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Natural products and their antioxidant potential

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ABSTRACT

A natural product is a chemical compound or substance produced by a living organism found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. Natural products have been the basis of treatment of human diseases and many higher plants contain novel metabolites with antimicrobial and antiviral properties. As an alternative medicine, people derived therapeutic materials from thousands of plants; however discovering medicines or poisons remains a vital question. Since reactive oxygen radicals play an important role in genesis of numerous human disease processes, antioxidants derived from consumable fruits, vegetables, spices and beverages have received considerable attention. The antioxidants protect our body systems from free radicals mediated damage at the cellular and molecular levels. The pool of free radicals production in our body stems mainly from the mitochondrial activity but the environmental factors such as xenobiotics, pollutants and other stressors also contribute in it enormously. This phenomenon generates imbalance between the oxidants (free radical species, FRS) and the innate antioxidants; a condition called as oxidative stress. Oxidative stress leads to onset of numerous disease processes including cancer, heart, lung, brain and kidney associated diseases, cell death and aging. Apart from the best-known antioxidants such as vitamins A, C and E, and the mineral selenium, some flavonoids (secondary metabolites) and vitamin precursors synthesised by plants are required to be taken from outside to establish the balance by quenching the excess FRS. The present review presents a comprehensive account of updated information available on natural products containing antioxidant potential with therapeutic implications.

KEYWORDS

Natural products;
Free radical species (FRS);
Antioxidants;
Oxidative stress;
Vitamins;
Flavonoids.

INTRODUCTION

Natural products are those that are found in nature and have biological or pharmacological activity for use in pharmaceutical drug design. They are produced by living organisms. It is difficult to synthesize natural products as they have very complex structure and synthesizing them is very costly. Drugs such as penicillin, morphine and paclitaxel (Taxol) are procured from their natural source. The process of extraction of these products is very expensive and time taking. In fact, there extraction from natural source is wasteful as it is too

expensive. For example in order to get one single dose of drug[1] paclitaxel one yew tree has to be cut. Medicines of natural product may be obtained from tissues of terrestrial plants, marine organisms or microorganism fermentation broths which are known as biorespecting.

Screening natural products

Natural products are kept for medicinal use and the activity of the compound thus obtained is known as active product and such a structure acts as a lead compound. Many of the medicines obtained today are directly procured from natural source. Thus the lead compound obtained is by total synthesis or it can be a starting point for a semisynthetic compound. It can also act as a template for structurally different total semisynthetic compound. The reason is that as most biologically active natural product compounds are secondary metabolites with very complex structures.

Traditional medicine

In the ancient times people were more dependent on the flora and fauna of traditional plants. They made many crude drugs by the root, stem and leaves of natural plants. The purgative for many centuries was the root of Rhubarb. Anthraquinone was the most significant chemical in rhubarb root and these are used as a lead compounds in designing of the laxative dantron[2].

Some systems, like traditional Chinese medicine or Ayurvedic were fully as sophisticated and as documented systems as western medicine. A study of ethnobotany can give clues as to which plants might be worth studying in more detail. The extensive records of Chinese medicine about response to Artemisia preparations for malaria also provided the clue to the novel antimalarial drug artemisinin. The therapeutic properties of the opium poppy (active principle morphine) known in Ancient Egypt, were those of the *Solanaceae* plants in ancient Greece (active principles atropine and hyoscine). The snakeroot plant was well regarded in India (active principle reserpine), and herbalists in medieval England used extracts from the willow tree (salicin) and foxglove (active principle digitalis - a mixture of compounds such as digitoxin, digitonin, digitalin). The Aztec and Mayan cultures of Mesoamerica used extracts from a variety of bushes and trees including the ipecacuanha root (active principle emetine), coca bush (active principle cocaine), and cinchona bark (active principle quinine). Ethnobotanist Richard Schutles lead to the discovery of new medicines[3]. The accupuncturists investigated Mayan medicine in wind in the blood, this had something in common to share with the old healers and they gathered some new information which was not available with anthropoligists[4].

Natural products, including plants, animals and minerals have been the basis of treatment of human diseases. History of medicine dates back practically to the existence of human civilization. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies. The future of natural products, drug discovery will be more holistic, personalized and involve wise use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community[5]. The foundation of the modern pharmaceutical industry was laid when techniques were developed to produce synthetic replacements for many of the medicines that had been derived from the forest. Natural products chemistry actually began with the work of Serturner, who first isolated morphine from opium. This, in turn, was obtained from opium poppy (*Papaver somniferum*) by processes that have been used for over 5000 years. Many such similar developments followed. Quinine from cinchona tree is well known. The following are a few examples[6]. In the early 1500s, Indian fever bark was one of the first medicinal plants to find appreciative consumers in Europe, taken from the cinchona tree (*Cinchona officinalis*), the bark was used as an infusion by native people of the Andes and Amazon highlands to treat fevers. Jesuit missionaries brought the bark back to Europe. By the early sixteenth century, this medicine was known as 'Jesuit fever bark', quite a transformation. The name coca (*Erythroxylum coca*) comes from an Aymara word meaning 'tree'. In Andean cultures, the leaves of the coca tree have been primarily chewed to obtain there benefits. From ancient times, indigenous people have added alkaline materials such as crushed seashells or burnt plant ashes to the leaves in order to accentuate the pharmacologically active moiety of coca. The jaborandi tree (*Pilocarpus jaborandi*) secretes

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alkaloid-rich oil. Several substances are extracted from this aromatic oil, including the alkaloid pilocarpine, a weapon against the blinding disease, glaucoma. American Indians on the island of Guadeloupe used pineapple (*Ananas comosos*) to reduce inflammation in wounds and other skin injuries, to aid digestion and to cure stomachache. In 1891, an enzyme that broke down proteins (bromelain) was isolated from the fresh juice of pineapple and was found to break down blood clots. Other pharmaceuticals that have their origin in botanicals include atropine, hyoscine, digoxin, colchicine and emetine. Reserpine, an anti-hypertensive alkaloid (*Rauwolfia serpentina*) became available as a result of work carried out by Ciba-Geigy in India. It appears that most of these early discoveries are mainly based on traditional medicines; many products could act as poisons in toxic doses.

Exploring traditional Indian and Chinese medicine systems

A major problem with traditional, indigenous medicine is discovering a reliable 'living tradition' rather than relying upon second-hand accounts of their value and use. In many parts of the world the indigenous systems of medicine have almost completely broken down and disappeared. In anthropological terms these are 'little traditions', while the Ayurvedic Indian and traditional Chinese systems are living 'great traditions'. The traditions are an excellent repository of knowledge about medicinal and poisonous properties of botanicals; researchers have mainly exploited poisonous sources. This is due to many reasons. First, it is relatively easy to present and demonstrate poisonous characteristics of botanicals. Secondly, there are no written documentation and poisonous characters are known after experimentation. Thirdly, poisonous characters are known when differences are made between ordinary and extraordinary material for pharmaceutical development. Fourthly, a considerable time period is required to experimentally demonstrate between true medicinal activities and safety profile.

There are a lot of organized database, and more exhaustive description of botanical material available that can be tested using modern scientific methods. Ayurveda and Chinese medical systems thus have an important role in bioprospecting of new medicines.

Interactive chemistry of natural products and biological processes

Pharmaceutical research took a major shape when alongside natural products; chemistry, pharmacologists, microbiologists and biochemists began to discover the chemistry of natural processes in human, animals, plants and microorganisms. Advances in synthetic organic chemistry led to the identification of many key chemical molecules that offered more opportunities to develop novel compounds. Many new drugs emerged by this route, particularly those now being used to treat infections, infestations, cancers, ulcers, and heart and blood pressure conditions. Many drugs were developed through random screening of thousands of chemicals. Examples of such drugs include sulphonamides, isoniazid, anti-psychotics, anti-histamines and penicillin. Emergence of the modern pharmaceutical industry is an outcome of all these different activities that developed a single molecule with highly selective activity for a wide variety of ailments. The drugs produced in many cases improved on nature, viz. and a whole new range of local anaesthetics were discovered. Cocaine avoided its dangerous effects on blood pressure; chloroquine is much less toxic than quinine. These successes and many more like them resulted in reduced interest in natural products drug discovery. Work on developing new drugs for the treatment of the world's major diseases, malaria, trypanosomiasis, filariasis, tuberculosis, schistosomiasis, leishmaniasis and amoebiasis came almost to a standstill. In addition, although botanical medications continued to be produced in every country, the clinical efficacy of these was usually not evaluated and the composition of these complex mixtures was only crudely analysed.

Knowledge derived from traditional Indian sources

Lag phase for botanical medicine is now rapidly changing for a number of reasons. Problems with drug-resistant microorganisms, side effects of modern drugs, and emerging diseases where no medicines are available, have stimulated renewed interest in plants as a significant source of new medicines. A number of synthetic drugs have adverse and unacceptable side effects. There have been impressive successes with botanical medicines, most notably quinghaosu, artemisinin

from Chinese medicine. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on Ayurvedic medicinal plants[7]. Numerous molecules have come out of Ayurvedic experimentation base, examples include rauwolfia alkaloids for hypertension, psoralens in vitiligo, holarrhena alkaloids in amoebiasis, guggulsterons as hypolipidemic agents, mucuna pruriens for Parkinson's disease, piperidines as bioavailability enhancers, baccosides in mental retention, picrosides in hepatic protection, phyllanthins as antivirals, curcumine in inflammation, with anolides, and many other steroidal lactones and glycosides as immunomodulators[8]. A whole range of chronic and difficult-to-treat diseases such as cancers, cardiovascular disease, diabetes, rheumatism and AIDS, all require new effective drugs. Most developing countries have relied and will continue to rely on traditional natural medicines due to the deterrence of high costs of modern allopathic medicines. Four out of ten Americans used alternative medicine therapies in 1997; total visits to alternative medicine practitioners increased by almost 50% from 1990 and exceeded the visits to all US primary care physicians[9]. Every medical system or therapy has certain advantages and limitations. Modern medicine is no exception to this[10]. Some of the prominent commercial plant-derived medicinal compounds include: colchicum, colchicine, betulinic acid, camptothecin, topotecan (Hycamtin®), CPT-11 (irinotecan, Camptosar®), 9-aminocamptothecin, delta-9-tetrahydrocannabinol (dronabinol, Marinol®), beta lapachone, lapachol, podophyllotoxin, etoposide, podophyllinic acid, vinblastine (Velban®), vincristine (leurocristine, Oncovin®), vindesine (Eldisine®, Fildesin®), vinorelbine (Navelbine®), docetaxel (Taxotere®), paclitaxel (Taxol®), tubocurarine, pilocarpine and scopolamine.

Antioxidants

Those molecules which are capable of slowing or preventing the oxidation of other molecules are antioxidant. In oxidation electrons are transferred from a substance to an oxidizing agent. Antioxidants terminate chain reactions by removing free radicals and thereby inhibit other oxidation reactions by being oxidised themselves. The reducing agents such as thiols, ascorbic acid or polyphenols[11] are also antioxidants.

Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. Low levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells. An important part of many human diseases is the use of antioxidant in pharmacology. For maintaining health and preventing diseases such as cancer and coronary heart diseases antioxidants are used as ingredients. Excess use of these ingredients may be harmful as well[12].

Antioxidants are substances or nutrients in our foods are those which can prevent or slow the oxidative damage to our body. When our body cells use oxygen, they naturally produce free radicals (by-products) which can cause damage. Antioxidants act as "free radical scavengers" and hence they prevent and repair damage done by these free radicals. Health problems such as heart disease, muscular degeneration, diabetes, cancer etc all contribute to oxidative damage. Immune defence is also enhanced by the antioxidants and therefore the risk of cancer and infection is minimized.

Classification of antioxidants

There are two broad divisions of antioxidants. These are hydrophilic i.e. soluble in water and hydrophobic when they are soluble in lipids. The water soluble antioxidants react with oxidants in cell cytosol and the blood plasma on the other hand are lipid soluble antioxidants that protect cell membranes from lipid peroxidation[12,13]. These compounds are either obtained from the body itself or from the diet[14]. There occurs wide range of distribution of antioxidants in the body fluids and tissues. The antioxidants present in cells are glutathione or ubiquinone on the other hand uric acid is more evenly distributed (TABLE 1). A few antioxidants are important as pathogens in contributing to the virulence factors[14].

Different antioxidants have synergistic and interdependent effects on one another with the various metabolites[15,16]. The functioning of one antioxidant is interdependent on other organism[14]. The protection offered by any one antioxidant is mainly dependent on concentration and reactivity towards particular oxygen species

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TABLE 1 : Different antioxidants and their concentrations in body fluids of humans.

Antioxidant metabolite	Solubility	Concentration in human serum (μM)[123]	Concentration in liver tissue (μmol/kg)
Ascorbic acid (vitamin C)	Water	50-60[101]	260 (human)[115]
Glutathione	Water	4[116]	6,400 (human)[25]
Lipoic acid	Water	0.1-0.7[117]	4 - 5 (rat)[118]
Uric acid	Water	200-400[55]	1,600 (human)[115]
Carotenes	Lipid	β-carotene: 0.5-1, retinol (vitamin A): 1-3[119]	5 (human, total carotenoids)[120]
α-Tocopherol (vitamin E)	Lipid	10-40[119]	50 (human)[115]
Ubiquinol (coenzyme Q)	Lipid	5[121,122]	200 (human)[32]

and status of antioxidant with which it is acting[14].

The antioxidant defense by some compounds and chelating transition metals and preventing them from catalyzing the production of free radicals is necessary for the cell. Particularly important is the ability to sequester iron, which is the function of iron-binding proteins such as transferrin and ferritin[11]. Selenium and zinc are commonly referred to as antioxidant nutrients, but these chemical elements have no antioxidant action themselves and are instead required for the activity of some antioxidant enzymes.

Ascorbic acid

Ascorbic acid or "Vitamin C" is a monosaccharide antioxidant, found in both the animals as well as plants so it is generally obtained from the food we eat and hence it is an essential vitamin[17]. Ascorbic acid as such is not required by the animals in their diets as they are produced in their bodies[18]. In cells, it is maintained in its reduced form by reaction with glutathione, which is catalyzed by protein disulfide isomerase and glutaredoxins[18,19]. Ascorbic acid acts as a reducing agent which can reduce and neutralize reactive oxygen species (ROS) such as hydrogen peroxide[20]. In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the antioxidant enzyme, ascorbate peroxidase, a function that is particularly important in stress resistance plants[21]. Although various antioxidants generally behave synergistically, ascorbic acid can degrade other antioxidants of the phytochemical family anthocyanin[22].

Glutathione

It is found in most of aerobic life[23] and it is a cysteine-containing peptide. Generally it is not required to be taken in the diet as it is synthesized from constituent amino acids inside the cell[24]. It has antioxidant properties and is maintained inside the cell by the enzyme glutathione reductase which inturn reduces glutathione peroxidases and glutaredoxins[25]. Since it maintains the cells in redox state, it is one of the most important antioxidants[23]. However, in some organisms there is replacement of glutathione by mycothiol in actinomycetes, or by trypanothione in the kinetoplastids[24,26,27].

Melatonin

It is one of the powerful antioxidants with an ability to crosses the cell membranes and blood brain barrier easily[28]. Melatonin unlike other antioxidants does not undergo redox cycling. Vitamin C acts as a pro-oxidants and promotes free radical formation. If Melatonin is oxidised once it cannot be reduced as it forms several stable end products with free radicals and hence it is termed as a terminal or suicidal antioxidant[29].

Tocopherols and tocotrioenols (Vitamin E)

It is a collective name for a set of eight related tocopherols and tocotrienols. These are fat –soluble vitamins with antioxidant properties[30,31]. The α-Tocopherol is the most important lipid soluble antioxidant, and it protects membranes from oxidation by reacting with lipid radicals produced during the lipid peroxidation chain reactions[30,31]. This reaction inturn is oxidised to α-tocopheroxyl radicals that can be recycled back to active reduced form through reduction by other antioxidants such as ascorbate, retinol or ubiquinol[32]. This reaction produces oxidised α-tocopherol and not water-soluble antioxidants, which inturn protects glutathione peroxidase 4 (GPX4)–deficient cells from cell death[33]. Still the roles of various forms of Vitamin E are still not very clear. The most important function of α-tocopherol is as a signalling molecule and it does not have any role in antioxidant metabolism[34,35]. But little is known about the functions of the other forms of Vitamin E, out of

which γ-tocopherol is a nucleophile that may react with electrophlie mutagens[36] and tocotrienols may be important in protecting neurons from damage[37].

Pro-oxidants activities of antioxidants

Antioxidants act as reducing agents as well as pro-oxidants eg. Vitamin C has an antioxidant activity when it reduces oxidizing substance such as hydrogen peroxide[38] and it also reduces metal ions that generate free radicals through Fenton reaction[39]. Vitamin C appears to have antioxidant action in the body[39,40]. Less research is done on other dietary antioxidants such as Vitamin E[41] or the polyphenols[42].

Antioxidant natural products possess digestive and antimicrobial properties

Digestion is a complex process and has indirect control on the body. If our digestive system is not in good shape, undigested food will collect in the intestine, leading to a number of digestive problems and autoimmune disorders. According to Ayurveda, foods and herbs are divided into three categories: Sattvic, meaning pure; Rajasic, which means energy; and Tamasic, meaning inertia-inducing. Sattvic foods such as fruits, some vegetables, ghee and milk, promote spiritual awakening and enlightenment. Rajasic foods, like garlic, onions and strong spices, create energy and vigour and increase sexuality and fertility. Tamasic foods produce drowsiness, sleepiness and dullness. Ayurvedic medicine counsels to eat more sattvic and rajasic foods, and fewer tamasic foods, which include meat and pesticides. Several Ayurvedic herbs are helpful in promoting strong digestion. Out of these, some are amla, Haritaki, bahera, trifla, ginger, long pepper, black pepper, turmeric, cumin, coriander, garlic and onion. These spices have a long history of use in India and China, and numerous studies have documented their digestive, anti-bacterial, anti-viral, anti-parasitic and antioxidant properties.

Amla (*Emblica officinalis*)

Amla fruit, also known as Indian gooseberry, is one of the richest sources of bioflavonoids and vitamin C. This plum sized fruit is revered for its anti-aging and immune-enhancing properties. Research has shown that the potency of 8.7 mg of natural vitamin C complex from amla is equivalent to 100 mg of synthetic vitamin C. In addition to its antioxidant properties, amla also has anti-fungal, anti-hepatotoxic, anti-inflammatory and rejuvenative properties.

Haritaki (*Terminalia chebula*)

Haritaki is a rich source of tannin, fructose, amino acids, succinic acid and beta-sitosterol. Clinical studies have demonstrated its anti-viral properties against cytomegalovirus and anti-bacterial properties against *E. coli*, salmonella and cholera. Ayurvedic literature notes haritaki's use as a digestive and eliminative of toxic accumulation.

Bahera (*Terminalia bellerica*)

Bahera is a rich source of tannins. It has shown remarkable results in treating symptoms of asthma and chronic sinusitis. Clinical trials have also shown its antihistaminic, anti-tussive, anti-bacterial and anti-fungal properties. A recent study conducted in Kerala in India has also shown an anti-HIV and antimalarial action.

Trifla

A combination of *Emblica officinalis*, *Terminalia chebula* and *Terminalia bellerica*, Trifla is an excellent digestive, eliminative and adaptogen. Trifla has also shown anti-viral properties against cytomegalovirus, herpes simplex and HIV virus *in vitro*. The antioxidant properties of trifla appear to be greater than vitamin C and vitamin E. Trifla is generally considered safe for use on a long-term basis.

Ginger (*Zingiber officinalis*)

It is a folk remedy for arthritis, dyspepsia, flatulence, colic, painful stomach conditions and nausea. Ginger has a wonderful digestive power, anti-inflammatory action and blood thinner. The recommended dosage is 2 g to 10 g with meals, but those on blood-thinning medication should not take more than 2 g per day.

Trikatu

It is an equal combination of black pepper, long pepper and ginger which is known as trikatu and has been used in a number of various Ayurvedic preparations. It is used in digestion and also enhances the availability of nutrients.

Turmeric

One of the most prized Ayurvedic herbs, turmeric

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is a powerful antioxidant and cancer protectant. It has also shown anti-bacterial properties against salmonella. While the role of Ayurvedic herbs can often be critical to proper digestion, Ayurvedic medicine also employs certain eating rituals that enable the digestive system to function optimally. When we eat our breakfast we should not drive immediately to work as our attention is less on the food than it is on the highway. Many studies have shown that people who eat in front of a television gain more weight. These sorts of distractions take attention away from food and digestion and place it on events or images far from the act of eating.

Natural products containing anti-HIV potential

It is an immunosuppressive disease caused by human immunodeficiency virus (HIV) which results into life-threatening infections and malignancies[43]. Although lot of research has been done and a number of antiviral therapy have come up AIDS is the leading cause of death worldwide. Calanolide A, a coumarin isolated from *Callophyllum lanigerum* and two other natural product derived molecules, DSB and 3-hydroxymethyl-4-methyl DCK are in phase II drugs for treatment of HIV infection.

Antibacterial and antioxidant properties of the methanol extracts of the leaves and stems of *Calpurnia aurea*

Calpurnia aurea is used for the treatment of amoebic dysentery and diarrhoea in animals, killing head lice in humans and ticks in animals, syphilis, diarrhoea, leishmaniasis, tapeworm, trachoma, *Tinea capitis*, wound, scabies, elephantiasis and different swellings[44-48]. In South Africa, Calpurnia leaves and powdered roots are used to destroy lice and to relieve itches. Unspecified parts are used to destroy maggots and the leaves are used to treat allergic rashes, particularly those caused by caterpillars. In East Africa, leaf sap is used to destroy maggots in wounds. In Nigeria, the seeds are used to treat abscesses. In Ethiopia, it is used to treat stomach complaints, headache, eye diseases, amoebic dysentery, scabies (skin infection caused by ticks) and as an insecticide[48,49].

Free radicals have been implicated in the causation of several diseases such as liver cirrhosis, atherosclerosis, cancer, diabetes, etc. and compounds that can scavenge free radicals have great potential in ameliorating these disease processes[50-54]. Antioxidants thus play an important role in protecting the human body against damage by reactive oxygen species[55,56]. Free radicals or reactive oxygen species (ROS) are produced *in vivo* from various biochemical reactions and also from the respiratory chain as a result of occasional leakage. These free radicals are the main culprits in lipid peroxidation[55]. Plants containing flavonoids have been reported to possess strong antioxidant properties[56,57].

Natural products from microorganisms have been the primary source of antibiotics, but with the increasing acceptance of herbal medicine as an alternative form of health care, the screening of medicinal plants for active compounds has become very important because these may serve as promising sources of novel antibiotic prototypes[58-60].

Chemical composition and antioxidant properties of *Salvia officinalis L*

The great demand of natural products such as essential oils supports the implantation of aromatic and medicinal plant cultures in Tunisia. *Salvia officinalis* (called sage) is a popular plant belonging to the family of Labiatae and is a native in the Mediterranean region[61]. The name "Salvia" comes from the Latin word meaning "the heal," which sums up the folkloric belief of its therapeutic properties for almost all kinds of aliments and its popularity in traditional medicine. The composition of the oil obtained has been studied during the two past decades. According to the literature the most important volatile constituents of *Salvia officinalis* are α-thujone, β-thujone, 1,8-cineole and β-caryophyllene. This chemical composition was found to be depending on the age of the plant parts, the climatic conditions, the season, the different plant parts and the culture site. Several studies have shown that the top of the aerial parts are the main contributors to its antioxidant activity[61].

Antioxidant properties of corn fibre oil

The development of oxidative rancidity in products is a serious concern because the rancidity can lead to undesirable flavours and odours as well as potentially toxic lipid oxidation products. While there are many effective synthetic antioxidants that can be used to suppress lipid oxidation, there is strong consumer interest in using natural products as antioxidants. Many com-

pounds, such as corn fibre, confer health benefits in addition to their antioxidant activity. Extracting corn fibre from the grain yields corn fibre oil, which consists of approximately equal amounts of oryzanol, β-sitosterol and linoleic acid. Oryzanol and β-sitosterol have been shown to lower plasma cholesterol. They also possess antioxidant activity in model systems.

Phytochemistry and antioxidant potential of mangosteen

Mangosteen is composed of an edible white interior pulp (botanically, an aril defined as flesh surrounding seeds) encased in a firm inedible pericarp dense in purple pigmentation. The most remarkable nutritional characteristic of mangosteen aril is its relative absence of essential macro- or micronutrients (TABLE 2). Many essential vitamins and minerals typically found in fresh citrus fruits either were not reported in these assays or could not be detected as their contents were very low[62,63]. With nutrient content so sparse, mangosteen appears not to qualify for "superfruit status" as other rare fruits having excellent nutrient and/or phytochemical contents, such as açai, goji ("wolfberry") and pomegranate. These antioxidant fruits are cast as "superfruits".

TABLE 2 : Nutrients with greater than 5% DRI found in mangosteen aril.

Nutrient	Content (per 100 g)	DRI (adults)	Approx % DRI
Carbohydrates	14-18 g*	130 g	12
Dietary fibre	1-5 g*	30 g	10
Vitamin C	1-7 mg*	75-90 mg	5
Folic acid	31 µg^	400 µg	8
Manganese	0.2 mg^	2 mg	5

DRI = Daily recommended intake; Range of values from 3 independent sources:[44,62,63,124]

Antioxidants from mangosteen

The health value of mangosteen juice relies on xanthones. The potential benefit of xanthones as antioxidant photochemical is useful to human health[62,64]. In recent years, mangosteen has attracted special attention for its xanthone extracts - garcinol and mangostin - having potential as anti-inflammatory agents with preliminary evidence for inhibiting cyclo-oxygenase (COX) enzymes and carcinogens[65,66]. The potential health value of mangosteen juice has cautioned the public to not assume health benefits without evidence from rigorous research including human clinical trials[62,64]. An understanding of the present state of xanthone research shows that human studies on xanthones are at least a decade away, as there are no approved programs for mangosteen in human research within the NIH database for clinical trials[67,68].

In vitro antioxidant properties of certain indigenous medicinal plants from Western Ghats of India

Nature still serves as the man's primary source for the cure of his ailments. The majority of the rich diversity of Indian medicinal plants is yet to be scientifically evaluated for such properties. However, the potential of higher plants as source for new drugs is still largely explored. The free radicals are chemical species, capable of independent existence; posses an unpaired electron on an orbital. They occur in the form of Superoxide, Hydroxyl radical (OH^-) and Peroxide ion (HO_2-). They are also known as Reactive Oxygen Species (ROS) or Reactive Oxygen Metabolite (ROM). These radicals are produced by body's normal use of oxygen and are also generated through environmental pollutants, cigarette smoke, automobile exhaust fumes, radiation, air pollution, pesticides, etc[69,70]. Mammalian cells possess elaborate defence mechanisms for radical detoxification. Key metabolic steps are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), which destroy toxic peroxides. In addition to antioxidant enzymes, nonenzymatic molecules, including thioredoxin, thiols, and disulfide-bonding play important roles in antioxidant defence systems. Some of the compounds are of an exogenous nature and are obtained from food, such as a-tocopherol, b-carotene, and ascorbic acid, and such micronutrient elements as zinc and selenium[69]. The medicinal properties of plants have been investigated in the recent scientific developments throughout the world, due to their potential antioxidant activities, no side effects and economic viability[71]. The majority of the active antioxidant compounds flavonoids, isoflavones, flavones, anthocyanins, coumarins, lignans, catechins, and isocatechins. In addition to the above compounds found in natural foods, vitamins C and E, β-carotene, and α-tocopherol are known to possess antioxidant potential[72-74]. Recently there has been an

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upsurge of interest in the therapeutic potentials of medicinal plants as antioxidants in reducing such free radical induced tissue injury[75].

Edibles with high content of antioxidants

Antioxidants are abundant in fruits and vegetables, as well as in other foods including nuts, grains and some meats, poultry and fish. The list below describes food sources of common antioxidants. Beta-carotene is found in many foods that are orange in colour, including sweet potatoes, carrots, cantaloupe, squash, apricots, pumpkin, and mangoes. Some green leafy vegetables including collard greens, spinach, and kale are also rich in beta-carotene. Lutein, best known for its association with healthy eyes, is abundant in green, leafy vegetables such as collard green, spinach, and kale. Lycopene is a potent antioxidant found in tomatoes, watermelon, guava, papaya, apricots, pink grapefruit, blood oranges, and other foods. Estimates suggest 85 percent of American dietary intake of lycopene comes from tomatoes and tomato products. Selenium is a mineral, not an antioxidant nutrient. However, it is a component of antioxidant enzymes. Plant foods like rice and wheat are the major dietary sources of selenium in most countries. The amount of selenium in soil, which varies by region, determines the amount of selenium in the foods grown in that soil. Animals that eat grains or plants grown in selenium-rich soil have higher levels of selenium in their muscle. In the United States, meat and bread are common sources of dietary selenium. Brazil nuts also contain large quantities of selenium. Vitamin A is found in three main forms: retinol (Vitamin A1), 3,4-didehydroretinol (Vitamin A2), and 3-hydroxy-retinol (Vitamin A3). Foods rich in vitamin A include liver, sweet potatoes, carrots, milk, egg yolks and mozzarella cheese. Vitamin C is also called ascorbic acid, and can be found in high abundance in many fruits and vegetables and is also found in cereals, beef, poultry and fish. Vitamin E, also known as alpha-tocopherol, is found in almonds, in many oils including wheat germ, safflower, corn and soybean oils, and also found in mangoes, nuts, broccoli and other foods.

Natural products help treat diseases due to their antioxidant properties

Researches have shown that brain is more liable to oxidative injury. This is due to the fact that metabolic rate is high and there are elevated levels of lipid peroxidation[76]. Therefore, to treat various forms of brain injury antioxidants are commonly used. The commonly used drugs are superoxide mimetics[77], sodium thiopental and propofol[19]. The experimental drug NXY-059[78,79] and ebselen[80] are being used for treatment of stroke. It is seen that these compounds prevent oxidative stress on neurons and thus prevent apoptosis and neurological damage. Nowadays, antioxidants are being used for treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis[81,82] and it also prevents noise-induced loss.

Natural products help prevent diseases

Cell damaging effects of free radicals can be met out by antioxidants. Those persons who consume antioxidants in the form of fruits and vegetables have a lower risk of heart disease and neurological problem[83]. It is well known that some types of fruits and vegetables prevent us from certain type of cancers[47]. As antioxidants supplements have no clear cut risks of chronic diseases such as cancer and heart disease[83,84]. Therefore, this suggests that flavonoids in fruits and vegetables or a complex of substances in other substances may contribute to better cardiovascular health of those persons who intake more fruits and vegetables[85,86]. Antioxidants help in prevention of other diseases such as macular degeneration[87], suppressed immunity due to malnutrition, and neurodegeneration[88]. Generally it is seen that people consuming Vitamin E supplements had a lower risk of developing heart disease[3,89]. More studies on this have given negative result[90,91]. Till date it is not clear whether the dietary supplements are capable of producing any significant decrease in oxidative stress[92]. By using controlled studies using antioxidant vitamins there is no reduction in either the risk of developing heart disease or the rate of progression of heart disease[93,94]. High doses supplementation of antioxidants showed their effect on healthy diet[95]. In a number of industrialized countries, health food companies and many nutraceuticals sell formulations of antioxidants as food supplements. Theses supplements are generally specific antioxidant chemicals such as resveratrol (from grape seeds or knotweed roots[96], combinations of antioxidants, like the "ACES" product that contain

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beta carotene, Vitamin C, Vitamin E and Selenium or herbs that contain antioxidants- such as garden tea and jiaogulan. Still researches are going on to find out which antioxidant is needed in what amounts[28,83,97,98]. Experiments have shown that moderate levels of oxidative stress might increase the life span of the worm *Caenorhabditis elegans*. But opposite results have come from yeast *Saccharomyces cerevisiae*[99]. In humans also the antioxidant supplements do not increase life span of humans[100]. Flavonoids commonly occur in plants and are components of human diet. However these have very strong antioxidant activities against peroxyl radicals[101].

The active compounds of plants, flavonoids, triterpenes and tannins may be regarded as possible active compounds against gastric lesions by acting as protective factors or increasing antioxidant activity. Three distinct mechanisms of protection by flavonoids have been identified: the alteration of GSH metabolism, quenching of reactive oxygen species and the inhibition of Ca^{2+} influx that signals the last step in the cell death cascade induced by glutamate[102].

Among the rich unexploited world flora a large number of species have folkloric medicinal uses. Extracts from the plants *Momordica charantia*[103], *Angelica archangelica*[104], *Carum carvi*[104], *Chelidonium majus*[104], *Iberis amara*[104], *Matricaria recutita*[104], *Melissa officinalis*[104], *Mentha piperita*[104], *Silybum marianum*[104], *Anthemis nobilis*[105], *Brassica oleracea*[105], *Matricaria chamomilla*[105], *Maytenus aquifolium*[105], *Symphytum officinalis*[105], *Sorocea blomplandii*[105], *Zolernia ilicifolia*[105] and *Glycyrrhiza glabra*[95] are used for the treatment of gastric ulcers and produce a dose-dependent anti-ulcerogenic activity associated with a reduced acid output and increased mucin secretion, an increase in PGE_2 release and a decrease in leukotrienes. The anti-ulcerogenic activity of the extracts of *Rhizophora mangle* L. indeed was due, at least in part, to the presence of tannins[106]. The anti-ulcerogenic activity of the extracts was also confirmed histologically. The cytoprotective effect of the extracts could be partially due to their flavonoid content and to their reactive oxygen species (ROS) scavenging property[106].

The lyophilized water extracts of the active principles of these medicinal plants are effective H^+ donors, reducing agents and H_2O_2 scavengers *in vitro*, showing that the bioactive components can act as primary and secondary antioxidants and scavenge free radicals[107]. The mature fruits of *Momordica charantia* L. (Cucurbitaceae) are used externally for the rapid healing of wounds and internally for the treatment of peptic ulcers in Turkish folk medicine[103].

The principal constituents of extracts of *Brassica oleracea*, originated in the Mediterranean, are glycosides, enzymes, vitamins A, B, C and compounds containing sulfhydryl groups[105]; *Anthemis nobilis* contents are azulene, flavonoids and sesquiterpene lactones; *Symphytum officinalis* is rich in alkaloids, allantoin, and mucilage. Aqueous extracts of *Matricaria chamomilla* have also shown the presence of sesquiterpene lactones, azulene, terpenic carbonyls, coumarins, resins and flavonoids[105].

The crude hydroalcoholic extract of *Rosmarinus officinalis* decreased the ulcerative lesion index produced by indomethacin, ethanol and reserpine in rats. The pharmacological mechanism has no relationship with nitric oxide or prostaglandins. The crude hydroalcoholic extract of *R.. officinalis* has active substances that increase the content of mucosal nonprotein sulfhydryl groups and antioxidant compounds which can react with N-ethylmaleimide.

Glycyrrhiza glabra (Papilionaceae) originated in the Mediterranean and the Middle East and has been used medicinally since at least 500 BC. Traditional uses include the treatment of peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, and infections. The primary active constituents of *G. glabra* are the triterpene glycoside glycyrrhizin, flavonoids (liquiritin and isoliquiritin), isoflavonoids (isoflavonol, kumatakenin, licoricone and glabrol), chalcones, coumarins (umbelliferone, herniarin), triterpenoids, and phytosterols[95]. Isoflavans from *G. glabra* have proved to be effective in protecting mitochondrial function against oxidative stresses[95].

Artemisia douglasiana Besser and its bio-active ingredient

In Argentina the aerial part of *A. douglasiana* Besser has been used in folk medicine as a cytoprotective agent against the development of gastric ulcers, external treatment of skin injury and dermal ul-

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cers. *A. douglasiana* Besser is a hexaploid species, a hybrid between *A. suksdorfi* Piper and *A. ludoviciana* Nutt. It is found on the western slopes of the US Rockies and in northern Baja California. The first report of its occurrence in Argentina was in 1967, in San Juan and Mendoza provinces, probably after introduction of the plant from Chile. It is known by the common name of "matico".

Phytochemical studies have shown that *A. douglasiana* is a species with a great diversity in secondary metabolite composition. Its major constituents are: sesquiterpene lactones, essential oils (azulene and chamazulene), flavonoids (rutin), vitamin B_6, ascorbic, palmitic, caffeic, glutamic, stearic, gallic and ferulic acids, sanlonine, lignans, betaine, coumarins and polyacetylenes[107].

The active principle of the plant is dehydroleucodine (DhL), a sesquiterpenoid lactone of the guiainolide type (Figure 1). DhL increases gastric glycoprotein synthesis[108], as confirmed by histological studies of the gastric and duodenal mucosa[111]. The *A. douglasiana* extract and DhL prevent lesions of the gastric mucosa induced by ethanol and other necrotizing compounds and the absolute ethanol-induced gastric injury[109].

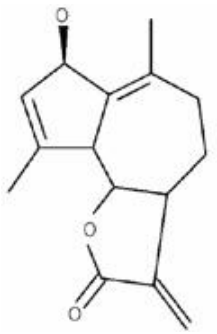

Figure 1 : Structure of the dehydroleucodine, the active principle of *Artemisia douglasiana* Besser.

Astroprotective effects of *Artemisia douglasiana* Besser and DhL

Recently, the antioxidant properties of *A. douglasiana* have been examined as a potential mechanism for its beneficial action. Thus, the antioxidant properties of *A. douglasiana* extract and its active principle, DhL, *in vitro* and their application to the biological oxidative stress system are currently being studied. The extract of the air-dried aerial parts of *A. douglasiana* showed significant cytoprotective activity.

The aqueous extract of *A. douglasiana* and its active principle possess anti-ulcer properties against ethanol- and acid-induced gastric mucosal damage. These effects have been interpolated from the pharmacological action of the extract on prostaglandin synthesis in gastric epithelium. The extract increases prostaglandin concentration in the gastric mucosa and protects the mucosa from damage induced by necrotizing agents.

In 1990, Giordano et al.[110] studied the cytoprotective action of *A. douglasiana* against the gastric lesion produced by acute administration of ethanol. The degree of erosion corresponded to a factor of 4.5 (large erosions and ulcerative perforations) in ethanol-treated rats and to a factor of only 0.5 in rats treated with both *A. douglasiana* extract and DhL before ethanol administration[111]. DhL prevented the gastric damage produced by 0.6N HCl, 0.2 N NaOH and 25% NaCl. Light and transmission electron microscopic studies showed that *A. douglasiana* and DhL pretreatment prevents the gross hemorrhagic lesions produced by ethanol[109].

Giordano et al.[109] showed that the presence of an exocyclic methylene group conjugated to a g-lactone appears to be a structural requirement needed for the biological activity exhibited for these compounds. These investigators concluded that the presence of the a-methylene-g-lactone moiety is a requirement for the cytoprotective activity, and the presence of the ß-substituted or unsubstituted cyclopentanone ring is not a structural requirement for cytoprotective activity, contrary to its requirement for antitumor, antimicrobial, and antifeedant properties[109].

In 1995, Piezzi et al.[112] showed that the stomachs of rats pretreated with DhL presented a reduction of lesions induced by acute oral ethanol administration[112]. No hemorrhage or hyperemia was observed. The epithelium of the mucosa had a cobblestone appearance, similar to that of control rats and was covered with a fine layer of mucus on the surface. The increased vascular permeability precedes the development of grossly visible mucosal hemorrhagic erosion. The cited investigators suggested that vascular damage plays an important role in the development of gross hemorrhagic erosion[112]. In the stomachs treated with DhL, filaments or gross deposits occur in the mucosa; they probably dilute noxious agents and provide a favourable environ-

ment for rapid epithelial reconstitution. This may be one of the gastric defence mechanisms involved in the protection of the superficial mucosa.

Several different mechanisms could be proposed to explain the massive and accelerated mucus release induced by DhL. The protective action of DhL seems to be related to endogenous prostaglandin and to the ability of the drug to stimulate mucus production. The fact that the increase in the thickness after DhL treatment is similar in stomach (83%) and duodenum (82%) suggests that both tissues present a similar secretory response to the drug. The protective action of DhL on gastric mucosa is not related to an antisecretory property since it does not decrease acid secretion, but triggers the defence mechanism of the mucosa.

Prostaglandins have been shown to increase the amount of luminal mucus and the resistance of the gastrointestinal tract to injury in several experimental models. They are believed to exert their cytoprotective actions through the stimulation of mucus and bicarbonate secretion, This maintains mucosal blood flow, and thereby enhances the resistance of epithelial cells to injury induced by cytotoxins.

In 1998, María et al.[113] found an increase in gastric prostaglandin E_2 levels, measured by radioimmunoassay in sub-chronically DhL-treated rats. It is also possible that DhL may alter the activity of certain receptors in the gastroduodenal mucosa, such as serotonin and/or muscarinic receptors. The muscarinic receptors mediate the secretion of gastric acid, pepsinogen, and mucus in gastric mucosa by stimulating the phosphoinositide second messenger system. It is also possible that massive mucus secretion after treatment with DhL is mediated by the activation of certain histamine receptors, such as the H_3 receptor, responsible for the increase in the amount of mucus in deep crypt cells of the fundic mucosa, by enhancing the synthesis of mucus. Interestingly, in 1999, Penissi and Piezzi[111] showed that DhL by itself increases histamine levels in gastroduodenal tissue. Further studies are required to assess the significance of these observations.

Antioxidant properties of *Artemisia douglasiana* Besser and DhL *in vitro*

One of the mechanisms proposed for the activity of DhL is that this compound increases prostaglandin concentration in the gastric mucus and protects the mucosa from damage induced by necrotizing agents, and may suppress active oxidant species production (96,80), involving sulfhydryl-containing compounds of the mucosa[110].

The antioxidant activity of *A. douglasiana* Besser[113] was evaluated by measuring the total reactive antioxidant potential (TRAP) and the total antioxidant reactivity (TAR) *in vitro*. The antioxidant activity of DhL was measured by chemiluminescence, evaluating the concentration necessary to decrease the initial luminescence by 50% (IC_{50}). TRAP and TAR were measured by luminol-enhanced chemiluminescence[114]. The addition of the antioxidant plant extract or DhL decreased chemiluminescence to basal levels for a period (induction time) proportional to the concentration of antioxidant until luminol radicals were regenerated. The system was calibrated using the vitamin E analogue Trolox (0.150 mM). A comparison of the induction time after the addition of known concentrations of Trolox and plant extract permitted the determination of TRAP values as equivalents of the Trolox concentration necessary to suppress the emitted luminescence to be obtained. The TAR index was calculated from the instantaneous decrease in luminescence associated with incorporation of the extract. The concentration necessary to decrease the initial luminescence by 50% (IC_{50}) was evaluated by plots of I^o/I against concentration, where I^o and I are the luminescence intensity before and after the incorporation of the scavenger[113].

The relationship between prostaglandins and leukotrienes, the arachidonic acid products of prostaglandin H synthase (PGHS) and 5-lipoxygenase, respectively, seems to be an important factor in gastric ulcers. Many phenolic compounds, including catecholamines, have been shown to modulate the PGHS and 5-lipoxygenase pathways of arachidonic acid[101].

Phenols have a dual effect on prostaglandin biosynthesis, with low concentrations stimulating and high concentrations inhibiting PGHS (Figure 2). Phenols stimulate prostaglandin synthesis by acting as reducing substrates for the oxidized intermediates of PGHS, thereby accelerating the peroxidase cycle and by functioning as electron-donating co-substrates for the peroxidase component of PGHS. Phenols inhibit the cyclooxygenase-2 activity of PGHS by competing for

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the arachidonic acid-binding site and by competitive reduction of PGHS. The modulation of hydroperoxide tone by phenols is probably the key element explaining the suppression of arachidonic acid metabolism by

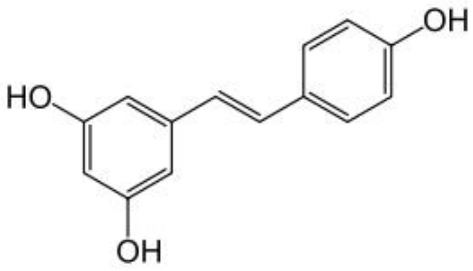

Figure 2 : Structure of the polyphenol antioxidant resveratrol

PGHS. The stimulatory effect of phenols on PGE_2 formation may be based on their action as co-substrates for the peroxidase reaction[101].

The extract of *A. douglasiana* and its active principle DhL significantly prevent the formation of gastric lesions induced by various necrotizing agents[113,114], and this activity could be due, in part, to their capacity for scavenging oxygen free radicals which may be involved in peptic ulcer development. *A. douglasiana* exhibits a varied system of primary and secondary metabolites that protect cells from changes driven by pro-oxidants. Other important components present in the *A. douglasiana* extracts are coumarins (benzopyrones). They are effective against oxidative stress by acting in a similar manner to flavonoids, i.e., inhibiting lipoxygenase and cyclooxygenase-2 pathways, inhibiting production of $O_2^{\cdot-}$ by neutrophils, scavenging $OH^{\cdot}$ and $O_2^{\cdot-}$ radical, inhibiting the activity of hypochlorous acid, and chelating iron ions[109].

The gastroprotective effect of *A. douglasiana* extracts and DhL on gastric mucosal injury may be mediated by local release of sensory neuropeptides, nitric oxide, and prostaglandin. Inhibition of lipid peroxidation and cyclooxygenase-2 is considered to be an important target for the chemoprevention of gastrointestinal ulcers. Further studies are needed to determine if *A. douglasiana* and DhL regulate the responses of the gastric mucosa to stress through mechanisms that include heat shock proteins, prostanoids and nitric oxide besides their antioxidant properties.

A. douglasiana and DhL have been shown to have antioxidant properties in a tube experiment, to protect the gastric mucosa from experimental ulcerations *in vivo*, and to accelerate the healing of gastric ulcers in humans. These results suggest that *A. douglasiana* and DhL may partly protect the gastric mucosa from acute injury and may promote the healing of chronic gastric ulcers by their antioxidant activity.

The extract of *A. douglasiana* Besser possesses significant free radical scavenging and antioxidant activity *in vitro*, but DhL proved to be less efficient as an antioxidant than the plant[113]. The therapeutic action of the extract of *A. douglasiana* Besser and DhL could be due, in part, to their ability to scavenge oxygen free radicals, which may be involved in ulcer and inflammatory diseases. Indeed, the main mechanism involved in the cytoprotective action of the compound is mucus secretion. DhL increases in the thickness of the adherent mucus gel layer[114]. These natural compounds are thought to possess significant gastrointestinal cytoprotective activity. *A. douglasiana* Besser and DhL may represent an attractive therapeutic option for gastric ulcers and inflammation, both as cytoprotective agents and as antioxidants for a wide range of clinical applications.

ABBREVIATIONS

FR	:	Free radical species
GPX4	:	Glutathione peroxidae 4
AIDS	:	Acquired Immunodeficiency Syndrome
HIV	:	Human Immunodeficiency Virus
OH^-	:	Hydroxide radical
HO^-	:	peroxide ion
ROS	:	Reactive Oxygen Species
ROM	:	Reactive Oxygen Metabolite
SOD	:	Superoxide dismutase
CAT	:	Catalase

CONCLUSION

Natural products have always been an important source of chemical tool compounds or drugs respectively in chemical biology and pharmaceutical research. Antioxidants defend our body at the cellular level and protect our good health for a life time. Our cells produce thousands of free radicals every day. Free radicals from the environment occur as an effect of stress,

pollution and unhealthy eating habits. Oxidation is a damaging but essential process that our bodies create to generate energy. Without proper nutrition, oxidation can contribute to any number of debilitating diseases, including cancer, heart disease and aging. Thus, the intake of natural products containing plenty of antioxidants protects us from number of diseases by promoting the strong immune-system.

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