Letter to the Editor

Is vitamin A an antioxidant?

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Vitamin A is an essential nutrient for humans and higher animals. It occurs in multiple forms in the body. The primary bioactive derivate, all-*trans*-retinoic acid, is the active ligand for three nuclear hormone receptors, the retinoic acid receptors (RARs; RARα, RARβ and RARγ), which mediate the large majority of vitamin A's biological effects, including most physiological effects such as cell differentiation, proliferation and apoptosis. These effects are relevant for a large array of pathways enabling the maintenance of a healthy immune response, the cardiovascular system, general development, embryonic development and skin- and epithelial-functions [1, 2, 3]. All-*trans*-retinal and 11-*cis*-retinal are vitamin A derivatives involved in the visual cycle where they act in photo-perception [4]. In addition to these active forms, all-*trans*-retinol is the primary homeostatically regulated vitamin A species within the body, and retinyl esters such as retinyl palmitate are the storage form that are mainly present in liver and some other organs [5]. In the context of dietary vitamin A intake, plant-derived vitamin A precursors are termed provitamin A carotenoids, comprising β-carotene, α-carotene and β-cryptoxanthin as three main representatives in our diet. These provitamin A carotenoids [6] serve as food-derived vitamin A precursors converted directly to retinol / retinyl esters in humans or in animals. Various animals serving directly (i.e. meat) or indirectly (i.e. milk/eggs) as human food sources convert further this provitamin A to retinol/ retinyl esters, which are then taken up as such by humans.

Historically, the term vitamin A comprises retinol / retinyl esters, retinal isomers, and retinoic acid isomers, as well as provitamin A carotenoids and this term vitamin A is often incorrectly associated with antioxidant activity (reviewed in [7, 8]). Recently, two reviews summarised and discussed this antioxidant activity [9, 10] and concluded that vitamin A, in the form of retinal and retinoic acid, as well as retinol and retinyl esters, have no direct antioxidant activity in humans [10], contrary to what is often claimed. Another recent review of carotenoids, focusing on provitamin A carotenoids, concluded that on a physiological and nutritional level, provitamin A carotenoids are likely not mediating their biological mechanisms primarily via antioxidant effects [9]. Rather than acting as direct antioxidants, these review articles concluded that the effects of vitamin A in the body involve serving as precursors for ligands for RARs and retinoid X receptors as well as also exerting an indirect antioxidant response via NF-κB and NRF2 signalling pathways [6, 9, 10].

We wish to note here, based on the large amount of data and references discussed in these reviews, which originated independently from both sides of the Atlantic, claiming that vitamin A (as retinol and retinyl esters), and even provitamin A carotenoids, are direct antioxidants *in vivo,* does not reflect the current state of understanding of this nutrient. This claim is particularly problematic when advertising vitamin A (as retinol and retinyl esters) and even provitamin A in food products and in dietary supplements [11]. Unfortunately, overdosing exclusively with vitamin A, mainly in the form of retinol or retinyl ester as food ingredients or dietary supplements that are already taken in sufficient or even high dose in Western countries [12], may result in moderate to even severe toxic effects such as mental / cognitive impairments, pruritus, headache, changes in skin and hair, an imbalanced immune response, muscle and bone pain, hyperlipidaemia and potential embryo-toxic effects

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[12, 13, 14, 15, 16, 17, 18]. Consequently, supplementation with vitamin A (as retinol/retinyl ester) may induce moderate to severe toxic side effects instead of the purported antioxidant defence [12].

It is our opinion that vitamin A and even provitamin A carotenoids do mainly not act as a direct antioxidant in the human body and therefore recommend regulatory bodies and companies fortifying food/selling supplements to reconsider carefully advertising vitamin A with the claim "antioxidant".

References

1. Balmer JE, Blomhoff R. Gene expression regulation by retinoic acid. J Lipid Res. 2002;43(11):1773–808.
2. Mangelsdorf DJ, Kliewer SA, Kakizuka A, Umesono K, Evans RM. Retinoid receptors. Recent Prog Horm Res. 1993;48:99–121.
3. Leid M, Kastner P, Chambon P. Multiplicity generates diversity in the retinoic acid signalling pathways. Trends Biochem Sci. 1992;17(10):427–33.
4. Saari JC. Vitamin A and vision. Subcell Biochem. 2016;81:231–59.
5. Blaner WS. Vitamin A signaling and homeostasis in obesity, diabetes, and metabolic disorders. Pharmacol Ther. 2019;197:153–78.
6. Böhm V, Lietz G, Olmedilla-Alonso B, Phelan D, Reboul E, Banati D, et al. From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations. Nutr Rev. 2021;79(5):544–73.
7. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med. 1999;26(5–6):746–61.
8. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements to prevent mortality. JAMA. 2013;310(11):1178–9.
9. Bohn T, Bonet ML, Borel P, Keijer J, Landrier JF, Milisav I, et al. Mechanistic aspects of carotenoid health benefits – where are we now? Nutr Res Rev. 2021;34(2):276–302.
10. Blaner WS, Shmarakov IO, Traber MG. Vitamin A and Vitamin E: Will the real antioxidant please stand up? Annu Rev Nutr. 2021;41:105–31.
11. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst Rev. 2004;18(4):CD004183.
12. EFSA. Tolerable upper intake levels for vitamins and minerals. EFSA; 2006. Available from: https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf
13. Snodgrass SR. Vitamin neurotoxicity. Mol Neurobiol. 1992;6(1):41–73.
14. Rutkowski M, Grzegorczyk K. Adverse effects of antioxidative vitamins. Int J Occup Med Environ Health. 2012;25(2):105–21.
15. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. Am J Clin Nutr. 2006;83(2):191–201.
16. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. N Engl J Med. 1995;333(21):1369–73.
17. Rühl R. Non-pro-vitamin A and pro-vitamin A carotenoids in atopy development. Int Arch Allergy Appl Immunol. 2013;161:99–115.
18. Allen LH, Haskell M. Estimating the potential for vitamin A toxicity in women and young children. J Nutr. 2002;132(9 Suppl):2907S–2919S.

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Conflict of interest
The authors declare that there are no conflicts of interest.

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