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Review Article
Insights of Antioxidants as Molecules for Drug Discovery

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Abstract

Oxidative stress is suggested as the root cause of aging and various human diseases like atherosclerosis, diabetes, cancer, stroke and neurodegenerative diseases. Researchers are advocating enrichment of body systems with antioxidants-the free-radical scavenging molecules, to correct vitiated homeostasis and prevent the onset as well as treat the disease caused/promoted due to free radicals and related oxidative stress. Antioxidants are also known to induce biosynthesis of other antioxidants or defense enzymes. Various studies and trials on antioxidant's potential as drugs are being carried out in the research community. Advance efforts are made to elucidate the importance of antioxidant therapy based on drug discovery from natural products like plants, animals, microalgae and microbes, isolation of active principles and further modification and refinement of active antioxidant molecules. Numerous antioxidants like superoxide dismutase, genistein, ellagic acid, epigallocatechin-3-*O*-gallate, indole-3-carbinol, lycopene, coenzyme Q10, quercetin, vitamin C and vitamin E have been found to be pharmacologically active. This review presents insights of the role of antioxidants in various diseases and their potential to act and contribute as efficient drug candidates for treatment of related diseases. The novel biomolecules that can be of benefit and act as novel antioxidant-based drug formulations for the treatment and prevention of complex diseases like Alzheimer's disease (AD), cancer, Parkinson's disease, rheumatoid arthritis, diabetes and neurodegenerative diseases are discussed and the scope with strategic development of newer therapies using them are explored.

Key words: Antioxidants, biomolecules, free radicals, Alzheimer's disease, cancer, Parkinson's disease, enzymes, macroalgae

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INTRODUCTION

Antioxidants are naturally occurring molecules that combat oxidative damage in biological entities by free-radical scavenging. An antioxidant achieves this by slowing or preventing the oxidation process that can damage cells in the body. Thus, antioxidants can also be termed as reducing agents. A free radical is any chemical species with one or more unpaired electrons and capable of independent existence. Once formed, radicals can react either with another molecule by different interactions or to another radical. Low levels of Reactive Oxygen Species (ROS) are indispensable in many biochemical processes, involving apoptosis[1], cell differentiation, immunity[2] and defense against pathogens[3]. On the contrary, high doses of ROS result in oxidative stress causing severe metabolic malfunctions and damage to biological macromolecules[4]. The ROS can cause DNA modifications in several ways, which involve degradation of bases, pyrimidine or sugar bound modifications, deletion or translocations and cross linking with proteins[5]. Antioxidants may exert their effect by various mechanisms, like suppressing the formation of active species by reducing hydroperoxides ($ROO^{\cdot}$) and hydrogen peroxides and also by scavenging active free radicals, sequestering metal ions, repairing and clearing. Some antioxidants are also known to induce biosynthesis of other antioxidants or defense enzymes. Figure 1 represents an overview of antioxidant action on oxidative stress.

Bioactivity of antioxidants is dependent on several factors like their physicochemical characteristics, structural criteria and in vivo radical generating conditions. They work by retarding oxidation. It intercepts a free radical before it can react with the substrate.

For instance, phenol (AOH), the reaction with ROO• is:

$$AOH+ROO\bullet \rightarrow AO\bullet+ROOH$$

This H-atom transfer reaction effectively stops the chain reaction. Therefore, antioxidants of therapeutic importance should have the property that they will react with the free radical before it reacts with the substrate and initiate the chain reaction.

Although synthetic drug discovery has evolved to a large extent, natural drug candidates are currently being explored for their potent and efficient response towards diseases. By applying the new techniques in a systemic manner to natural drug discovery, there are chances of increase in current efficiency as well as identifying and developing new drugs of natural origin. Efficient antioxidants from natural sources have been reported in various studies. Thus, diet derived and drug-derived antioxidants may be important in providing protection and treatment for a number of diseases. For example, various marine algae have been reported to contain anticancerous compounds which show antioxidant activity and were studied for their therapeutic properties[6]. Over past few decades, free radical theory has significantly stimulated interest in the role of dietary antioxidants in preventing many human diseases like cancer, stroke, atherosclerosis, rheumatoid arthritis, diabetes and neurodegeneration[7].

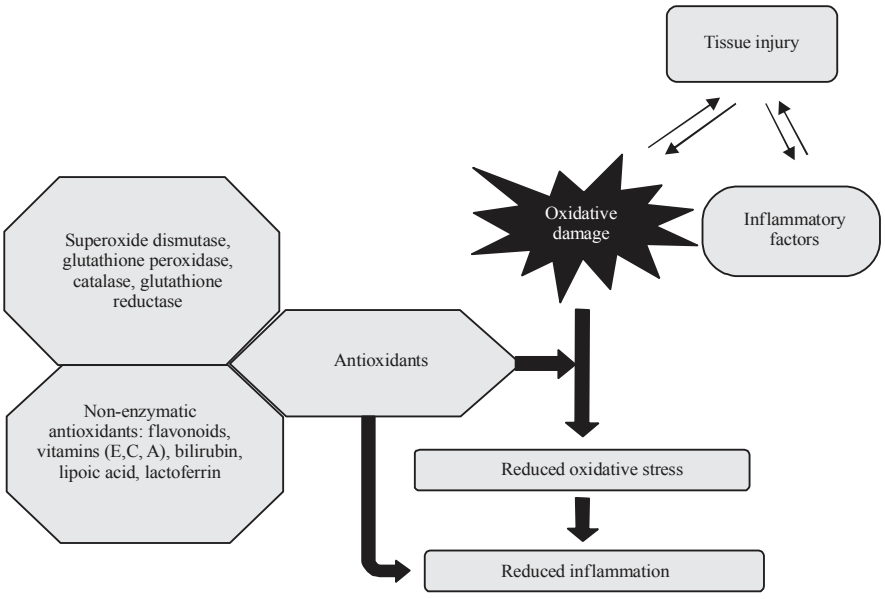

Fig. 1: Overview of antioxidant action

Studies report that many medicinal plants that have been traditionally used for disease treatment possess antioxidant activities. They are reported with high content of polyphenol compounds which contribute significantly to the antioxidant properties[8].

DRUG CANDIDATES OF NATURAL ORIGIN

Since a long time, natural products have been closely linked and used as traditional medicines[8]. Natural product and their derivatives have historically been invaluable as a source of therapeutic agents. The pharmacological, clinical and chemical studies of these traditional medicines, predominantly derived from plants established the basis for most of the early medicines like, morphine[9], quinine[10] and pilocarpine[11]. Farnsworth and Morris[12] reported that nearly 119 compounds derived from 90 plant species could be considered as important drugs currently used in many countries out of which 77% have been derivatives of plants used in traditional medicine[13]. In 1991, the analysis of bestselling pharmaceuticals revealed that the half of them were either natural or their derivatives[14]. Out of 87 approved drugs, 62% were of natural origin or modeled on natural product parents. 15 were natural products, 25 were semi-synthetic derivatives and 14 may be classified as being based on natural product models[15]. During 1970- 1980 the investigation of natural products as novel sources of therapeutics in the western pharmaceutical industry reached its peak which led to the heavy production of non-synthetic molecules. The small- molecule New Chemical Entities (NCEs) were introduced during 1981-2002, approximately half were based on natural products, semi-synthetic product analogs or synthetic compounds based on natural products[16].

Infectious diseases are the second leading cause of death and there is an urgent need for discovery of new drugs to combat them as well as new evolving drug- resistant pathogens. Numerous natural products have been identified that represent antibacterial agents displaying unique modes of action and properties. During 2001-2005, 23 naturally derived new drugs were introduced into the market for the treatment of diseases like fungal and bacterial infections, diabetes, cancer, dyslipidemia, AD, Gaucher's disease, atopic dermatitis etc.[17].

Natural product drug discovery has several drawbacks when compared to synthetic chemical drug discovery. These may include:

- Natural products are often synthesized in small quantities and present as a mixture in extracts, due to which there is a requirement of labor intensive and time taking purification process.
- There are high possibilities of rediscovering known compounds while screening natural product libraries. This is caused by lack of dereplication (a process by which the chemical and biological characteristics of the unknown compounds are compared with chemical and biological characteristics of known compounds from databases to eliminate previously identified compounds) methodologies for both compounds in the natural product libraries and natural product sourcing.
- Natural products are structurally complex and their modification using organic chemistry is challenging.

Although having such limitations, the natural products are considered to be good drug candidates and hence technological advancements and development of new methods have revolutionized the screening of natural products and offer a unique opportunity to re-establish natural products as the main source of drug candidates. The recent advancements may include development of streamlined screening processes, improved natural product sourcing and advancements in organic synthetic methods, combinatorial biosynthesis and microbial genomics. The past few years witnessed major developments also in areas like fermentation optimization, purification, dereplication and structure elucidation of natural products, which enabled much faster access to sufficient number of pure compounds.

Actinomycetes have been widely investigated and used as a major source of novel microbial metabolites but their potential seems boundless. To these, natural sources can be added to investigate the rational design of novel structure types within certain classes of microbial metabolites using genetic engineering[14].

Plants and microbes are well known to produce secondary metabolites, required for their survival and can be used as efficient drug candidates. Naturally occurring compounds like polyphenols in fruits, vegetables, beverages and cereals are plant secondary metabolites and generally involved in defense against aggression by pathogens and UV radiations[18]. It has been reported that long- term consumption of polyphenol-rich diet offers protection against cancer, diabetes, cardiovascular diseases, neurodegenerative diseases and osteoporosis. It is well known that polyphenol- rich food and beverages may increase plasma antioxidant capacity.

Despite the success into natural products, the research has experienced a slight decline during past decades. It is a lengthy process, usually ten or more years starting from the initial discovery to the subsequent launch of a new drug[17]. This decrease in the discovery of natural candidates has been attributed to number of factors which includes high throughput screening against defined molecular targets. Advances in molecular biology, genomics and cellular biology led to rise in number of targets and encouraged shortened drug discovery time lines.

SOURCES OF ANTIOXIDANTS

Biological antioxidants fall into two main categories: Low-molecular-weight compounds that are chemical reducing agents such as ascorbic acid, tocopherol, reduced glutathione and their derivatives/precursors and relatively high-molecular-weight compounds/complexes, usually polyunsaturated macrocyclic aromatics that form a coordination bond with transition metal ions, referred to as "catalytic antioxidant mimetics" because they mimic the structures/functions of endogenous antioxidant enzymes. They rapidly react with and diminish ROS and are themselves regenerated thereafter. Also, there are other compounds that may exert intracellular "antioxidant" effects although they are not chemically reducing agents. These compounds may either chelate free transition metal ions to prevent them from catalyzing hydroxyl radical generating Fenton reactions or inhibit certain enzymes that participate in the generation of active metabolites of some medicinal drugs (mostly CYP450). A variety of plant extracts, which are essentially a natural antioxidant solution (mostly a mixture of polyphenols, flavonoids and thiols) have also been studied to determine their protective effectiveness.

It is evident that the oxidants contribute to the development of many of the common diseases like cancer, stroke, arthritis, heart attacks, cataract[19,20]. Living organisms are continuously exposed to oxidants of endogenous and exogenous origin. Endogenous sources include mitochondrial respiration, enzymes like xanthine oxidase and lipoxygenase[20,21], whereas exogenous sources involve natural dietary constituents, natural radioactive gasses, UV radiation, environmental pollutants[19,20]. The body defense against oxidative stress are antioxidants synthesized by the body and antioxidant vitamins taken up in diet[19,20]. The body synthesizes antioxidant proteins (transition metal binding proteins, catalase, etc.) and a number of small molecules, some of which are the end product of different metabolic pathways (urate, bilirubin).

Microbes as sources of antioxidants: It is well established that oxidative damage have a part in pathogenesis of atherosclerosis, cancer, cirrhosis and other chronic diseases. *Bifidobacterium longum* ATCC 15708 and to a lesser extent *Lactobacillus acidophilus* ATCC 4356 showed inhibition of linoleic acid peroxidation and scavenged free radicals[22]. *Pediococcus pentosaceus* 16:1 and *Lactobacillus plantarum* 2592 were found to produce antioxidants whereas, *Lactobacillus paracasei* F19 showed slightly less production but another *L. paracasei* did not exert antioxidant activity emphasizing that these characteristics are strain dependent[23]. Another study showed obligately homofermentive *Lactobacilli* produced high antioxidant activity but this was highly strain dependent among facultative and obligately heterofermentive *Lactobacilli*[24]. Ergothioneine is synthesized by bacteria and fungi and is concentrated to very low levels in many mammalian tissues from the diet[25,26]. Its function is unclear but studies support antioxidant role presented by this unusual thiol in animals[27,28].

Certain probiotics have been reported for the protection against oxidative stress and the ability to decrease the risk of accumulation of reactive oxygen metabolite[29-31]. Studies have reported strains of *Lactobacillus* and *Bifidobacteria* present antioxidative properties[32,33] and thus, they can be used to prepare fermented dairy products and also probiotics that improve total antioxidant status and minimize the markers of oxidative stress in healthy people[34]. The metabolic activities of probiotics may have antioxidant effect by preventing the generation of oxidant compounds in the intestine or by scavenging them[35].

Macroalgae as a source of antioxidants: Though, antioxidant benefits associated with terrestrial plants have been accepted widely, relatively little importance has been placed on the merits of consuming marine macroalgae for the same benefit. Marine algae are a rich source of proteins, vitamins and minerals, a great variety of secondary metabolites with diverse biological activities. A number of potent antioxidant compounds have been isolated and identified from different types of edible seaweeds. Various natural antioxidants such as polyphenols, especially phlorotannins are derived from brown algae, which play an important role in preventing lipid peroxidation[36]. The following table (Table 1) enlists the potential drug molecules from macroalgae.

Plants as sources of antioxidants: Plants are natural sources of antioxidants that can be used to enhance the properties of food, for both preservation and nutritional purposes. Current

Table 1: Potential drug molecules from macroalgae and the disease they target

Potential drug molecule	Source macroalgae	Action towards disease/Disease targeted
Vitamin C	*Ulva reticulate*	Reduced hepatic oxidative stress[37]
Mannitol and volemitol	*Pelvetia canaliculata*	Inhibited H_2O_2-induced Superoxide dismutase depletion in Caco-2 cells[38]
Phycobilins, phycoerythrin and phycocyanin	*Porphyridium* sp.	Inhibited the replication of retroviruses[39]
Lycopene	*Chlorella marina*	Arthritis[40]
C-phycocyanin	*Spirulina platensis*	Suppressed inflammation by inhibiting the production of pro-inflammatory cytokines and by inhibiting the expressions of inducible nitric oxide synthase and cyclooxygeanase-2[41]
Kahalalide F (KF)	*Elysia rubefescens*	Prostate cancer breast cancer and colon cancer[42]
Xanthone	*Wardomyces Anomalus*	Atherosclerosis, dementia and cancer[43]
Scytonemin	*Cyanobacterium Stigonema* sp.	Excellent drug as protein kinase inhibitors to have antiproliferative and anti-inflammatory activities[44]
Curacin-A,	*Lyngbya majuscule*	Antiproliferative, inhibits the polymerization of the tubulin and it also displays the inhibitory activity selectively on colon, renal and breast cancer-derived cell lines[45]
Apratoxin A	*Lyngbya boulloni*	Adenocarcinoma[46]
Coibamide A	*Leptolyngbya*	Cytotoxicity against NCIH460 lung and mouse neuro-2a cells[47]
Borophycin	*Nostoc linckia* and *N. spongiaeformevar tenue*	Cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma activity[48]
Condriamide-A	*Chondria* sp.	Colorectal cancer[49]
Fucoidan	*Ascophyllum nodosum*	Antitumour, anticancer, Antimetastatic[50]
Caulerpenyne	*Caulerpa* sp.	Anticancer, antitumour and antiproliferating[51]
Meroterpenes, Usneoidone	*Cystophora* sp.	Antiumour[52]
Cyptophycin 1	*Nostoc linckia*	Cytotoxicity against human tumor cell lines and human solid tumors[53]
Cryptophycin 8	*Nostoc spongiaeforme*	Greater therapeutic efficiency and lower toxicity than cryptophycin 14 *in vivo*[54]
Scytonemin	*Stigonema* sp.	Antiproliferative and anti-inflammatory activities[55]
Largazole	*Symploca* sp.	Antiproliferative activity[5]

research is highlighting the role of phytochemicals including flavonoids, phenolic acids and phenylpropanoids as important factors that contribute to the antioxidant activity of the diet[56]. It has been investigated that polyphenols possess ideal structural chemistry for scavenging free radicals and more effective antioxidants than Vitamin E and C[57].

Citrus fruits are abundant in flavonoids. The genus Citrus is characterized by the substantial accumulation of flavanone glycosides which are not found in other fruits, at the expense of accumulation of anthocyanins and flavanols. Grapes contain predominantly naringin which constitute 88% of flavanones in the juice. Naringin also predominates the juice of sour oranges (56-71%). Lemon peel contains two flavanone glycosides, eriocitrin and hesperidin. Citrus fruits also contain various other flavones, polymethoxylated flavones, like sinensetin and nobiletin in orange peel[56].

Grapes and wine contain a large number of polyphenols in the concentration range of 1.0-1.8 μg mL^{-1}. The total antioxidant activity of a range of red wines[57] varies from 12-14 mM for California Pinot Noir, Rioja and Bouzy Rouge, to about 16 mM for Australian Shiraz and 23 mM for Chianti and Bordeaux.

Catechins, catechingallate esters and gallocatechin have been investigated to hold importance as dietary antioxidants. The consumption of green tea has been associated with lowered risks of cardiovascular diseases through decreased serum cholesterol and triacylglyceride[57]. Theaflavins are formed during manufacturing of black and oolong tea from the enzymatic oxidation of flavonoids and catechin by polyphenol oxidases. It is found to possess *in vitro* antioxidative properties against lipid peroxidation, in membranes and microsomes of erythrocytes[58]. It suppresses mutagenic effects induced by hydrogen peroxide. A major polyphenolic constituent of green tea, epigallocatechin gallate suppresses the production of hydrogen peroxide and superoxide radicals by tumor promoter- activated human neutrophils.

The role of flavonoids in scavenging the free radicals and their mechanism of action has been extensively studied[59,60]. The total number of hydroxyl groups and the configuration are the determining factors in the mechanism of antioxidant activity shown by flavonoids. Precisely, the B- ring hydroxyl configuration is important scavenger for Reactive Oxygen Species (ROS)[61]. Moreover, the presence of a 3′ 4-catechol structure and 6-hydroxyl group in the B-ring potentiates inhibition of lipid peroxidation as well as scavenging of free radicals[62,63]. Flavonoids are well known for inhibiting the enzyme responsible for superoxide anion production, such as xanthine oxidase[64]. They are also known for inhibition of various enzymes e.g., enzymes of lipoxygenase and cyclooxygenase pathway[65] and glutathione S-transferase, NADH oxidase and mitochondrial succinoxidase, all involved in the generation of ROS[66].

Carotenoids have also been found to be efficient chemical and physical quenchers of O_2 and other ROS and are potentially active agents against ROS-mediated disorders. Clinical studies on β carotene, lycopene, zeaxanthin and lutein support the observation that sufficient intake of carotenoid- rich fruits and vegetables significantly reduced the risk of some chronic diseases[67].

Animals as sources of antioxidants: Antioxidant properties of ascorbate are well known[68]. U.S Recommended Daily Allowance (RDA) for ascorbate based on its function in collagen synthesis[69] and not on its antioxidant properties. On the contrary, the RDA for α-tocopherol is based on antioxidant activity since this is its only well-established physiological function[70].

The results shown by Frei *et al.*[71] demonstrated that ascorbate can completely prevent the initiation of detectable peroxidative damage to plasma lipids by aqueous peroxyl radicals. They also demonstrated that ascorbate is the only endogenous antioxidant in human blood plasma that can completely protect lipids from detectable peroxidative damage induced by aqueous peroxyl radicals. Under this kind of oxidative stress, ascorbate is much more effective antioxidant than protein thiols, α-tocopherol, urate or bilirubin. Ascorbate virtually traps all peroxyl radicals in the aqueous phase before they can diffuse into plasma lipids.

Selenium (Se), a trace mineral is an essential nutrient of fundamental importance to the human body. Selenocysteine is a component of selenoproteins some of which perform vital enzymatic functions[68]. Glutathione peroxidases is the best example in which Se functions as the redox center that catalyzes the reduction of H_2O_2 and phospholipid hydroperoxides to harmless products like water and alcohols[72]. This helps in maintaining the membrane integrity and reduces the oxidative damage to biomolecules like lipids, lipoproteins and DNA. Se consumed in supplements and food exists in various organic and inorganic forms including selenocysteine (animal source), selenomethionine (animal and plant sources and supplements) and selenite (supplements). Liver, crab meat, poultry and fish are major sources of Selenium.

Enzymes and other biomolecules as antioxidants: Enzymes that are known to have antioxidant properties include superoxide dismutase (SOD), catalase (CAT), glutathione

peroxidase (GSHPX) and Glutathione Reductase (GR). Non-enzymatic antioxidants include a variety of free radical quenchers such as vitamin A (retinol), vitamin C-(ascorbic acid), vitamin E (tocopherol), thiols including glutathione (GSH), bilirubin, ferritin, flavonoids and micronutrients (iron, copper, zinc, selenium).

Superoxide dismutase (SOD, EC 1.15.1.1) discovered by McCord and Fridovich[73] plays an important role in the defense mechanism of biological cells exposed to oxygen. The SOD represents a group of enzymes that catalyze the dismutation of O^{2-} and the formation of H_2O_2. This reaction is recognized as an antioxidant system that protects cells from superoxide toxicity.

Catalase (CAT, EC 1.11.1.6) is one of the major antioxidant enzymes[74]. It is one of the first enzymes to be purified and crystallized and is present in every cell and particularly in cell structures that use oxygen in order to detoxify toxic substances and produce H_2O_2. Catalase converts H_2O_2 into water and oxygen[75,76].

Glutathione peroxidase (GPX, EC 1.11.1.9) exists in cell cytosol and mitochondria and has the ability to transform H_2O_2 into water. This reaction uses GSH and transforms it into oxidized glutathione (GSSG). The GPX and CAT have the same action upon H_2O_2 but GPX is more efficient with high ROS concentration whereas CAT has an important action with lower H_2O_2 concentration.

Glutathione reductase (GR, EC 1.6.4.2) is a key enzyme of glutathione metabolism and is widespread among all tissues and blood cells. It a flavin enzyme involved in the defense of the erythrocyte against hemolysis. This enzyme catalyzes the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH) in the presence of NADPH and maintains a high intracellular GSH/GSSG ratio of about 500 in red blood cells[77]. The GR is important not only for the maintaining the required GSH level but also for reducing protein thiols to their native state.

Glutathione-S-transferase (GST, EC 2.5.1.18) catalyzes the conjugation with glutathione of a number of electrophilic xenobiotics, including several carcinogens, mutagens and anticancer drugs[78]. These electrophiles are made less reactive by conjugation with glutathione and the conjugates are thought to be less toxic to the cell.

Taurine, the end product of cysteine metabolism have been reviewed for antioxidant and membrane protective properties[79]. Bilirubin and biliverdin may protect vitamin A and linoleic acid from the oxidative destruction in the intestinal tract[80]. In fact, bilirubin contains an extended system of conjugated double bonds and a reactive oxygen atom and thus is able to possess antioxidant properties. During heme degradation in birds, reptiles and amphibians, biliverdin is produced in the first step and excreted directly without being further reduced to bilirubin. Thus, biliverdin could play a role as a hydrophilic antioxidant in these creatures, whereas in mammals, the polar and nontoxic biliverdin is reduced to a highly specific NADPH-requiring reaction to form potentially toxic, non-polar bilirubin. It then undergoes energetically expensive conjugation reaction before being secreted into bile[81]. Bilirubin associates strongly with albumin and is distributed into entire blood circulation. This suggests that one role of bilirubin may be to act as a powerful chain-breaking antioxidant[82].

NATURAL ANTIOXIDANTS AND THEIR ROLE AS DRUGS

The naturally occurring antioxidants in low-density lipoproteins (LDLs) and plasma protect cells from oxidation[83,84]. Increased lipid peroxidation and decreased antioxidant protection generate epoxides that may spontaneously react with nucleophilic centers in the cell and thereby covalently bind to DNA, RNA and protein[85]. Such a reaction may lead to cytotoxicity, allergy, mutagenicity and/or carcinogenicity, depending on the properties of the epoxide in question[86]. Polyphenolic compounds such as flavanoids inhibit oxidation of low- density protein and reduce thrombotic tendency[87]. Flavanoids present in regularly consumed food reduces the risk of coronary heart diseases in elderly men[87]. The use of vitamin E and vitamin C has proved to be very effective for the non-alcoholic fatty liver disease[88]. Several diseases (such as rheumatoid arthritis and inflammatory bowel disease) are accompanied by excessive phagocyte activation and resulting tissue damage, to which ROS contribute. Some low-molecular-mass substances, such as uric acid, ascorbate (vitamin C), glutathione, tocopherol (vitamin E), ubiquinol, ergothioneine, hypotaurine and lipoic acid, may act as antioxidants in the human body. Long-term antioxidant supplementation can decrease both endogenous and exogenous oxidative DNA damage in lymphocytes[89].

Gallic acid acts as an antioxidant and helps to protect cells against oxidative damages induced by the toxins. The GA is a strong chelating agent and forms complexes of high stability with iron (III)[90,91]. Antioxidant capacity of gallate esters against hydroxyl, azide and superoxide radicals has also been reported[92,93]. N-acetylcysteine's (NAC) has the ability to reduce extracellular cystine to cysteine and as a source of sulfhydryl groups. Administration of NAC in intoxicated animals mainly stimulates glutathione synthesis, enhances glutathione-S-transferase activity, promotes detoxification by inhibiting

xenobiotic biotransformation and also acts as a powerful nucleophile capable of scavenging free radicals[94,95]. A number of researchers suggested that NAC is effective as a chelating agent in reducing the toxicity of heavy metal when it is administrated on intoxicated animals[94,96,97]. It contains a precursor of cysteine which is used in GSH biosynthesis. Thus, it acts as a ROS scavenger as well as increases GSH level in animals[98,99].

Peroxiredoxin (Prdx) is a family of antioxidant enzymes[100]. Studies have shown that mice lacking Prdx1 are viable and fertile but have a shortened lifespan owing to the development of severe hemolytic anaemia and several malignant cancers (beginning at about 9 months), both of which are also observed at increased frequency in heterozygotes. The hemolytic anaemia is characterized by an increase in erythrocyte reactive oxygen species, leading to protein oxidation, hemoglobin instability, Heinz body formation and decreased erythrocyte lifespan. The malignancies include lymphomas, sarcomas and carcinomas and are frequently associated with loss of Prdx1 expression in heterozygotes, which suggests that this protein functions as a tumor suppressor. Prdx1-deficient fibroblasts show decreased proliferation and increased sensitivity to oxidative DNA damage, Prdx1 is an important defense oxidant against aging[100].

The development and discovery of several novel molecules/drugs/natural medicinal compositions based on antioxidant have satisfied majority of aspects of complex pathogenic steps in diseases for which only disease/risk factor modifying therapies are available. It is difficult to show unequivocally whether or not antioxidants are in fact effective for prevention and/or treatment of diseases and, if so, whether it is by the action of scavenging free radicals. Solid data showing the correlation between antioxidant capacity and successful pharmacological properties has not been reported. The current drug discovery paradigm is shifting from addressing single molecular targets to multiple one. Free radicals are implicated in the initiation and progression of many diseases, especially neurodegenerative disorders[101-103]. For example, evidences suggest the involvement of free radicals in the onset of diabetes and in the development of diabetic complications[104]. Studies in animal models and Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) patients demonstrated that antioxidants are effective in preventing experimental diabetes and reducing the severity of diabetic complications.

In recent years a great deal of effort has been devoted to finding multipotent antioxidant that combines radical scavenging activity and enzyme inhibiting potential into a single structure. Cocktails of other drugs and multipotent antioxidants could be an alternative approach to address multiple targets (including radicals). Multifunctional antioxidant can be obtained by two approaches (i.e., screening in compound or drug libraries or rational design by the pharmacophores). The screening approach is dependent on basic biological and chemical research on synthetic compounds and natural products and also to an extent, upon serendipitous findings. The second approach attempts to design and synthesize hybrid molecules, linking an antioxidant group to one or more enzyme-inhibitor pharmacophore.

Chemical Abstracts (SciFinder) listed 248 papers during the period 2000-2002 containing the word-pair 'curcumin and antioxidant[105]. The molecule has been shown to possess a range of pharmacological properties, including anti-inflammatory, anticoagulant and anticarcinogenic activities, among others[106-108]. Curcumin was identified as an efficient Ab-aggregation blocker (IC50 <1 mM)[107,108] and a good metal (Cu^{2+}) chelator[109-110]. The integration of radical scavenging, metal-ion chelating, Ab-aggregation inhibition with anti-inflammatory properties suggest curcumin a very promising multipotent ligand for the treatment of AD[111]. In addition to curcumin, flavonoids such as quercetin, gossypetin, myricetin, epicatechin-3-gallate, quercitrin, isoquercitrin and rutin are also multifunctional antioxidants that might be useful in the treatment of AD. They have long been known to be excellent radical scavengers, endowed with strong metal chelating ability[112]. Moreover, some of them can block Ab or tau protein aggregation[113-116]. In addition, xanthones, a special class of flavonoids, were also identified as efficient radical scavengers[117,118], Monoamine oxidase (MAO) (including isoenzymes A and B) inhibitors[119,120] and potential acetylcholinesterase (AChE) inhibitors[119]. Four antioxidants viz., glycyrrhisoflavone, licocoumarone, myristicin, E-piceatannol exhibit MAO-inhibitory potential, which makes them as well as related compounds, attractive candidates for testing against AD.

As for the other pharmacological effects, antibacterial, antineoplastic, anti-inflammatory and platelet-aggregation inhibition are the most common activities. Because radicals are implicated in the etiology of cancer and inflammation, it is logical that antioxidants can possess antineoplastic and anti-inflammatory properties. However, it is somewhat unexpected to observe the antibacterial properties of many antioxidants. This finding is advantageous to the food industry because both effects are highly desirable to keep foods as fresh as possible. Natural products are important sources for new drugs and are also good lead compounds suitable for further

modification during drug development. Secondary metabolites from natural sources are often perceived as showing more "drug-likeness and biological friendliness than totally synthetic molecules" making them good candidates for further drug development[121,122]. Terrestrial microorganisms are a plentiful source of structurally diverse bioactive substances and have provided important contributions to the discovery of antibacterial agents including penicillins, cephalosporins, aminoglycosides, tetracyclines and polyketides[123]. Current therapeutic applications of metabolites from microorganisms have expanded into immunosuppressive agents (e.g., cyclosporins and rapamycin), cholesterol-lowering agents (e.g., lovastatin and mevastatin), anthelmintic agents (e.g., ivermectin), antidiabetic agent (acarbose) and anti-cancer agents (e.g., pentostatin, peplomycin and epirubicin)[15,124].

Apomorphine hydrochloride obtained from poppy is a potent dopamine receptor agonist used to treat Parkinson's disease. Tiotropium bromide obtained from *Atropa belladonna* is used for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Nitisinone is a modification of mesotrione, a herbicide based on the natural product leptospermone has been used successfully as a treatment of hereditary tyrosinaemia type 1 (HT-1), a severe inherited disease of humans caused by a deficiency of fumarylacetoacetate hydrolase (FAH), leading to accumulation of fumaryl and maleylacetoacetate and progressive liver and kidney damage[125]. Galantamine hydrobromide is an Amaryllidaceae alkaloid obtained from *Galanthus nivalis*. It has been used traditionally in Bulgaria and Turkey for neurological conditions and was launched onto the market as a selective acetylcholinesterase inhibitor for AD treatment, slowing the process of neurological degeneration by inhibiting acetylcholinesterase as well as binding to and modulating the nicotinic acetylcholine receptor[121]. Everolimus is an orally active 40-O-(2-hydroxyethyl) derivative of rapamycin, originally produced from *Streptomyces hygroscopicus*. Everolimus exhibits its immunosuppressive effect by blocking growth factor (interleukin (IL)-2 and IL-15) mediated proliferation of hematopoietic (T cells and B cells) and non-hematopoietic (vascular smooth muscle cells) cells through inhibiting p70 S6 kinase, leading to arrest of the cell cycle at the G 1/S phase[126]. Telithromycin is a semi- synthetic derivative of the 14-membered macrolide, erythromycin A, isolated from *Saccharopolyspora erythraea* and retains the macrolactone ring as well as a D-desosamine sugar moiety. It inhibits protein synthesis by interacting with the peptidyltransferase site of the bacterial 50S ribosomal subunit and exhibits antibacterial effect on respiratory tract pathogens resistant to other macrolides[127].

The extracts of various seaweeds and especially, brown algae *Hydroclathrus clathratus* and *Padinna arbarescences*[128] have shown to inhibit the monkey and human cancer cell lines. The crude and purified extracts demonstrated antioxidant activity and suppressed tumor in mouse models. Studies show that cardiovascular diseases (CVD) represent a continuum of processes including oxidative stress, vascular remodeling, endothelial dysfunction and inflammatory processes[129]. Shimazu *et al.*[130] evaluated the association between traditional Japanese dietary patterns and CVD and concluded that antioxidant rich foods, including seaweeds decreased the CVD risk. Extensive research reveals the human health aids of naturally occurring antioxidant compounds. *In vitro* trials have claimed anti-viral, anti-inflammatory, anti-tumor, anti-mutagenic, anti-cancer and hepatoprotective properties[131-133] (Table 2).

Many studies[134] have shown that superoxide anions produced by macrophages infiltrated into the virus-infected organs is implicated in the development of severe influenza-associated complications. Selected antioxidants, such as pyrrolidine dithiocarbamate, N-acetyl-L-cysteine, glutathione, nordihydroguaiaretic acid, thujaplicin, resveratrol, (+)-vitisin A, ambroxol, ascorbic acid, 5,7,4-trihydroxy-8-methoxyflavone, catechins, quercetin 3-rhamnoside, iso-quercetin and oligonol, inhibit the proliferation of influenza virus and scavenge superoxide anion. The combination of antioxidants with antiviral drugs synergistically reduces the lethal effects of influenza virus infections. These results suggest that an agent with antiviral activity combined with antioxidant activities could be a drug of choice for the treatment of severe influenza-associated complications.

ROLE OF ANTIOXIDANTS IN MEDICINAL DRUG-INDUCED OXIDATIVE STRESS

Most medicinal drugs have adverse effects that induce oxidative stress, an imbalance of generation and detoxification of reactive oxygen species. So, it is a reasonable assumption that the antioxidant might alleviate the toxicity induced by these drugs. Although there are concerns regarding the "adverse effects" of antioxidant supplementation for the purpose of alleviating oxidative stress induced by medicinal drugs (i.e., toxicities of the antioxidants, other possible drug interactions), supplements have always interested pharmacists and are reported to be beneficial to some extent.

Table 2: A summarized table of the potential drug molecules, their sources and the disease they target

Potential drug molecule	Source (Plant/Microbial)	Disease targeted
Apomorphine hydrochloride	*Papaver somniferum*	Parkinson's disease[135]
Tiotropium bromide	*Atropa belladonna*	Bronchospasm associated with chronic obstructive pulmonary di4.sease (COPD)[136]
Nitisinone	*Callistemon citrinus*	Her5.editary tyrosinaemia type 1 (HT-1)[125]
Pitavastatin	*Penicillium citrinum*	Dyslipidemias[137]
Galantamine hydrobromide	*Galanthus nivalis*	Alzheimer' s disease[121]
Everolimus	*Streptomyces hygroscopicus*	Blocking growth factor (interleukin (IL)-2 and IL-15) mediated proliferation of hematopoietic (T cells and B cells) and non-hematopoietic (vascular smooth muscle cells) cells through inhibiting p70 S6 kinase, leading to arrest of the cell cycle at the G 1 /S phase[126]
Telithromycin	*Saccharopolyspora erythraea*	Antibacterial effect on respiratory tract pathogens resistant to other macrolides[127]
Quercetin	Berries, parsley, capers, buckwheat, onions and peppers, Citrus fruits, apple	Alzheimer's disease, Parkinson's disease[112]
Cucurmin	*Curcuma longa*	Alzheimer's disease[112]
Gossypetin	*Hibiscus sabdariffa*	Alzheimer's disease[112]
Myricetin	vegetables, fruits, nuts, berries, tea, red wine	Alzheimer's disease[112]
Rutin	*Ruta graveolens*	Alzheimer's disease[112]
Epicatechin-3-gallate	Green tea, buckwheat, grape	Alzheimer's disease[112]
Catechins	Cocoa, prune juice, broad bean	Cardiovascular diseases[138]
Theaflavins	Black tea	Lipid peroxidation, in erythrocytes membranes and microsomes[58]
Naringin	Citrus fruits, especially grapes	Parkinson's disease[56]
Sinensetin	Citrus aurantium	Cancer, Cardiovascular diseases[56]

Comprehensive studies have been made of the possible roles of antioxidants in preventing oxidative damage induced by medicinal drugs. It has generally been found that antioxidants do play a positive role to some extent.

Drug-induced hepatotoxicity is common and its actual frequency is hard to determine due to incomplete observation of exposure and underreporting difficulties in detection or diagnosis. For example, certain drugs containing a nitro-aromatic moiety or drugs interacting with nuclear receptors such as phenobarbital may cause organ-selective toxicity or may potentiate the toxicity of other drugs[139,140]. Several natural products have been reported to date to alleviate the drug-induced toxicity. The dietary nature and less adverse reactions of these natural products provide them an extra favour over other candidates of supplementary medication. The most extensively investigated natural products for hepatoprotection are silymarin, resveratrol, curcumin and gingko due to their high efficacies, low or no toxicity and easy availabilities. As an adjuvant therapeutic drug, ginkgo appears to be promising in diabetics with respect to ischemic myocardium injury[141]. Intake of *Ginkgo biloba* extract may alter the hepatic metabolism by modulating hepatic drug metabolizing enzymes, altering the level of antioxidant enzymes and endogenous antioxidants such as GSH.

Sutherlandia frutescens (SF) is a legume native to southern Africa and is most utilized general medicinal plant[142]. It has been found to have great versatility in its effects on various types of disorders, including infections (such as flu, TB, chicken pox, urinary tract infection and diarrhea). The anti-inflammatory effect of SF relies on its capability of scavenging phagocyte-derived oxidative species. Phytochemical investigations of the SF plant showed that it contains significant amounts of γ-amino butyric acid and L-canavanine, pinitol, flavonol glycosides and triterpenoid saponins that may be pharmacologically relevant. The great diversity in the possible antioxidant metabolites present in SF indicates that SF extract might be a promising candidate as antioxidant supplementation as well as a solution for medicinal-drug induced oxidative stress.

N-acetylcysteine (NAC), a synthetic thiol, is a free-radical scavenger and a precursor of glutathione (the main endogenous antioxidant). However, the negative charge of NAC at physiological pH limits its bioavailability. N-acetylcysteineamide (NACA) is neutral in charge and is believed to have higher lipophilicity than NAC. Experiments were designed to determine the potential protective ability of NACA against different oxidative drugs. The studies revealed that NACA seems to be a broad-spectrum protector that prevents oxidative damage. This emphasizes NACA's potential

for serving as a clinical protective antioxidant for patients who receive potentially dangerous oxidative drugs[143].

FUTURE PROSPECTS

Various studies and trials on antioxidants potential as drugs are going on in the research community. They can be efficient molecules for treatment as well as prevention of a large number of diseases. The approach of development of genetically modified plants can be used to yield vegetables with high levels of certain compounds to increase antioxidant availability. Tomatoes containing 3 times more lycopene concentration and 'Orange cauliflower' are found to be rich in carotene concentration[144]. The Vegetable and Fruit Improvement Centre at Texas A and M University is a leading hub in this area and created world's first 'super-vegetables' about a decade ago for example-purple carrot breed containing 40% more beta-carotene content than usual carrots. The enrichment of eggs with vitamin E, selenium, carotenoids and dihydroxy acetone (DHA) has also improved its nutritional value with increased antioxidant status. The effect of antioxidant supplements or dietary antioxidants in vivo is best studied using combinations of validated methods for measurement of oxidative damage and where a particular disease is being investigated, the end point of the disease. This could be thought of as a part of the approach for future antioxidant supplementation and intervention studies of any type.

The recent advancement is the free radical trapping in the neonatal plasma. The use of antioxidants that traps radicals and thereby reduce the chain length of oxidation are referred to as secondary or chain breaking antioxidants. Tartrate resistant acid phosphatase (TRAP) test was used to for assessing postnatal changes in the total radical trapping capacity of the plasma in the preterm baby[145].

The incurability of metastatic cancer can be studied through the molecular pathways which revealed the cancer pathways through the DNA sequencing which are useful in studying antioxidant and oxidant derived lead compounds which reduce the severity of incurable cancers and reduces the mortality[146].

Traditional medical knowledge can be explored and diverse natural leads may be found and drugs can be prepared with a fusion of ancient wisdom and modern science. Being a strategy of natural product based drug discovery, after identification of the natural product leads, preparation of molecular fingerprints of their chemical composition, applying new synthetic organic methodologies, biotransformation, combinatorial biosynthesis and a combination of these approaches for the modification of the leads would generate a pool of novel and structurally diverse analogs that can be screened for much improved and new activities. According to research, the regulation of gene expression by means of antioxidants, oxidants and redox state has emerged as a novel target that has promising therapeutic implications[147]. Thus, advance efforts are necessary to fully illuminate the importance of antioxidants as therapy.

SIGNIFICANCE STATEMENTS

Present review highlights the role of antioxidants in prevention as well as treatment of disorders which occur due to free radicals.

The review also includes various antioxidant molecules of different origin that can be considered as potent drug candidates for life threatening diseases.

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