Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Controlled Release 113 (2006) 189–207
journal of controlled release
www.elsevier.com/locate/jconrel

Review

Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective

D. Venkat Ratnam, D.D. Ankola, V. Bhardwaj, D.K. Sahana, M.N.V. Ravi Kumar *

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Phase-X, S.A.S. Nagar, Mohali, Punjab, India - 160062

Received 31 January 2006; accepted 26 April 2006
Available online 13 May 2006

Abstract

Antioxidants are emerging as prophylactic and therapeutic agents. These are the agents, which scavenge free radicals otherwise reactive oxygen species and prevent the damage caused by them. Free radicals have been associated with pathogenesis of various disorders like cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders and are implicated in aging. Several antioxidants like SOD, CAT, epigallocatechin-3-*O*-gallate, lycopene, ellagic acid, coenzyme Q_{10}, indole-3-carbinol, genistein, quercetin, vitamin C and vitamin E have been found to be pharmacologically active as prophylactic and therapeutic agents for above mentioned diseases. Antioxidants are part of diet but their bioavailability through dietary supplementation depends on several factors. This major drawback of dietary agents may be due to one or many of the several factors like poor solubility, inefficient permeability, instability due to storage of food, first pass effect and GI degradation. Conventional dosage forms may not result in efficient formulation owing to their poor biopharmaceutical properties. Principles of novel drug delivery systems need to be applied to significantly improve the performance of antioxidants. Novel drug delivery systems (NDDS) would also help in delivery of these antioxidants by oral route, as this route is of prime importance when antioxidants are intended for prophylactic purpose. Implication of NDDS for the delivery of antioxidants is largely governed by physicochemical characteristics, biopharmaceutical properties and pharmacokinetic parameters of the antioxidant to be formulated. Recently, chemical modifications, coupling agents, liposomes, microparticles, nanoparticles and gel-based systems have been explored for the delivery of these difficult to deliver molecules. Results from several studies conducted across the globe are positive and provided us with new anticipation for the improvement of human healthcare.

Keywords: Antioxidants; Biopharmaceutics; Controlled delivery; Intestinal permeability; Peroral; Pharmacokinetics; Solubility; Targeted delivery

Contents

Abbreviations: AP, ascorbyl palmitate; CAT, catalase; DCFH-DA, dichlorodihydrofluorescein diacetate; CD, cyclodextrin; CoQ_{10}, coenzyme Q_{10}; CS, chitosan; DNA, deoxyrebose nucleic acid; DMAB, didodecyldimethyl ammonium bromide; DSS, dextran sulfate sodium; EA, ellagic acid; EGCG, epigallocatechin-3-*O*-gallate; GIT, gastrointestinal tract; GALT, gut associated lymphoid tissue; GPx, glutathione peroxidase; ICAM, intracellular adhesion molecule; IDE, idebenone; I3C, indole-3-carbinol; LAA, lipoamino acid; LAT, liposomal α-tocopherol; NAC, *N*-acetylcysteine; NDDS, novel drug delivery systems; PECAM, platelet endothelial cell adhesion molecule; PEG, polyethylene glycol; PLGA, poly lactide-co-glycolic acid; PMMA, poly methyl methacrylate; PNC, polymeric nanocarriers; PVA, polyvinyl alcohol; ROS, reactive oxygen species; SEDDS, self-emulsifying drug delivery systems; SLN, solid lipid nanoparticle; SOD, superoxide dismutase; UV, ultraviolet radiation.

* Corresponding author. Tel.: +91 172 2214683 89 2055; fax: +91 172 2214692.
E-mail addresses: mnvrkumar@niper.ac.in, mnvrkumar@yahoo.com (M.N.V.R. Kumar).

0168-3659/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2006.04.015

1. Introduction

In recent years, antioxidants have gained a lot of importance because of their potential as prophylactic and therapeutic agents in many diseases. The discovery of the role of free radicals in cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders, aging and other diseases has led to a medical revolution that is promising a new paradigm of healthcare. Although not many antioxidants are listed in pharmacopoeias, extensive research is being carried out globally on these agents, and most of them have been proven pharmacologically active. Traditionally, herbal medicines with antioxidant properties have been used for various purposes and epidemiological data also points at widespread acceptance and use of these agents. Presently, the active constituents from these herbal sources are extracted, purified and tested for their activities. Results are promising their benefits in prevention and therapy in many of the aforesaid diseases. The global market of antioxidants is increasing rapidly, because of the increased health risk in a constantly polluting environment. These agents also have cosmetic applications, further fuelling research by industry and academia to explore these molecules and their analogues.

Free radicals are highly reactive molecules or chemical species containing unpaired electrons that cause oxidative stress, which is defined as “an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage” [1]. Oxidative stress can damage lipids, proteins, enzymes, carbohydrates and DNA in cells and tissues, resulting in membrane damage, fragmentation or random cross linking of molecules like DNA, enzymes and structural proteins and even lead to cell death induced by DNA fragmentation and lipid peroxidation [2]. These consequences of oxidative stress construct the molecular basis in the development of cancer, neurodegenerative disorders, cardiovascular diseases, diabetes and autoimmune disorders.

Human antioxidant defense is equipped with enzymatic scavengers like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase; hydrophilic scavengers like urate, ascorbate, glutathione and flavonoids; lipophilic radical scavengers such as tocopherols, carotenoids and ubiquinol. The defense also comprises enzymes involved in the reduction of oxidized forms of molecular antioxidants like glutathione reductase, dehydroascorbate reductase. Apart from these scavengers, there exists cellular machinery, which maintains a reducing environment, for example regeneration of NADPH by glucose-6-phosphate dehydrogenase. Some of these agents synthesized by cell itself; however, majority including ascorbic acid, lipoic acid, polyphenols and carotenoids are derived from dietary sources. In disease conditions, the defense against ROS is weakened or damaged and the oxidant load increases. In such conditions, external supply of antioxidants is essential to countervail the deleterious consequences of oxidative stress.