{th}$ month of life, a critical period for the maturation of visual function takes place, involving the development of certain capacities, such as contrast and spatial sensitivity, perception of colours, movement and speed, shape recognition and depth perception. Many practices used in the delivery room, while efficient as therapy approaches, may be hazardous for the future functions of the infant, such as analgesics administered to the mother, techniques used for minimizing heat loss in the infant, clamping the umbilical cord, phototherapy used to treat jaundice, and the use of 100% oxygen or assisted ventilation in newborns showing signs of asphyxiation. All of these procedures can cause a notable increase in free radicals, leading to retinal damage in the infant. Therefore, maintaining a proper balance between oxidants and antioxidants could help to prevent ocular damage in newborns, especially those born prematurely. Lutein and zeaxanthin could play an important role in protecting the retina in newborns due to their protective and antioxidant properties [8] (see table I).

| ACTIVITY OF LUTEIN |
|---|
| Inhibition of oxidative stress |
| Antioxidant activity |
| Antiradical activity |
| Anti-inflammatory activity |
| Stabilization of cell membranes |
| Induction of detoxifying enzymes |
| Improvement of the immune system |
| INDICATIONS TO USE OF LUTEIN |
| Prevention of age-related macular degeneration |
| Prevention of cataracts |
| Promoting the health and normal function of the eye |
| Protection from reactive oxygen species (ROS) |

Table I. Activity and indication to use of lutein.

## Lutein in neonatal nutrition

Several studies have shown a direct correlation between the plasma lutein levels of the mother and the newborn [9], and it has been shown that lutein and zeaxanthin concentrations are two or three times higher than those of other carotenoids, when present in the mother's diet. Gossage and colleagues [10] have hypothesized that lutein could be actively secreted into breast milk, and not passively diffused like other carotenoids. Moreover, Sommerburg and colleagues [11] have found that colostrum contains carotenoids, in particular lutein, in concentrations up to five times higher than the so called mature breast milk (140 μm/l). Therefore, breast milk is the primary source of lutein to newborns, and breastfed babies generally have higher plasma levels of this carote-

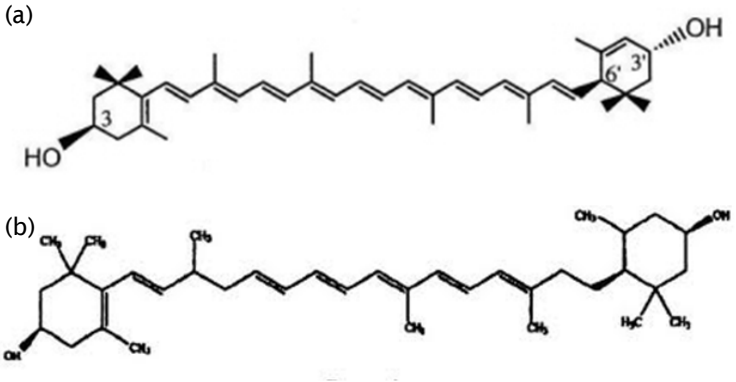


Fig 1: chemical formulas of lutein (a) and zeaxanthin (b).

noid than babies fed with infant formula. In a statement released in Geneva in 2006, the World Health Organization (WHO) evaluated the safety and potential toxic effects of certain dietary supplements, including lutein.

The Food & Drug Administration (FDA) has approved the use of lutein in infant formulae at a maximum safe concentration of 2 mg/Kg/day. Currently in Italy there are no available commercial infant formulae enriched with carotenoids, while in some other countries a formula containing egg phospholipids as a source of lutein is available [12,13]. Various double blind studies have compared infants who were given lutein with control subjects who received a placebo; the results clearly show a protecting action in the retina for the lutein treatment. Currently, multicentric studies are in progress to assess and quantify the efficacy of lutein administration in infants with ROP, and to analyze the effects of lutein on neonatal visual acuity development.

## Conclusions

Newborns, especially premature infants, require several nutritional elements essential for a healthy and fast development, since during the last gestational weeks they have not been able to benefit from the nutritional substances from the mother; however, their gastrointestinal and renal functions have yet to be fully developed, reducing the absorption and retention of important micronutrients such as lutein. Humans do not synthesize lutein, and therefore the mother needs to maintain a lutein-rich diet in order for this carotenoid to be passed to the infant via breast milk. Such diet should include yellow fruits and vegetables, green leafy vegetables (spinach, cabbages, broccoli etc.), as well as egg yolks [14].

In conclusion, lutein and zeaxanthin play a key role in the prevention of retinal pathologies, and could help to prevent the pathological evolution of incomplete retinal vascularization in premature newborns.

## References

1. Kanski JJ: Oftalmologia Clinica, Edit by Edi Ermes, 2008; Cap 13: 371-440.
2. Zimmer JP, Hammond BR: Possible influences of lutein and zeaxanthin on the developing retina. Clin Ophthalmol 2007; 1: 25–35.
3. Schwedhelm E. Maas R, Troost R, Boger RH: Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. Clin Pharmacokinet 2003; 42: 437-459.
4. Sommerburg OG, Siems WG, Hurst JS, Lewis JW, Kliger DS, van Kuijk FJ: Lutein and zeaxanthin are associated with photoreceptors in the human retina. Curr Eye Res 1999; 19: 491-495.
5. Christen WG, Liu S, Glynn RJ, Gaziano JM, Buring JE: Dietary carotenoids, vitamins C and E, and risk of cataract in women: a prospective study. Arch Ophthalmol 2008; 126: 102-109.
6. Mares-Perlman JA, Millen AE, Ficek TL, Hankinson SE: The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease. Overview J Nutr 2002; 132: 518-524.
7. Sato R, Helzlsouer KJ, Alberg AJ, Hoffman SC, Norkus EP, Comstock GW: Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2002; 11: 451-457.
8. Yeum KJ, Ferland G, Patry J, Russell RM: Relationship of plasma carotenoids, retinol and tocopherols in mothers and newborn infants. J Am Coll Nutr 1998; 17: 442-447.
9. Moukarzel AA, Bejjani RA, Fares FN: Xanthophylls and eye health of infants and adults. J Med Liban 2009; 57: 261-267.

10. Gossage CP, Deyhim M, Yamini S, Douglass LW, Moser-Veillon PB: Carotenoid composition of human milk during the first month postpartum and the response to ß-carotene supplementation. Am J Clin Nutr 2002; 76: 193-197.
11. Sommerburg O, Meissner K, Nelle M, Lenhartz H, Leichsenring M: Carotenoid supply in breast-fed and formula-fed neonates. Eur J Pediatr 2000; 159: 86-90.
12. Leung IY, Sandstrom MM, Zucker CL, Neuringer M, Snodderly DM: Nutritional manipulation of primate retinas, II: effects of age, n-3 fatty acids, lutein, and zeaxanthin on retinal pigment epithelium. Invest Ophthalmol Vis Sci 2004; 45: 3244-3256.
13. Jewell VC, Mayes CB, Tubman TR, Northrop-Clewes CA, Thurnham DI: A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. Eur J Clin Nutr 2004; 58: 90-97.
14. Sommerburg O, Keunen JE, Bird AC, van Kuijk FS: Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. Br J Ophthalmol 1998; 82: 907–910.