

Review

Antioxidant-Based Therapies in Male Infertility: Do We Have Sufficient Evidence Supporting Their Effectiveness?

Angela Maria Amorini ^{1,†} , Ilaria Listorti ^{2,†}, Gabriele Bilotta ², Romina Pallisco ², Miriam Wissam Saab ¹, Renata Mangione ³, Benedetta Manca ⁴, Giacomo Lazzarino ^{3,5,*} , Barbara Tavazzi ^{3,6,*} , Giuseppe Lazzarino ^{1,7,*}  and Pasquale Bilotta ⁸

¹ Department of Biomedical and Biotechnological Sciences, Division of Medical Biochemistry, University of Catania, Via S. Sofia 97, 95123 Catania, Italy; amorini@unict.it (A.M.A.); mirisaab@gmail.com (M.W.S.)

² Alma Res Fertility Center, Laboratory of Biology and Embriology, Via Parenzo 12, 00199 Rome, Italy; laboratorio@almares.it (I.L.); bilotta.oblomov@gmail.com (G.B.); romina.pallisco@almares.it (R.P.)

³ Department of Basic Biotechnological Sciences, Intensive and Perioperative Clinics, Catholic University of the Sacred Heart of Rome, Largo F. Vito 1, 00168 Rome, Italy; renata.mangione@unicatt.it

⁴ Department of Pharmacy and Biotechnology (FaBiT), University of Bologna, Via Imerio 48, 40126 Bologna, Italy; benedetta.manca4@unibo.it

⁵ UniCamillus—Saint Camillus International University of Health Sciences, Via di Sant' Alessandro 8, 00131 Rome, Italy

⁶ Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy

⁷ LTA-Biotech srl, Viale Don Orione, 3D, 95047 Paternò, Italy

⁸ Alma Res Fertility Center, Laboratory of Obstetrics and Gynecology, Via Parenzo 12, 00199 Rome, Italy; pasquale.bilotta@almares.it

* Correspondence: giacomo.lazzarino@unicamillus.org (G.L.); barbara.tavazzi@unicatt.it (B.T.); lazzarig@unict.it (G.L.)

† These Authors equally contributed to this work.



Citation: Amorini, A.M.; Listorti, I.; Bilotta, G.; Pallisco, R.; Saab, M.W.; Mangione, R.; Manca, B.; Lazzarino, G.; Tavazzi, B.; Lazzarino, G.; et al. Antioxidant-Based Therapies in Male Infertility: Do We Have Sufficient Evidence Supporting Their Effectiveness?. *Antioxidants* **2021**, *10*, 220. <https://doi.org/10.3390/antiox10020220>

Academic Editors: Cristian O'Flaherty and Giulia Collodel
Received: 16 December 2020
Accepted: 29 January 2021
Published: 2 February 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Under physiological conditions, reactive oxygen species (ROS) play pivotal roles in various processes of human spermatozoa. Indeed, semen requires the intervention of ROS to accomplish different stages of its maturation. However, ROS overproduction is a well-documented phenomenon occurring in the semen of infertile males, potentially causing permanent oxidative damages to a vast number of biological molecules (proteins, nucleic acids, polyunsaturated fatty acids of biological membrane lipids), negatively affecting the functionality and vitality of spermatozoa. ROS overproduction may concomitantly occur to the excess generation of reactive nitrogen species (RNS), leading to oxidative/nitrosative stress and frequently encountered in various human pathologies. Under different conditions of male infertility, very frequently accompanied by morpho-functional anomalies in the sperm analysis, several studies have provided evidence for clear biochemical signs of damages to biomolecules caused by oxidative/nitrosative stress. In the last decades, various studies aimed to verify whether antioxidant-based therapies may be beneficial to treat male infertility have been carried out. This review analyzed the results of the studies published during the last ten years on the administration of low-molecular-weight antioxidants to treat male infertility in order to establish whether there is a sufficient number of data to justify antioxidant administration to infertile males. An analysis of the literature showed that only 30 clinical studies tested the effects of the administration of low-molecular-weight antioxidants (administered as a single antioxidant or as a combination of different antioxidants with the addition of vitamins and/or micronutrients) to infertile males. Of these studies, only 33.3% included pregnancy and/or live birth rates as an outcome measure to determine the effects of the therapy. Of these studies, only 4 were case-control studies, and only 2 of them found improvement of the pregnancy rate in the group of antioxidant-treated patients. Additionally, of the 30 studies considered in this review, only 43.3% were case-control studies, 66.7% enrolled a number of patients higher than 40, and 40% carried out the administration of a single antioxidant. Therefore, it appears that further studies are needed to clearly define the usefulness of antioxidant-based therapies to treat male infertility.