



Absorption of Lutein vs Lutein Esters: do we know the differences?

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Key Conclusions

- There is no published study showing the bio-equivalence of lutein vs. lutein esters.
- Prior to absorption, lutein esters require conversion into lutein by hydrolysis of the fatty acids.
- A conversion rate of 2:1 between lutein esters and lutein is theoretical and does not reflect what happens in the human body.
- Absorption of lutein and lutein esters is affected by several variables such as period of supplementation, formulation, dietary fat, and age.
- Because Bowen's and Johnson's studies do not address all the pharmacokinetic factors referred above, they cannot prove bio-equivalence between lutein and lutein esters.

There is increasing evidence that lutein plays an important role in eye health. Several clinical studies have shown that consumption of lutein from foods (1,2) and from supplements containing lutein (3,4) or lutein esters (5-7) can increase serum lutein levels and macular pigment density. According to the scientific evidence available, only free lutein is found in the human serum regardless of its original dietary source. Lutein esters must be de-esterified before they are absorbed by the body. As it will be discussed below, there is no conclusive clinical study showing the absorption equivalence between these compounds. Furthermore, to understand their differences, we will present some of the factors that affect absorption including, chemical structure, and pharmacokinetic variables.

1. Chemical differences

Lutein and lutein esters are chemically distinct compounds with different physico-chemical properties. Lutein esters are typically found in nature as diesterified forms of lutein, with two fatty acid groups occupying the sites of the hydroxyl groups normally found in lutein (Figure 1) (8). These fatty acids must be cleaved off for the body to obtain the lutein it is unable to synthesize (9). Lutein contains no esterified fatty acids, and therefore can be directly absorbed by the body.

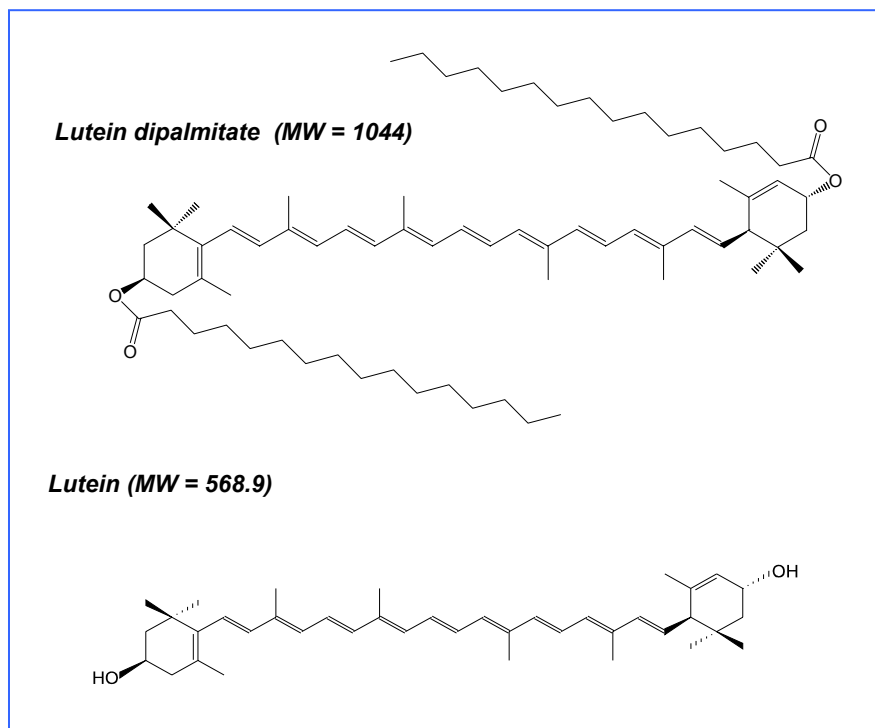


Figure 1. Lutein and lutein dipalmitate

3. Pharmacokinetic variables

3.1. Duration of supplementation

Published studies suggesting equivalence of lutein and lutein esters have not taken into account the pharmacokinetic variables affecting absorption (17,20). One important variable is the time it takes for lutein to reach steady-state levels in the blood. Depending on the dosage administered, the lutein concentration in the serum may take six to eight weeks to reach its steady state levels and up to six months to increase Macular Pigment Optical Density (MPOD) irrespective of the source of the compound. Hence, only parallel supplementation for periods longer than six weeks result in a meaningful comparison between the serum levels of different sources of lutein.

3.2. Formulation

Lutein and lutein ester formulations are important variables to consider while conducting bioavailability studies. As reported by Bowen et al. (20), the use of lutein as an oil suspension in soft gel capsules and lutein diesters as a powder in hard gel capsules was a major confounder in their

study not permitting a reliable conclusion regarding their relative absorption. In fact, the authors concluded that “*formulation dissolution is an important factor in lutein bioavailability and should be evaluated before a supplement and dose are selected for use in clinical trials*”. Moreover, it is imprecise to estimate the conversion of lutein esters into lutein using a theoretical 2:1 ratio, which is premised on molecular weight differences and assumes 100% hydrolysis. These estimates are imperfect since the extent of hydrolysis of lutein esters into lutein in the human body is unknown. As it happens with other de-esterification reactions, this hydrolysis depends on the activity of human intestinal enzymes. Moreover, published data suggests hydrolysis of lutein esters into lutein occurs with an efficacy well below 5% (14, 15). Therefore, the use of a 2:1 ratio is not based on scientific data in humans.

3.3. Dietary fat

Whereas carotenoids, in general, require the presence of fat for intestinal absorption (13), esterified carotenoids, such as lutein esters, appear to require substantially more fat in the diet to be absorbed. Roodenburg *et al.* reported that increasing the fat content of the diet twelve-fold had no effect on β -carotene or α -carotene absorptions, but doubled the amount of lutein absorbed from lutein esters (16).

3.4. Age

Age may play a role in the human body’s ability to absorb lutein. A generalized decrease in enzyme activity is associated with the normal aging process in humans. In a study performed at Tufts University by Dr. Elisabeth Johnson’s group and recently published in the Journal of Nutrition (17), the authors described a statistically significant negative correlation between age and serum lutein levels for individuals who consumed lutein esters supplements. This was not observed in the group supplemented with lutein. These findings suggest that the capacity to hydrolyze lutein esters into lutein declines with age. Considering that age is, obviously the major risk factor for developing AMD, supplementation with higher doses of lutein may be needed with increasing age. This is an important factor to consider when choosing a source of supplemental lutein for the elderly.

4. Published studies

Two attempts have been made to compare the absorption of lutein and lutein esters from formulations containing FloraGLO[®] as the source of lutein and Xangold[®] as the source of lutein esters (17, 19). Extending the arguments presented above regarding one-time dosages or short-term (below six weeks) administrations of lutein, we present additional reasons why the following studies do not clarify the issue of the relative absorption of lutein versus lutein esters.

4.1. Dr. Elisabeth Johnson and her collaborators from Tufts University recently published a study providing daily doses of lutein from four different sources to ten volunteers over nine days (17). The authors reported no differences between the absorption of 6 mg of lutein from spinach, 6 mg of lutein supplements, or 10.23 mg lutein esters supplements. At first glance, these findings contradict the studies published by Castenmiller et al (1999) and Van het Hof et al (1999):

- Castenmiller et al. (1999) (18) compared the absorption of lutein in 70 subjects consuming a control diet, a carotenoid supplement providing 6.6 mg lutein per day, and four preparations of spinach providing an average of 11.5 mg lutein/day for three weeks. Results indicated that supplemental lutein was twice as available as lutein from spinach.
- Van het Hof et al. (1999) (3) compared the absorption of lutein in 55 subjects consuming a low vegetable diet providing 2.7 mg lutein/day, a high vegetable diet providing 10.7 mg lutein/day, and a supplement providing 12 mg lutein per day for four weeks. Serum lutein concentrations were significantly greater (60%) in the supplemented group compared to the high vegetable diet group, containing similar amounts of lutein.

Dr. Johnson's group (17) suggested that the differences between their study and data previously published might be due to increased fat in eggs (55-60%), compared to only 30% in the previous studies (18,3). This correlates with study results from Breithaupt et al. (19), which reported an increase in absorption of zeaxanthin esters compared to zeaxanthin when consumed as part of a meal containing 48% fat. These levels of fat, which exceed the level recommended by the American Heart Association (*i.e.*, below 30% of total calories from unsaturated fat), may be responsible for the elevated absorption of the esterified carotenoids. As mentioned above, Roodenburg *et al.* (16) reported that twice as much lutein was released from lutein esters when these were consumed with a meal comprised of 36g of fat versus one containing only 3g. This dependence on a high-fat diet for absorption was not observed for α -carotene or for β -carotene. Unsterified carotenoids, such as

lutein, α -carotene and β -carotene do not require enzymatic cleavage before absorption. Therefore, the fat content of the diet may affect it's the absorption of lutein to a much lesser extent.

4.2. In a study published by Dr. Phyllis Bowen's research team (20), 18 volunteers received a single dose of lutein or lutein esters. As discussed above, this does not reflect steady state levels of lutein. Nevertheless, the authors concluded that esterification does not impair lutein ester bioavailability. The author's conclusion is consistent with previous evidence showing that lutein esters are a source of lutein in humans. However, this study does not provide evidence on the bio-equivalence between lutein and lutein esters. Other weaknesses of the study in comparing lutein and lutein esters are:

- The two molecules were taken in different formulations (lutein as an oil suspension in soft gel capsules and lutein diesters as a powder in hard gel capsules) not permitting a reliable conclusion regarding their relative absorption. In fact, the authors concluded that *“formulation dissolution is an important factor in lutein bioavailability and should be evaluated before a supplement and dose are selected for use in clinical trials”*.
- The dosages administered were based on per kilogram body weight. This is an unusual way of proving bio-equivalence of two compounds as it is unknown how body weight affects the metabolism of xanthophylls and, if so, whether such an effect is the same for lutein and lutein esters. The rationale for the dosing protocol used is not provided either. It is unclear why certain subjects received 0.5 $\mu\text{mol/kg}$ body weight, while others received 0.67 $\mu\text{mol/kg}$ body weight. Moreover, the report fails to define which subjects received lutein or lutein esters.
- Finally, the meals given together with the supplements differed significantly in fat content (11.6 – 23 total g). As fat is known to have a considerable impact on the absorption of lutein from lutein esters, a justification is needed to explain why the fat content was not controlled and kept constant for all the meals accompanying the supplementation.

In conclusion

There are no published studies showing the bio-equivalence of lutein and lutein esters. Important factors such as supplementation period, formulation, dietary fat, and age may affect the kinetics of these compounds. The studies of Johnson and Bowen briefly discussed above do not address all these factors and, hence, are inconclusive regarding the absorption or the bioavailability of lutein versus lutein esters.

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