Advances in Essential Oils and Natural Products

Volume - 5

Chief Editor

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Preface

Essential oils are natural products derived from aromatic plants, traditionally used worldwide for disinfection, as anti-inflammatory, relaxing and stimulating substances and with potential and modern exploitation in clinical medicine. Essential oils are commonly used in the food and cosmetic industries. They can be used as natural alternatives to synthetic preparations to prevent and treat infectious diseases. They are used traditionally to treat other conditions like the respiratory tract, digestive system, gynecological, endocrine, cardiovascular, nervous system, and skin infections. Many of them also have shown anticancer activities. The essential or volatile oils are extracted from the flowers, barks, stem, leaves, roots, fruits and other parts of the plant by various methods. The essential oils are found to be more beneficial when other aspects of life and diet are given due consideration. The applications of essential oils are diverse. Widely used in cosmetics and perfumes, they also have medicinal applications due to their therapeutic properties and agro-alimentary uses because of their antimicrobial and antioxidant effects. India is one of the few countries in the world having varied agro climatic zones suitable for the cultivation of most essential oil bearing plants. Due to increased awareness of health hazards associated with synthetic chemicals coupled with the increased cost of petroleum products, the use of essential oils has been gradually increasing. The Essential oils were an luxury in the last few decades but now they have become the day-to-day usage commodities in the life of the common people also.

I hope this volume will be welcomed by all those engaged in the study of essential oils and natural products.

Dr. Rakesh Kumar Joshi
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Chief-editor

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Chapter - 5

Antioxidants: Natural vs. Synthetic Compounds, Applications and Future Perspectives

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Abstract

Antioxidants were used to prevent oxidation in foods which lead to rancidity and browning, DNA oxidation and have many positive physiological effects in humans. The concentration and the absorption mechanism of natural antioxidants are important in obtaining the maximum beneficial effect. The sources of antioxidants must be carefully considered to maximize absorption and avoid the toxicity of higher concentration of synthetic groups. An organized effort to educate individuals about foods rich in natural antioxidants and the ability to recognize the major synthetic antioxidants on food labels would be highly beneficial, though more research needs to be done to fully understand their physiological effects. Synthetic antioxidants are widely used in food industries to prevent oxidation of food matrices. They are also used as food supplements for various health benefits such as anti-cardiovascular diseases and anti-aging. However, chronic consumption of synthetic antioxidants has been linked to various diseases including cancer. Concrete evidence showing their health hazards is limited. Further studies on technological, health and hazard aspects of synthetic antioxidants and their natural counterparts are required in order to get better understanding of these groups of compounds

Keywords: Natural antioxidant, oxidative stress, synthetic antioxidant, future prospects

Introduction

The use of oxygen as the final acceptor of the electrons in the oxidation of energy substances of food origin allows aerobic organisms to produce a high amount of metabolic energy [1]. The high aerobic organisms' ability to produce ATP is associated with the continuous production of radicals and

other Reactive Oxygen Species (ROS) that originate as side products of oxidative metabolism. The concept of antioxidant is defined, along with a discussion of the existent classification criteria: enzymatic and non-enzymatic, preventative or repair-systems, endogenous and exogenous, primary and secondary, hydrosoluble and liposoluble, natural or synthetic [2]. Primary antioxidants are mainly chain breakers, able to scavenge radical species by hydrogen donation. Secondary antioxidants are singlet oxygen quenchers, peroxide decomposers, metal chelators, oxidative enzyme inhibitors or UV radiation absorbers [3]. The specific mechanism of action of the most important representatives of each antioxidant class (endogenous and exogenous) in preventing or inhibiting particular factors leading to oxidative injury in the cell [4]. Mutual influences, including synergistic effects are presented and discussed. Prooxidative influences likely to occur, as for instance in the presence of transition metal ions, are also reminded [5].

Many studies have been conducted with regard to free radicals, oxidative stress and antioxidant activity of food, giving antioxidants a prominent beneficial role, but, recently many authors have questioned their importance, whilst trying to understand the mechanisms behind oxidative stress [6]. Many scientists defend that regardless of the quantity of ingested antioxidants, the absorption is very limited, and that in some cases prooxidants are beneficial to human health [7]. The detection of antioxidant activity as well as specific antioxidant compounds can be carried out with a large number of different assays, all of them with advantages and disadvantages [8]. The controversy around antioxidant *in vivo* benefits has become intense in the past few decades and the present review tries to shed some light on research on antioxidants (natural and synthetic) and prooxidants, showing the potential benefits and adverse effects of these opposing events, as well as their mechanisms of action and detection methodologies [9, 10]. It also identifies the limitations of antioxidants and provides a perspective on the likely future trends in this field.

Oxidative stress

Oxidative stress is defined as an excessive production of reactive oxygenated species that cannot be counteracted by the action of antioxidants, but also as a perturbation of cell redox balance. Reactive oxygenated/ nitrogenated species are represented by superoxide anion radical, hydroxyl, alkoxyl and lipid peroxyl radicals, nitric oxide and peroxynitrite [11]. This chapter is focused on the action of the reactive oxygenated species in inducing oxidative injury of the lipid membrane components, as well as on the ability of antioxidants (of different structures and sources, and following different mechanisms of action) in fighting against oxidative stress [12].

Oxidative stress determines structure modifications and function modulation in nucleic acids, lipids and proteins. Oxidative degradation of lipids yields malondialdehyde and 4-hydroxynonenal, but also isoprostanes, from unsaturated fatty acids [13]. Protein damage may occur with thiol oxidation, carbonylation, side-chain oxidation, fragmentation, unfolding and misfolding, resulting activity loss. 8-hydroxydeoxy guanosine is an index of DNA damage [14].

The involvement of the reactive oxygenated/nitrogenated species in disease occurrence is described. The unbalance between the oxidant species and the antioxidant defense system may trigger specific factors responsible for oxidative damage in the cell: over-expression of oncogene genes, generation of mutagen compounds, promotion of atherogenic activity, senile plaque occurrence or inflammation [15, 16]. This leads to cancer, neurodegeneration, cardiovascular diseases, diabetes, and kidney diseases. Various abiotic stresses lead to the overproduction of Reactive Oxygen Species (ROS) in plants and animals which are highly reactive and toxic causing damage to proteins, lipids, carbohydrates and DNA thus leads to oxidative stress [17]. This oxidative stress causes damage to tissues and results in large number of diseases. Antioxidants neutralize the effects of ROS and thus help in preventing diseases. Antioxidants can be natural or synthetic. Natural antioxidants can be taken up through diet as they are present in fruits, vegetables and spices [18]. There are also certain synthetic antioxidants like BHT and BHA that also inhibit oxidation. However, these synthetic antioxidants have now been reported to be dangerous to humans so the search for non-toxic antioxidants have intensified in the recent years

Reactive Oxygen Species (ROS) initially considered as only damaging agents in living organisms further were found to play positive roles also [19]. This chapter describes ROS homeostasis, principles of their investigation and technical approaches to investigate ROS-related processes. Especial attention is paid to complications related to experimental documentation of these processes, their diversity, spatiotemporal distribution, relationships with physiological state of the organisms [20]. Imbalance between ROS generation and elimination in favor of the first with certain consequences for cell physiology has been called “oxidative stress”. Although almost 30 years passed since the first definition of oxidative stress was introduced by Helmut Sies, to date we have no accepted classification of oxidative stress [21]. In order to fill up this gape here classification of oxidative stress based on its intensity is proposed. Due to that oxidative stress may be classified as basal oxidative

stress (BOS), low intensity oxidative stress (LOS), intermediate Intensity Oxidative Stress (IOS), and High Intensity Oxidative Stress (HOS) [22]. Another classification of potential interest may differentiate three categories such as Mild Oxidative Stress (MOS), Temperate Oxidative Stress (TOS), and finally Severe (Strong) Oxidative Stress (SOS) [23]. Perspective directions of investigations in the field include development of sophisticated classification of oxidative stresses, accurate identification of cellular ROS targets and their arranged responses to ROS influence, real *in situ* functions and operation of so-called "antioxidants", intracellular spatiotemporal distribution and effects of ROS, deciphering of molecular mechanisms responsible for cellular response to ROS attacks, and ROS involvement in realization of normal cellular functions in cellular homeostasis [24].

Natural antioxidants

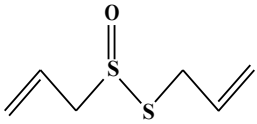
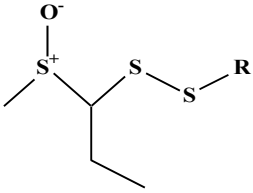
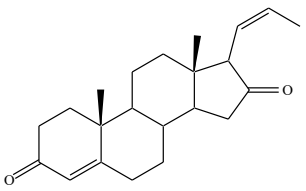
The interest in natural antioxidants is determined by the universality of their action in various redox systems and consequently broad spectra of possible applications: antioxidative phytochemicals are considered as functional ingredients for pharmaceuticals, functional foods, dietary supplements, animal feed, cosmetics and other products [25]. For instance, the interest in natural antioxidants to be used for the stabilization of lipid-containing foods has increased remarkably because of the emerging information about possible toxicity of synthetic antioxidants as well as consumer preferences towards natural food additives. Plants are the keystone of life on Earth and an indispensable resource for humans. Everything humans consume depends directly or indirectly from plants [26]. Plants regulate the water cycle, distributing and purifying water through transpiration. They store carbon and regulate the amounts of carbon dioxide and oxygen in the air. Plants also recycle the air people breathe. Most importantly, plants are a significant source of medicines. Ever since time immemorial plants are customary to cure a large number of diseases or physical strength of the body in humans [27].

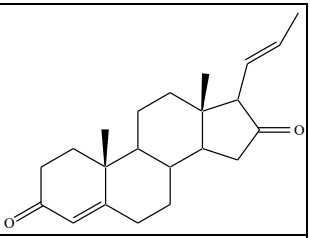
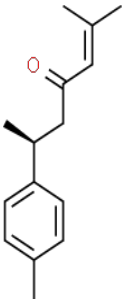
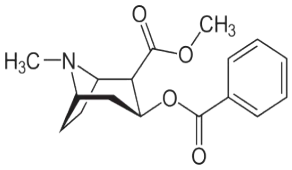
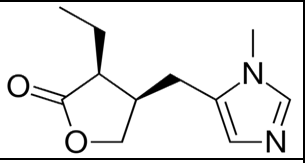
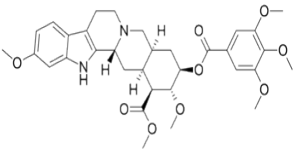
Medicinal plants are used by the worldwide population and have negligible side effects and low cost effectively compared to other systems of medicine. With the changing scenario, there is a need to enhance and promote the conservation and cultivation of natural resources for medicinal plants [28]. In addition to the requirement for conservation of medicinal plants it has also become important to protect and patent the traditional and alternative medicines [29]. Traditional system of medicines derived from plants continue to be broadly practiced in many countries on many accounts [30]. Population

rise, side effects of several synthetic drugs, inadequate supply of drugs, high cost of other treatment, and development of resistance to currently used drugs for infections have led to increased emphasis on the use of plant materials [31]. Different plant materials like leaves, flower, fruit, bark, root used to derive herbal medicines, flower and fruits are mainly used in cosmetic products in personal care, many essential oils mostly obtained from leaves, flower and fruit used in aromatherapy and other medicinal purposes [32]. So, from all these reported data we conclude that plants have become the essence of life on the earth today.

Presently, research is focused on the isolation of biologically active compounds from natural sources in the area of those diseases where presently available drugs are not significantly effective. Also herbal medicines are experiencing greater resurgence as many people are turning their attention from modern synthetic drugs toward parallel traditional medicines which are also known as alternative medicine [33]. At present time, a lot of drugs are directly derived from medicinal plants and these drugs have been used without any structural modification by many pharmaceutical industries [34]. During the past few years, a large number of novel compounds have been isolated from plants, and many of these substances have been demonstrated to possess interesting biological activities. Secondary metabolites have played a priceless role in drug discovery [35].

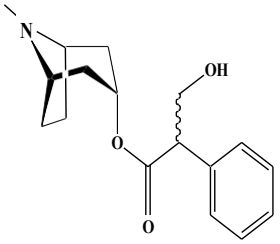
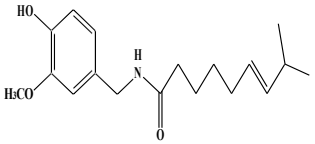
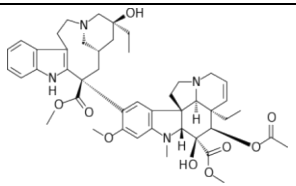
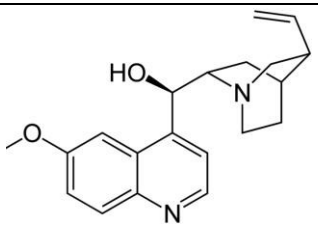
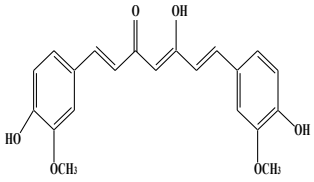
Table 1.2: Use and structure of drugs derived from medicinal plants

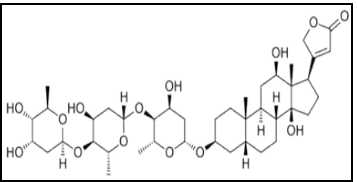
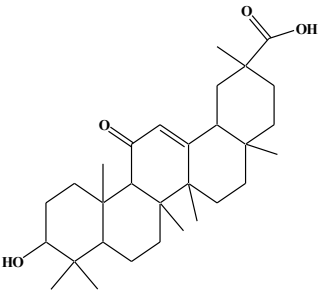
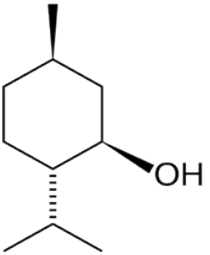
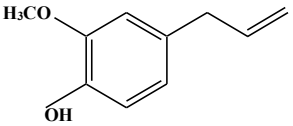
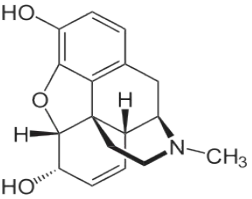
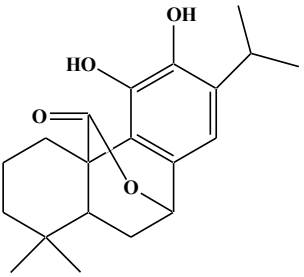
Plant name	Drug	Used in ailment	Structure
Allium sativum	Alliin	Cardioprotective, antidiabetic	
Allium caepa	Cepaene	Reducing cholesterol	
Commiphora mukul	Z-guggulsterne	*Antiplatelet,* improving thyroid	

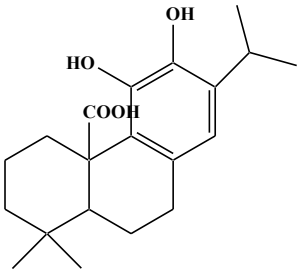
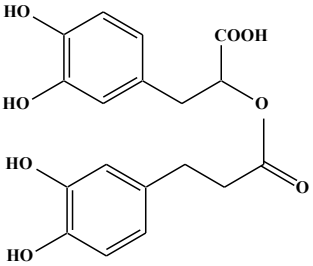
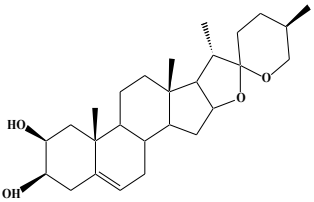
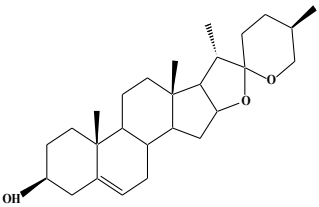
	E-guggulsterne	Reduce cholesterol, improving the liver ability	
Curcuma longa	turmerone	Antifungal, Anti-inflammatory, antidermatophytic	
Erythroxylum coca	Cocaine	Local anesthetics, cerebral stimulant (Narcotic use)	
Pilocarpus jaborandi	Pilocarpine	Treatment of glaucoma	
Rauwolfia serpentina	Reserpine	Antihypertensive, tranquilizer	

Phenolic and polyphenolic compounds play an important role as a natural antioxidant. Phenolic compounds, ubiquitous in plants, are an essential part of the human diet and are of considerable interest due to their antioxidant properties and potential beneficial health effects [36]. These compounds range structurally from a simple phenolic molecule to complex high-molecular-weight polymers [37]. There is increasing evidence that consumption of a variety of phenolic compounds present in foods may lower the risk of health disorders because of their antioxidant activity [38]. When added to foods,

antioxidants control rancidity development, retard the formation of toxic oxidation products, maintain nutritional quality, and extend the shelf-life of products [39]. Due to safety concerns and limitations on the use of synthetic antioxidants, natural antioxidants obtained from edible materials, edible by-products and residual sources have been of increasing interest [40]. This contribution summarizes both the synthetic and natural phenolic antioxidants, emphasizing their mode of action, health effects, degradation products and toxicology. Some phenolic natural antioxidant drugs are mentioned in the below table.

Plant name	Drug	Used in ailment	Structure
Atropa belladonna	Atropine	Mydriatic, anhydrotic, anti spasmodic	
Capsicum annuum	Capsaicin		
Catharanthus roseus	Vinblastine	Hodgkin's lymphoma, choriocarcinoma	
Cinchona officinalis	Quinine	Analgesic, antipyretic, antimalarial	
	Curcumin	Antianxiety, antioxidant, treatment of obesity	

Digitalis lanata	Digoxin	Cardiotonic	
Glycyrrhiza glabra	Glycyrrhetica acid	Anti-inflammatory, peptic ulcer treatment	
Mentha arvensis, *Mentha piperita*	Menthol	Local anesthetic, counterirritant, Antipruritic, counterirritnt, stimulant	
Ocimum sanctum	Eugenol	Reduction in total cholesterol, antioxidant	
Papver somniferum	Morphine	Narcotic analgesic	
Rosemarinus officinalis	Carnosol	Antioxidant, antidiabetic, anticancerous	

	Carnosinic acid	Antioxidant, antidiabetic, neuroprotective	
	Rosmarinic acid	Antioxidant, antipertensive effect	
Trigonella foenum graecum	Diosgenin	Reduce cholesterol, antioxidant	
	Gitogenin	Antioxidant	

Synthetic antioxidants

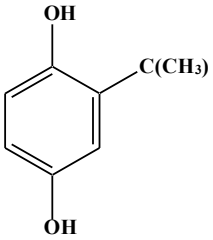
Synthetic antioxidants are chemically synthesized compounds since they do not occur in nature and are added to food as preservatives to help prevent lipid oxidation. Unlike natural antioxidants, synthetic antioxidants are widely used in the food industry; they are characterized by a diverse source of raw materials, mature technology, low price [41], few side effects [42], good scavenging activity and ease of procurement. Due to the inherent instability of natural antioxidants, several synthetic antioxidants have been used to stabilize fats and oils. At present, the most commonly used synthetic antioxidants in food are phenolic antioxidants [43, 44], for example, butylated hydroxyanisole

(BHA) (E-number 320, food additive), Butylated Hydroxytoluene (BHT) (E-number 321, food additive), Tertiary Butylhydroquinone (TBHQ) (E-number 319, food additive) and Propyl Gallate (PG) (E-number 310, food additive), which can be used for the protection of dietary fats and oils. Butylated Hydroxytoluene (BHT) and Butylated Hydroxyanisole (BHA) were originally developed to protect petroleum from oxidative gumming [45]. However, these compounds have been used as antioxidants in human foods since 1954 and are perhaps the most common antioxidants used in those foods today. BHT and BHA not only have similar names, but similar structures and antioxidant activity and are often used together in fats and oils. Despite the fact that both BHT and BHA are included in the list of substances that are "generally accepted as safe" [46]. Certain chronic toxicity studies have implicated BHT as potential tumor promoter when fed at high levels. In contrast, BHA and BHT, may both be important inhibitors of carcinogenesis, probably by way of their antioxidant function [47]. Thus, there have been some attempts to remove these antioxidants, TBHQ (tert-butylhydroxyquinone) is another synthetic antioxidant which is widely used in the feed industry. Like BHT and BHA, TBHQ has a benzene ring or phenol structure. Other examples of synthetic antioxidants are Propyl Gallate (PG), Dodecyl Gallate (DG), Octylgallate (OG) and Ethylene Diaminetetraacetic Acid (EDTA) [48].

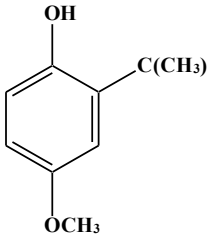
Synthetic phenolic antioxidants (SPAs) can interact with the peroxides generated by food under certain conditions to block the pathway of food deterioration, so they play a very important role in improving food stability and extending food shelf life [49]. Therefore, the proper use of antioxidants can not only bring good economic benefits to producers but also bring safer food to consumers.

The toxicity of BHA, BHT and TBHQ has been investigated extensively using a variety of experimental conditions. Research shows that the acute toxicity of BHA is low, with a lethal dose 50 (LD50) value in mouse and rat >2000 mg/kg b.w. [50]. Researches show that BHA has a strong cytotoxic effect on human astrocytes [51, 52] and developmental toxicity on zebrafish embryos/ larvae [53]. The results of zebrafish embryo toxicity test (ZFET) showed that BHT had cardiotoxicity and might be a potential teratogen for aquatic organisms [54]. For PG, *in vivo* study showed that it can induce testicular toxicity by damaging mitochondrial or ER function and inhibiting testicular development related genes [55].

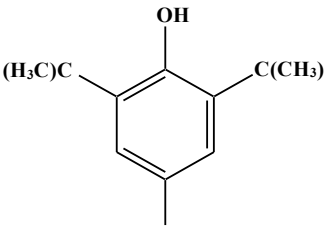
Structure of some synthetic antioxidants



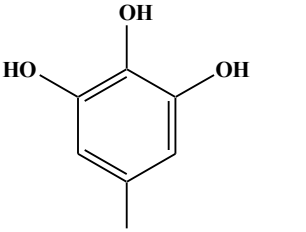
Tertiary butylhydroquinone (TBHQ)



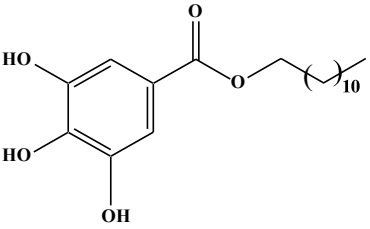
Butylated hydroxyanisole (BHA)



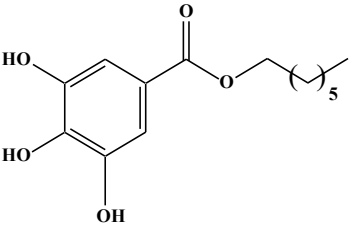
Butylated hydroxytoluene (BHT)



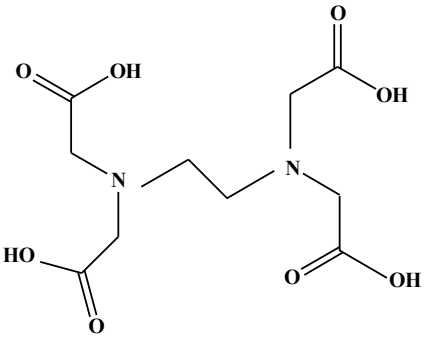
Propyl gallate



Dodecyl gallate



Octylgallate



Ethylene diaminetetraacetic acid

Future consideration

Antioxidants are an indispensable component of the ROS-dependent signaling network and a means of defense against excessive production of ROS. Although recent studies cast some doubt on the benefits of longterm antioxidant supplementation, which can be partly attributed to the tendency of the organism to maintain redox homeostasis, harmful sequelae of antioxidant deficiency are obvious [56]. There are numerous examples of successful use of antioxidants to ameliorate pathologic sequelae of oxidative stress. New ways of antioxidant delivery, i.e. including nanoparticles, have been proposed and new antioxidants, targeted specifically to mitochondria, the main cellular source of ROS, have been synthesized and are tested. Another approach can consist of stimulation of expression of genes coding for antioxidant proteins or antioxidant gene therapy [57]. Careful studies of their effects and side-effects are needed. On the other hand, the broad preference for compounds of natural origin cannot be ignored and is a stimulus for the search for new efficient antioxidants in nature. Taking into account that oxidative stress depends both on the ROS production and their removal by antioxidants, inhibitors of ROS-producing enzymes are also tested and may find applications for amelioration of effects of oxidative stress such compounds may also be treated as antioxidants in a broader (biomedical) sense [58]. Considering all these aspects, one may expect that the field of antioxidant research is likely to remain quite active in the years to come. There is increasing evidence that consumption of a variety of phenolic compounds present in natural foods may lower the risk of serious health disorders because of their antioxidant activity, amongst other mechanisms. Mode of action of different phenolic compound in specific body organs needs to be found. Due to safety and other limitations surrounding the use of synthetic antioxidants, natural antioxidants obtained from edible sources, by-products and co-products are alternative sources of interest [59]. Further studies on the isolation of phenolic compounds using complementary methods and their effects on antioxidant status in animal models and human subjects are needed to evaluate their potential benefits. In addition it is necessary to further confirm lack of toxicity and bioavailability of such natural phenolic extract. Delivery of isolated phenolics as dietary supplements or functional food ingredients for health promotion and disease risk reduction may also be helpful in improving the efficacy of such materials [60].

In foods that may undergo oxidation, antioxidants function as an inhibitor of oxidation reactions through various mechanisms. Nevertheless, some foods are deficient in natural antioxidants and can easily deteriorate during

processing or in storage, necessitating the use of synthetic antioxidants. However, most synthetic antioxidants are effective at low concentrations, and the addition of higher levels may lead to a pro-oxidant effect [61]. Additionally, large doses of synthetic antioxidants have been reported to impart safety problems. Therefore, caution must be taken when selecting and adding antioxidants in food systems. Meanwhile, the safety of natural antioxidants should not be taken for granted as antioxidants from natural sources are attracting more and more attention. The best way to get a variety of antioxidants in the diet is to eat foods that represent all the colors of the rainbow. Each color provides its own unique antioxidant effects. Bright orange, deep yellow fruits and vegetables like carrots, sweet potatoes, and apricots provide one type of antioxidant. Red foods like tomatoes provide another. Green vegetables, such as broccoli and cabbage, and blue or purple foods, like blueberries, each have their own antioxidant packages [62].

Conclusion

Antioxidants, regardless of their origin natural or synthetic play a crucial role in mitigating oxidative stress, thereby enhancing overall health and potentially extending lifespan. In a balanced diet, the inclusion of natural antioxidants sourced from plants, fruits, vegetables and herbs is recommended due to their enhanced bioavailability, minimal side effects, and synergistic advantages. Synthetic antioxidants demonstrate efficacy and economic viability; however, concerns regarding their safety, toxicity, and long-term health implications persist.

In comparison to synthetic antioxidants, natural molecules exhibit enhanced safety and environmental friendliness; however, they demonstrate reduced stability and effectiveness. Innovative extraction methods, structural alterations, and advancements in nanotechnology have the potential to enhance their medicinal efficacy. Antioxidants find application in pharmaceuticals, food preservation, cosmetic formulations and biological research methodologies. Advancements in science indicate that the integration of antioxidants into novel formulations and delivery technologies is expected to enhance their efficacy and broaden their applications. A comprehensive approach incorporating both natural and synthetic antioxidants will be essential moving forward. Enhancing the stability, potency and safety of natural antioxidants, as well as developing safer synthetic alternatives, necessitates continuous research. The extraction and manufacture of sustainable antioxidants will contribute to environmental conservation efforts. Antioxidant research presents significant potential for enhancing human

health and combating oxidative damage. An interdisciplinary approach that integrates chemistry, biology, pharmacology, and technology is essential to enhance their applicability.

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