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HISTORICAL JOURNEY FROM PLANT TO MEDICINAL PLANT: AN OVERVIEW

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ABSTRACT

Plants are a life line of earth. Medicinal plants are important sources for pharmaceutical manufacturing throughout the world. Plants have the ability to synthesize a wide variety of chemical compounds that are used to perform important biological functions. According to the World Health Organization (WHO) approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care. Modern pharmacopoeias contain at least 25% of drugs derived from plants while in fast developing countries such as China and India, the contribution is 80 percentages. The interest of public in alternative therapies like natural products, especially those derived from plants has increasing day by day. The traditional medicine and ecological awareness suggest that natural products are harmless. The blind dependence on synthetic drugs is over and people are returning to the natural products with hope of safety and security. The Ayurveda and Unani system of medicine uses about 700 species, Siddha having 600, and modern medicine around 30 species. About 8,000 herbal remedies have been included in Ayurveda, 67 in Rigveda, 81 in Yajurveda, 290 in Atharvaveda. Moreover the Charak Samhita and Sushrut Samhita have described the therapeutics properties of more than 1270 species of plants. Therefore, the present review has been aimed to delineate the medicinal properties of various plants and journey of plants to therapeutics actions in a variety of pathological conditions.

Key Words: ***Antioxidant, Ethanobotany, Ayurveda.***

INTRODUCTION

Throughout the ages, humans have relied on nature for their basic needs such as production of food stuffs, shelter, clothing, means of transportation, fertilizers, flavors and fragrances, and, not the least, medicines. Plants have been

utilized as medicines for thousands of years and have formed the sophisticated traditional medicine systems. The ancient people treated illness by using plants, animal parts, and minerals that were not part of their usual diet.

All cultures have long folk medicine histories that include the use of plants. Even in ancient cultures, people scientifically collected information on herbs and developed well defined herbal pharmacopoeias. Modern pharmacopoeias contain at least 25% of drugs derived from plants some of which are synthetic analogues, built on prototype compounds isolated from plants [1]. The medicinal plants were initially used in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations [2,3]. The isolation of active compounds began with the isolation of morphine from opium in the early 19th century [4]. The interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants has increased [5]. This interest in drugs of plant origin is due to several reasons, namely, conventional medicine can be inefficient (e.g. side effects and ineffective), abusive and incorrect use of synthetic drugs results in side effects and a large percentage of the world's population does not have access to conventional pharmacological treatment. The traditional medicine and ecological awareness suggest that natural products are harmless.

Natural products are staging a comeback and herbal 'renaissance' is happening all over the globe. The blind dependence on synthetic drugs is over and people are returning to the natural products with hope of safety and security. According to the World Health Organization (WHO) approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care [6]. It has been estimated that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as China and India, the contribution is as much as 80%. Thus, the economic importance of medicinal plants is much more to countries such as India and China. These countries provide two third of the plants used in modern system of medicine.

In India, drugs of herbal origin have been used in traditional systems of medicines such as *Ayurveda*, *Unani* and *Siddha* since ancient times. Among these systems, *Ayurveda* is most developed and widely practiced in India. The *Ayurveda* system of medicine uses about 700 species, *Unani* 700, *Siddha* 600, and modern medicine around 30 species. The drugs are derived either from the whole plant or from different parts, like leaves, stem, bark, root, flower, seed, etc. Some drugs are prepared from excretory plant product such as gum, resins and latex. Even the Allopathic system of medicine has adopted a number of plant-derived drugs. About 8,000 herbal remedies have been included in *Ayurveda*. The *Rigveda* has recorded 67 medicinal plants, *Yajurveda* 81 species, *Atharvaveda* 290 species; *Charak Samhita* and *Sushrut Samhita* have described the properties and uses of 1100 and 1270 species of plants [7].

Medicinal plants can be used as crude extracts in various pharmaceutical preparations, when they are considered as phytopharmaceutical preparations or natural medicines. A medicinal plant is any plant used in order to relieve, prevent or cure a disease or to alter physiological and pathological process, or any plant employed as a source of drugs or their precursors [8]. A natural medicine is any manufactured medicine obtained exclusively from plants either in the crude state or as a pharmaceutical formulation [9]. The present review focused on the therapeutic discovery from plants.

DRUG DISCOVERY FROM PLANTS

Researches on pharmacognosy, chemistry, pharmacology and clinical therapeutics have been carried out on *Ayurvedic* medicinal plants and many of the major pharmaceutical corporations have renewed their strategies in favor of natural products drug discovery. Numerous drugs have entered the international pharmacopoeia through the study of ethnopharmacology and traditional medicine [10].The research and development (R & D) thrust in the pharmaceutical sector is focused on development of new innovative plant based drugs through investigation of leads from the traditional system of medicine [11]. About 60% of anticancer and 75% of anti-infective drugs approved from 1981 to 2002 could be traced to natural origins [12]. Combinatorial chemistry approaches based on natural products from traditional medicine are being used to create screening libraries that closely resemble drug-like compounds [13]. The information presented on sources of new drugs from 1981 to 2007 indicates that almost half of the drugs approved since 1994 are based on natural products. Thirteen natural product related drugs were approved from 2005 to 2007. A lead compound is a prototype compound that has desired biological or pharmacological properties but with certain undesirable properties which can be overcome by modification of the structure [14]. Advances in synthetic methodologies have made it possible to make analogues of the original lead compound from natural sources with improved pharmacological or pharmaceutical properties [15]. Morphine from opium, for example, which continues to be used as a highly effective analgesic for the relief of terminal pain, has also served as a lead for the design of numerous drugs including analgesics such as pethidine, pentazocine and the cough suppressant dextromethorphan (Figure 1) [16]. Similarly Salicylic acid, an active ingredient of willow bark has been used as lead to design a safer synthetic analogue aspirin used in the treatment of pain and fever [17].

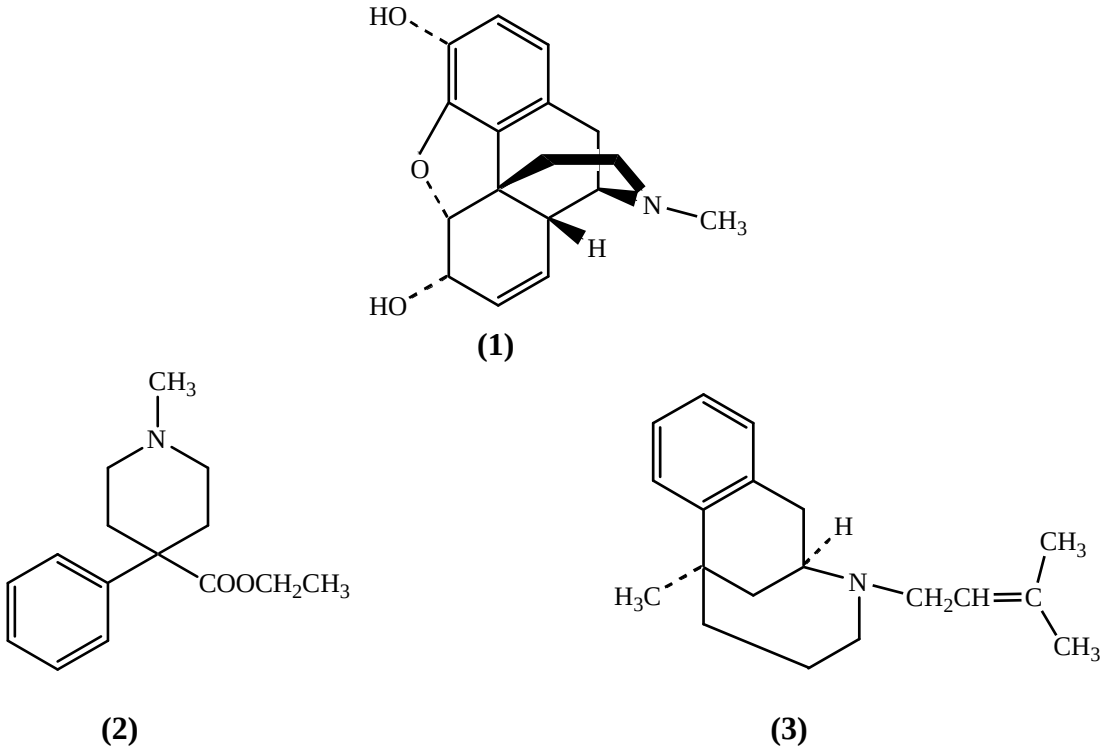


Figure 1: Structures of Morphine (1), Pethidine (2), Pentazocine (3)

The ability of plants to make a particular stereoisomer of a bioactive compound has ensured that, in many cases, they remain the ultimate source of certain medicinal compounds. In the USA, 50% of the chemotherapeutic drugs used in the treatment of cancer in 2004 have their origin in plants [18]. The combined use of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology have made it possible to exploit the vast diversity of chemical structures and biological activities of natural products [19].

Natural products have also made an important impact in the area of antimalarial drugs. The first antimalarial drug was quinine, which led to the development of other antimalarial drugs such as chloroquine [20]. Arteether is an another potent antimalarial drug derived from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* L. (Asteraceae), a plant used in traditional Chinese medicine. Other derivatives of artemisinin are under clinical trials in Europe (Figure 2) [21, 22].

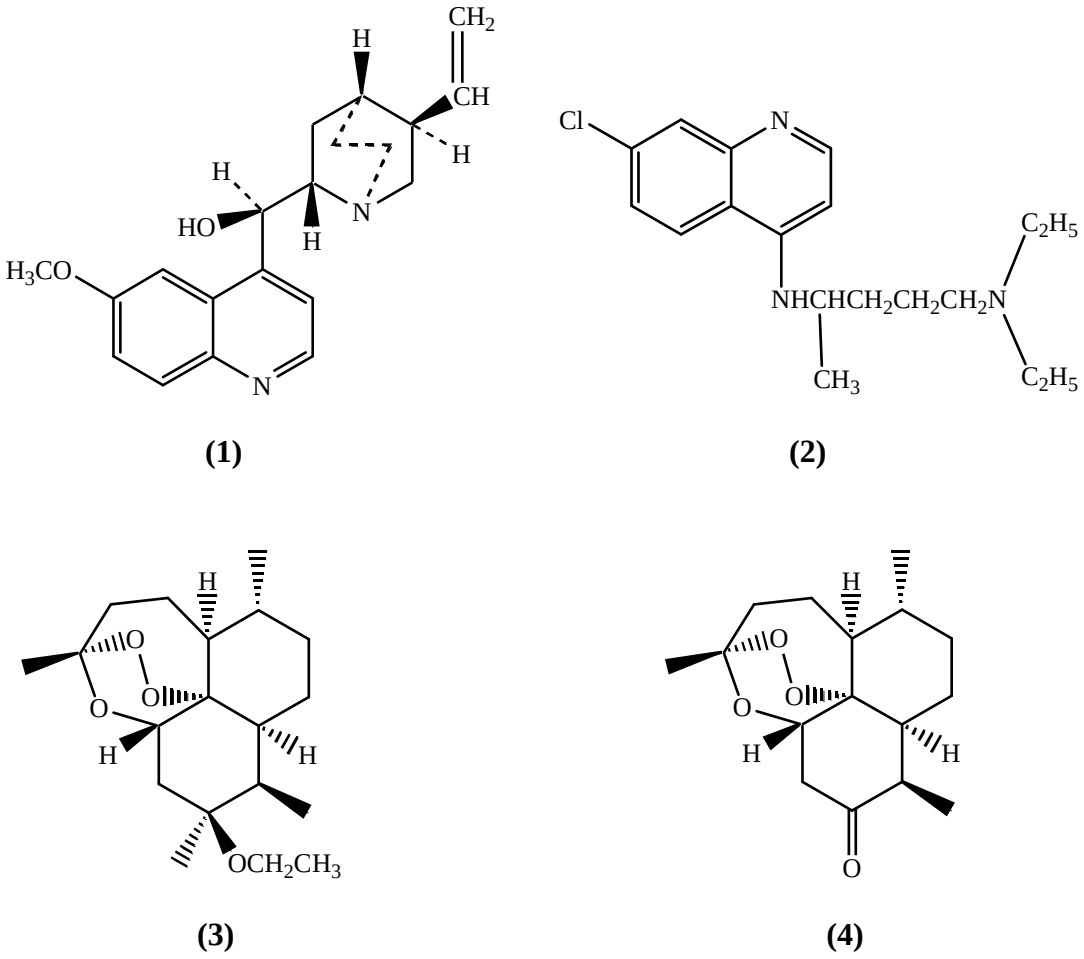


Figure 2: Structures of Quinine (1), Chloroquine (2), Arteether (3), Artemisinin (4)

Drug discovery from medicinal plants has played an important role in the treatment of cancer. Most of the current anticancer drugs are synthesized against the backbone of one or another natural product. Approximately 40% anticancer drugs available between 1940 and 2002, were derived from plant sources [23]. Anticancer drugs, such as paclitaxel and its derivatives docetaxel, obtained from the extracts of the English yew tree, *Taxus brevifolia* are used to treat ovary, breast, and other cancers (Figure 3) [24].

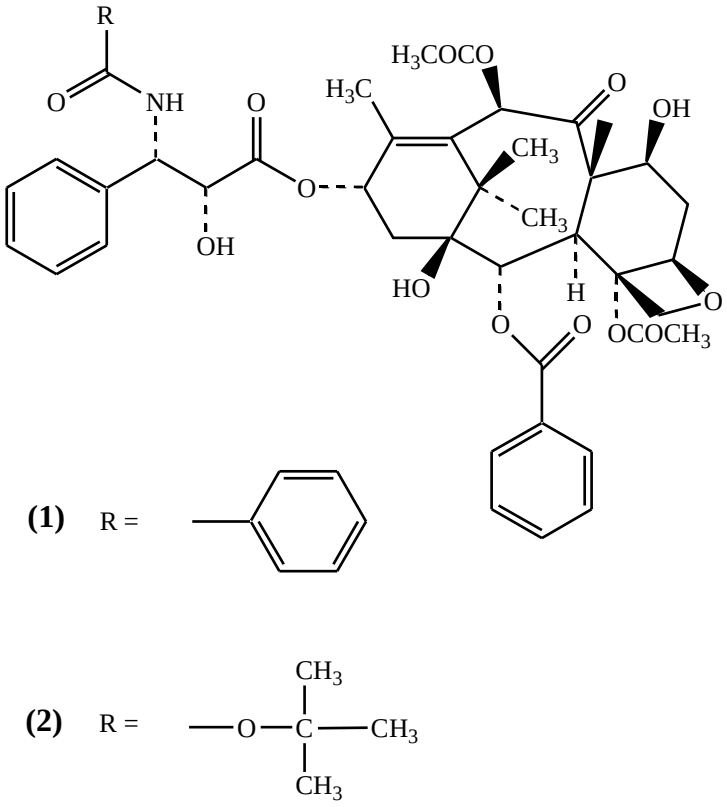
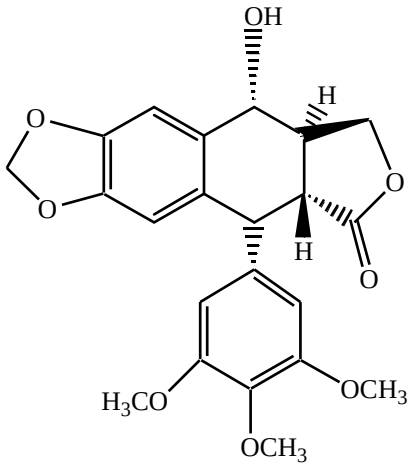


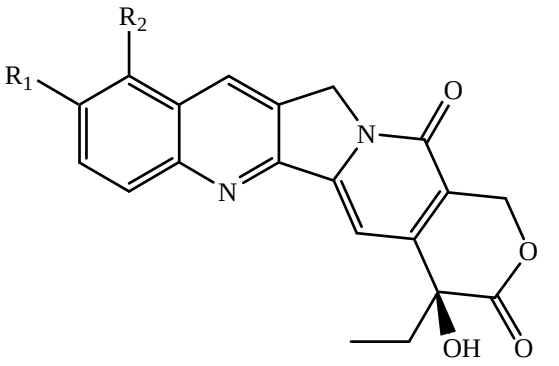
Figure 3: Structures of Paclitaxel (1), Docetaxel (2)

Another prominent molecule is podophyllotoxin, isolated from the resin of *Podophyllum peltatum* L. (Berberidaceae). Podophyllotoxin has been synthetically modified into etoposide and tenoposide, which are used to treat lung and testicular cancer. A quinoline alkaloid camptothecin isolated from *Camptotheca acuminata* inhibits the action of topoisomerase I, resulting in cell death. This compound as its sodium salt is proved to be extremely active against leukaemia and solid tumours. The molecule has given rise to other anticancer drugs such as topotecan and irinotecan. Camptothecin and these analogues have been investigated to treat a wide variety of cancers. Other important molecules include vincristine and vinblastine isolated from *Catharanthus roseus* L. (Figure 4) [25,26,27].

Cardiology has also been benefited greatly with the introduction of many drugs, based on natural products. Cardiac glycosides have been used for the treatment of cardiac arrest. An example is digitoxin (Figure 5) from *Digitalis*. *Rauwolfia* alkaloids have been used in the management of cardiovascular conditions such as arrhythmias and hypertention [28].



(1)



(2) R_1 = H R_2 = H

(3) R_1 = OH R_2 = $-CH_2-N(CH_3)_2$

Figure 4: Structures of Podophyllotoxin (1), Camptothecin (2), Topotecan (3)

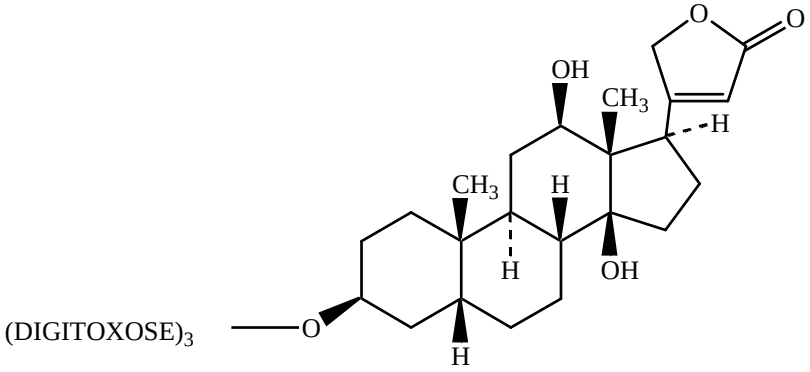


Figure 5: Structure of Digitoxin

Respiratory disorders can also be treated by phytotherapy. Ephedrine (Figure 6) and theophylline have been used as bronchodilators in the management of asthama and bronchitis [29]. Tiotropium has been introduced in the United States market for treatment of chronic obstructive pulmonary disease (COPD). Tiotroprium is an inhaled anticholinergic bronchodilator, based on ipratropium, a derivative of atropine that has been isolated from *Atropa belladonna* L. (Solanaceae) and other members of the Solanaceae family [30,31]. In addition, compounds such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicine and phorbol esters, all obtained from plants, are important tools used in pharmacological, physiological and biochemical studies [32].

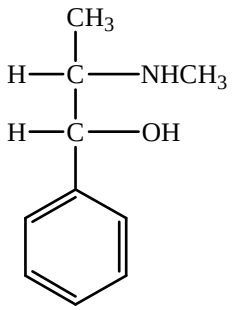


Figure 6: Structure of Ephedrine

Nowadays antioxidants have gained a lot of importance because of their potential as prophylactic and therapeutic agents in the diseases caused by free radicals. Although not many antioxidants are listed in pharmacopoeias, extensive research is being carried out globally on these agents, and most of them have been proven pharmacologically active. Traditionally, natural medicines with free radical scavenging properties have been used for various purposes. Presently, the active constituents from these natural sources are tested for their free radical scavenging potential. A number of plants included in *Ayurveda* such as *Emblica officinalis, Curcuma longa*, *Momordica charantia, Swertia chirata* and *Withania somnifera* have been studied by various researchers for their antioxidant potential. The global market of antioxidants is increasing rapidly, because of the increased health risk in a constantly polluting environment. These agents also have cosmetic applications, further fuelling research by industry and academia to explore these molecules and their analogues [33,34]. Thus Plants are of enormous importance in the free radical and antioxidant field. They supply us with the essential biradical, O_2. Plants expose themselves to high levels of O_2 and so are rich in antioxidant defenses and repair systems against oxidative damage [35].

In the last two decades there has been an explosive interest in the role of oxygen-free radicals in experimental and clinical medicine [36]. It has long been known that oxygen (O_2) is toxic to aerobic organisms

when they are exposed to it in concentrations greater than that of normal air, and the main cause of this toxicity is the intracellular reduction of O_2 into highly reactive chemical species or free radicals [37].

FREE RADICALS AND OXIDATIVE STRESS

The presence of free radicals in biological materials was discovered less than 50 years ago [38]. Free radicals, oxidative stress, and antioxidants have become commonly used terms in modern discussions of disease mechanisms. Free radical metabolism seems to occupy a central and remarkably common position in the mechanisms of many seemingly unrelated types of human diseases [39]. The body is normally in a steady state condition with free radicals being continuously generated and quenched. Free radicals, predominantly oxy radicals are generated under physiological conditions during aerobic metabolism. A small portion of these radicals play important roles in physiological processes and the remaining are inactivated by cellular antioxidant defense systems [40,41]. The free radicals are known to play a dual role in biological systems, since they can be either harmful or beneficial to living organisms [42]. Beneficial effects of free radicals involve physiological roles in cellular responses for example in defense against infectious agents and in the function of a number of cellular signaling systems. One further beneficial example of free radicals at low concentrations is the induction of a mitogenic response. In contrast, at high concentrations, they can be important mediators of damage to cell structures, including lipids, membranes, proteins and nucleic acids. The delicate balance between beneficial and harmful effects of free radicals is a very important aspect of living organisms and is achieved by mechanism called “redox regulation”. The process of “redox regulation” protects living organisms from various oxidative stresses and maintains “redox homeostasis” by controlling the redox status *in vivo* [43,44,45].

These unpaired electrons are very reactive with adjacent molecules such as lipids, proteins, and carbohydrates and can cause cellular damage [46]. Excess of free radicals can result from tissue damage and hypoxia, overexposure to environmental factors a lack of antioxidants, or destruction of free radical scavengers.

When the production of damaging free radicals exceeds the capacity of the body’s antioxidant defenses to detoxify them, a condition known as oxidative stress occurs. The cellular injury caused by oxidative stress has been linked to over 200 clinical disorders, many of which are seen in ICU patients units [47].

TYPES OF FREE RADICALS

Intracellular free radicals, with an unpaired electron, are often called reactive species. The reactive species have been broadly classified into reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS include a

number of chemically reactive molecules derived from oxygen and represent the most important class of radical species generated in the living systems [48]. Some of these molecules are extremely reactive, such as the hydroxyl radical, while some are less reactive such as superoxide and hydrogen peroxide. In Table 1, the most common intracellular forms of reactive species are listed together with their symbols [49].

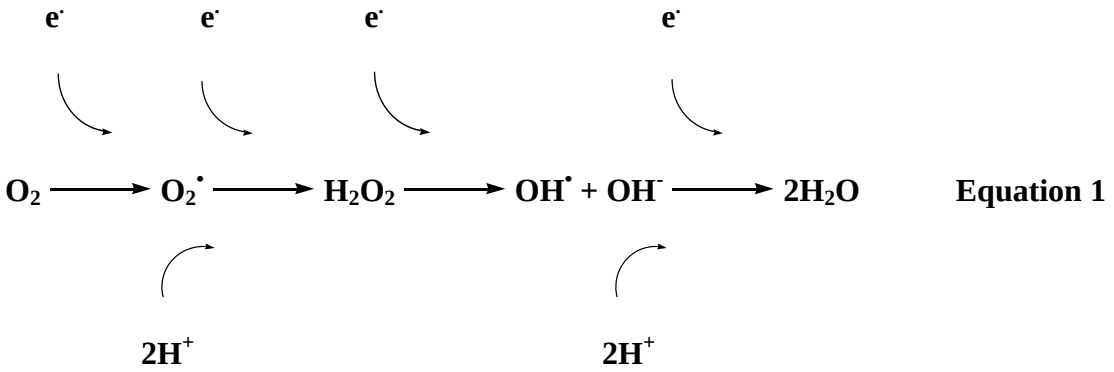
GENERATION OF FREE RADICALS

Molecular oxygen itself is a radical, it has two unpaired electrons in its outer orbital and its reactivity results from this biradical property. Most of the oxygen taken by human cells is reduced to water via the actions of mitochondrial cytochrome oxidase. This requires the addition of four electrons to each oxygen molecule. The intermediate steps of oxygen reduction are formation of superoxide anion radical ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$), corresponding to reduction by one, two and three electrons, respectively.

Table 1: Types of intracellular reactive species

Reactive Oxygen Species	***Symbol***
Superoxide anion radical	$O_2^{\bullet -}$
Hydroxyl radical	$OH^{\bullet}$
Hydroperoxyl radical	$HOO^{\bullet}$
Peroxyl radical	$ROO^{\bullet}$
Alkoxyl radical	$RO^{\bullet}$
Hydrogen peroxide	H_2O_2
Singlet oxygen	$^1O_2$
Reactive Nitrogen Species	***Symbol***
Nitric oxide	$NO^{\bullet}$
Nitrogen dioxide	$NO_2^{\bullet}$
Peroxynitrite anion	$ONOO^-$

The step-wise reduction of molecular oxygen through one electron transfers, producing and also connecting the ROS molecules listed in Table 1, can be summarized as follows: (Equation 1) [50,51].



Equation 1

The addition of one electron to molecular oxygen forms the superoxide anion radical ($O_2^{\bullet-}$). The production of $O_2^{\bullet-}$ occurs mostly within the mitochondria of a cell during energy production when a small number of electrons "leak" to oxygen prematurely. The $O_2^{\bullet-}$ is not highly reactive but has been implicated in the pathophysiology of a variety of diseases. $O_2^{\bullet-}$ arising either through metabolic processes or following oxygen activation by physical irradiation, is considered the "primary" ROS, and can further interact with other molecules to generate "secondary" ROS, either directly or prevalently through enzyme- or metal-catalysed processes [52].

H_2O_2 is not a free radical but is still highly important because of its ability to penetrate biological membranes. It plays an important role in the production of more reactive ROS species including (hypochlorous acid) HOCl (Equation 2) by the action of myeloperoxidase, an enzyme present in the phagosomes of neutrophils and, most importantly in the formation of $OH^{\bullet}$ via the oxidation of transition metals [53].

$$H^+ + Cl^- + H_2O_2 \longrightarrow HOCl + H_2O \qquad \textit{Equation 2}$$

Hydrogen peroxide is formed in *vivo* by the reduction of two molecules of $O_2^{\bullet-}$ with two protons in the presence of enzymes such as superoxide dismutase (SOD)(Equation 3) [54].

$$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \longrightarrow H_2O_2 + O_2 \qquad \textbf{Equation 3}$$

The hydroxyl radical ($OH^{\bullet}$) is the neutral form of the hydroxide ion. The $OH^{\bullet}$ has a high reactivity, making it a very dangerous radical with a very short *in vivo* half-life of approximately 10^{-9} seconds. The $OH^{\bullet}$ is formed from H_2O_2 in a reaction catalyzed by metal ions such as ferrous ions (Fe^{2+}) or copper ions (Cu^{+}), often bound in complex with different proteins or other molecules. This is known as the Fenton reaction (Equation 4). $O_2^{\bullet-}$ also plays an important role in the generation of $OH^{\bullet}$ by recycling or reducing the metal ions [55,56].

$$Fe^{2+}/Cu^{+} + H_2O_2 \longrightarrow OH^{\bullet} + OH^- + Fe^{3+}/Cu^{2+} \qquad \textbf{Equation 4}$$

Additional radicals derived from oxygen that are formed in the living systems are peroxyl radicals ($ROO^{\bullet}$). Peroxyl radicals are high-energy species that are involved in deoxyribonucleic acid (DNA) cleavage and modification of proteins. The simplest peroxyl radical is the hydroperoxyl radical ($HOO^{\bullet}$), which is the protonated form of $O_2^{\bullet-}$ [57]. Nitric oxide ($NO^{\bullet}$) is an abundant reactive radical that acts as an important oxidative molecule in a large variety of physiological processes, such as neurotransmission, blood pressure regulation, defense mechanisms, smooth muscle relaxation and immune regulation. It is a small molecule that contains one unpaired electron and is, therefore, a radical. $NO^{\bullet}$ is generated in biological tissues by specific nitric oxide syntheses (NOS), which metabolize arginine to citrulline with the formation of $NO^{\bullet}$ via a five electron oxidative reaction [58]. Overproduction of reactive nitrogen species is called nitrosative stress. This may occur when the generation of reactive nitrogen species in a system exceeds the system's ability to neutralise and eliminate them. Nitrosative stress may lead to nitrosylation reactions that can alter the structure of proteins and so inhibit their normal function. $NO^{\bullet}$ and the $O_2^{\bullet-}$ may react together to produce significant amounts of a much more oxidatively active molecule, peroxynitrite anion ($ONOO^{-}$), which is a potent oxidising agent that can cause DNA fragmentation and lipid oxidation (Equation 5) [59].

$$NO^{\bullet} + O_2^{\bullet-} \longrightarrow ONOO^{-} \qquad \textit{Equation 5}$$

OXIDATIVE STRESS AND HUMAN DISEASES

Reactive oxygen species are formed through a variety of events and pathways. It has been estimated that one human cell is exposed to approximately 1.5×10^5 oxidative reactive species a day [60]. ROS or RNS at low or moderate levels are vital to human health. However, when there is a free radical overproduction or antioxidant defense systems are weakened cellular damage can appear. (Figure 7)

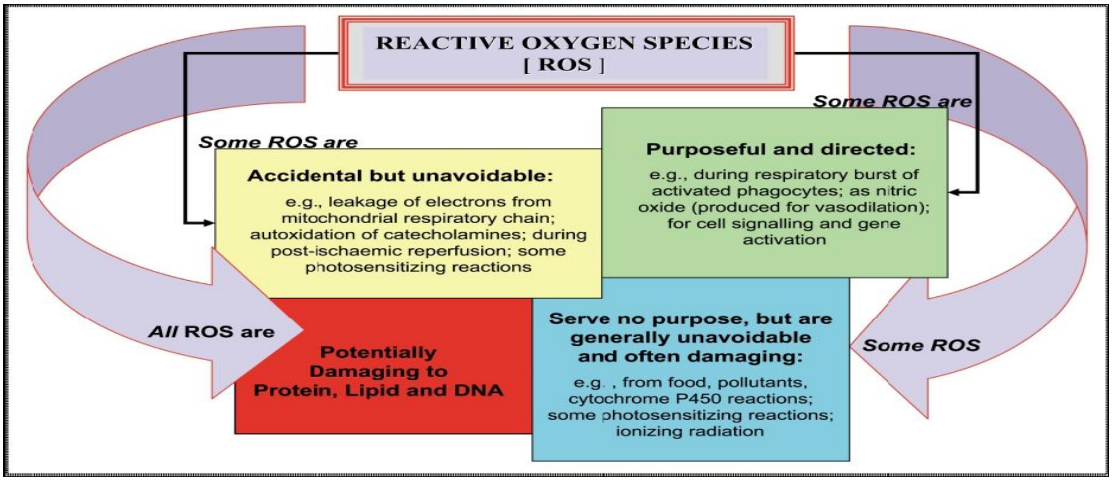


Figure 7: Reactive oxygen species

All the cellular components, lipids, proteins, nucleic acids and carbohydrates are damaged by reactions with oxygen free radicals, giving rise to metabolic and cellular disturbances. The highly reactive hydroxyl radical ($OH^{\bullet}$) causes damage to DNA and other biological molecules [61]. Lipid peroxidation is probably the most extensively investigated process induced by free radicals. Polyunsaturated fatty acids (PUFAs) are highly susceptible to reactions with free radicals. Peroxidation of lipids may lead to a radical chain reaction. These degenerative chain reactions in lipid membranes are usually accompanied by the formation of a wide variety of products, including alkanes and carbonyl compounds. Since some of these products are toxic, they may serve as second messengers in free radical mediated damage [62].

ROS can attack almost any cellular structure or molecule. However, with respect to aging and cancer, DNA is considered a major target. ROS may cause DNA-protein cross links, single or doublestranded DNA cross links, DNA breaks, damage to the deoxyribose-phosphate backbone as well as specific chemical modifications of purine and pyrimidine bases [63]. Permanent modification of genetic material resulting from such oxidative damage represents the first step involved in mutagenesis, carcinogenesis and ageing. DNA damage can result either in arrest or induction of transcription, induction of signal transduction pathways, replication errors and genomic instability, all of which are associated with carcinogenesis [64]. In addition to ROS, RNS, such as peroxynitrites and nitrogen oxides, have also been implicated in DNA damage [65].

Free radical activity has also been shown to oxidize and cross-link proteins including enzymes and connective tissue. The amino acid residues of proteins are highly susceptible to oxidative attack. Oxidative damage to these macromolecules can lead to enzyme inactivation, mutation, membrane disruption, increased atherogenicity of low density lipoproteins, mitochondrial dysfunction, and cell death. Thus oxidative stress is thought to make a significant contribution to ageing and in the development of various diseases such as: Cardiovascular diseases (stroke and hypertension), neurologic diseases (Multiple sclerosis, alzheimer's disease, parkinson disease), arthritis, cancer, gastric ulcers, muscular dystrophy and liver diseases (Figure 8) [66,67]. The pathogenesis of rheumatoid arthritis is due to the generation of ROS and RNS at the site of inflammation. Oxidative damage and inflammation in various rheumatic diseases were proved by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to controls [68]. In a disease such as Alzheimer's disease numerous experimental and clinical studies have demonstrated that oxidative damage plays a key role in the loss of neurons and the progression to dementia. The production of β-amyloid, a toxic peptide found in the brain of patients suffering from Alzheimer's disease, is due to oxidative stress and plays an important role in the neurodegenerative processes [69].

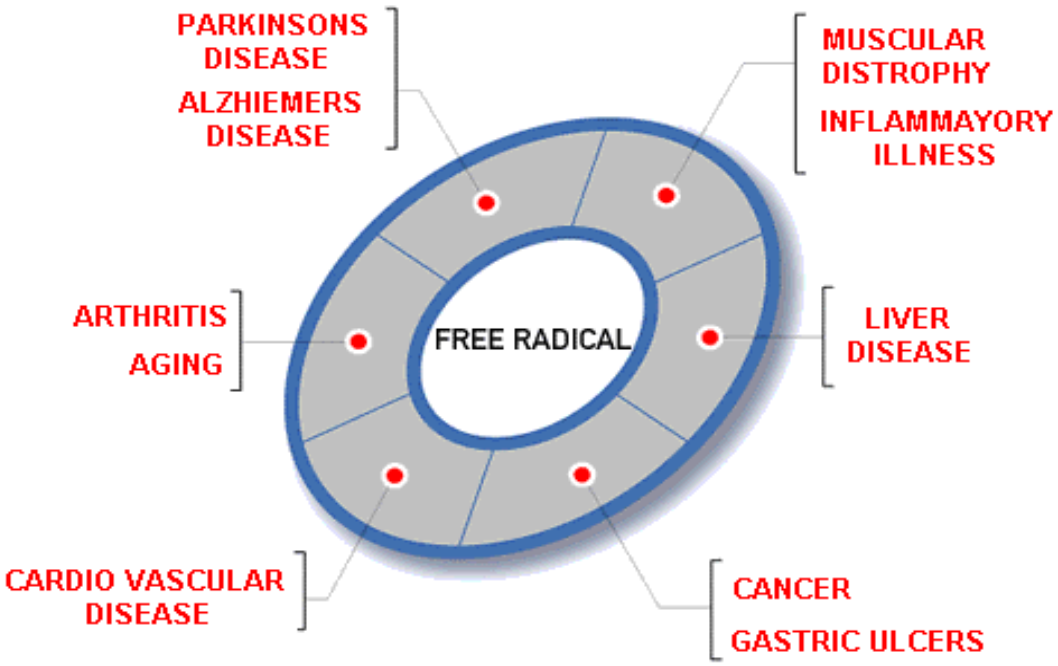


Figure 8: Diseases due to free radicals

ANTIOXIDANTS

They are capable of stabilizing, deactivating, or scavenging free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well being. Our body implements various antioxidants, some of which are dietary antioxidants. These antioxidants help restrain potential free radical damage that could occur in our bodies. If one looks back into the evolution of human diet, it can be observed that in the Paleolithic age human intake of plant derived antioxidants is considered to have been many times higher than current intake [70]. A good antioxidant should: specifically quench free radicals, chelate redox metals, regenerate other antioxidants within the "antioxidant network", have a positive effect on gene expression [71].

When an antioxidant destroys a free radical, this antioxidant itself becomes oxidized by donating electrons to the free radicals (Figure 9). Therefore, the antioxidant resources must be constantly restored in the body. Thus, while in one particular system an antioxidant is effective against free radicals.

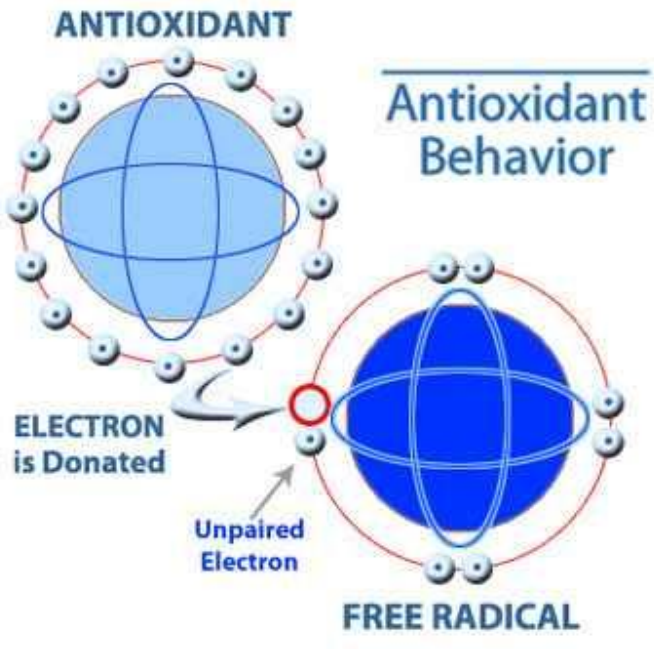


Figure 9: Action of an antioxidant

CLASSIFICATION OF ANTIOXIDANTS

Antioxidants can be classified into two major groups, i.e. enzymatic and non-enzymatic antioxidants. Some of these antioxidants are endogenously produced which include enzymes, low molecular weight molecules and enzyme cofactors. Among non-enzymatic antioxidants, many are obtained form dietary sources. Dietary antioxidants can be classified into various classes, of which phenolic compounds is the largest class. Phenolic compounds consist of phenolic acids and flavonoids [71] The other classes of dietary antioxidants include vitamins, carotenoids, organosulfural compounds and minerals (Figure 10).

ENZYMATIC ANTIOXIDANTS

Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), etc. SOD and CAT are the primary enzymes, which are not consumed and have a high affinity for ROS. They are among the most potent antioxidants known in nature. Therefore, it may be hypothesized that the enzymes afford more effective protection against pathological conditions arising due oxidative stress such as inflammation. SOD catalyzes the dismutation of $O_2^{\bullet-}$ into oxygen and to the less reactive species H_2O_2. CAT is located in a cell organelle called the peroxisome. The enzyme very efficiently promotes the conversion of hydrogen peroxide to water and molecular oxygen (Equation 6).

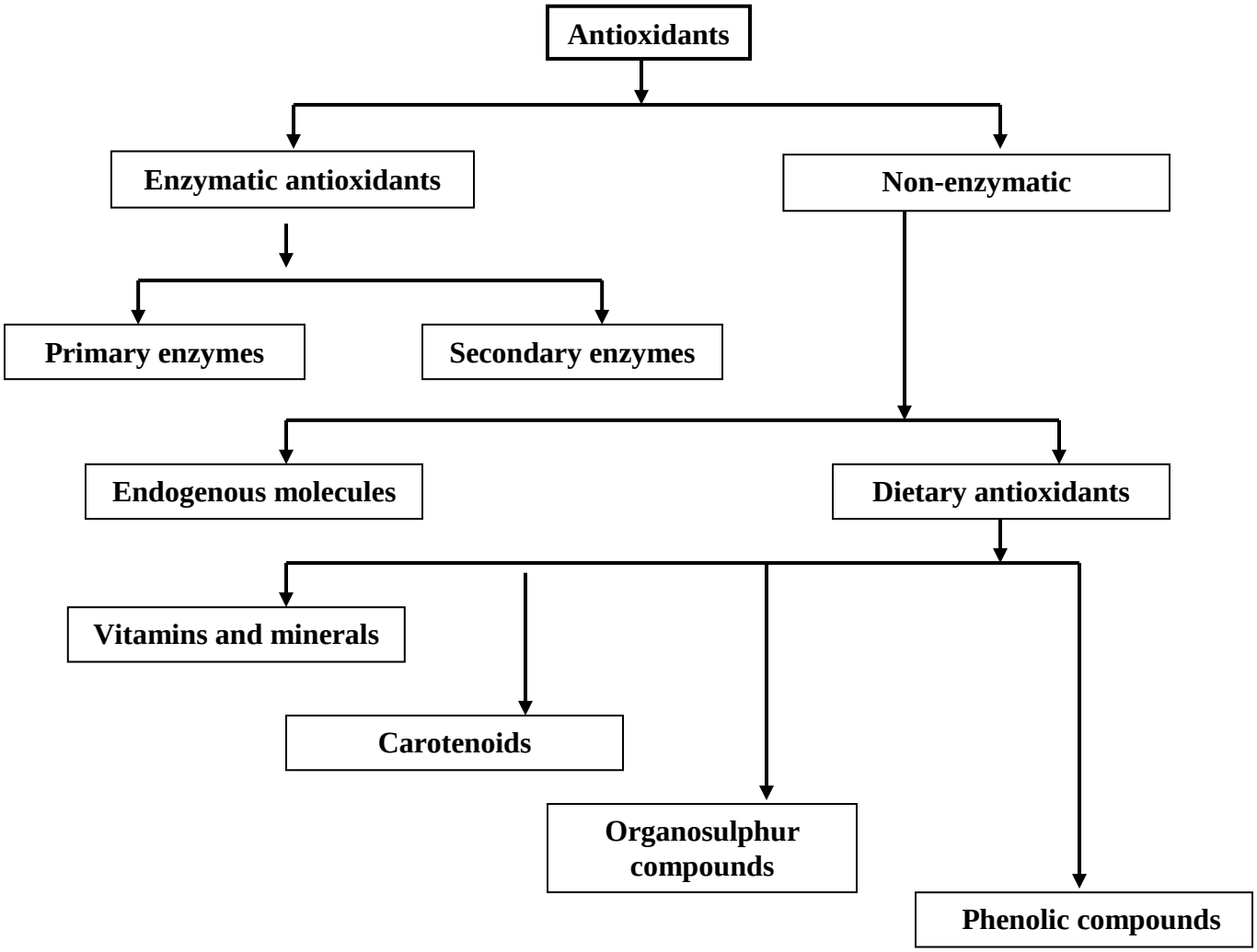


Figure 10: Classification of antioxidants

In addition, CAT acts on toxic compounds such as phenols, formic acid, formaldehyde and alcohols by peroxidative reaction.

$$2H_2O_2 \longrightarrow 2H_2O + O_2 \qquad \text{Equation 6}$$

These free radical scavenging enzymes have been found to change qualitatively and quantitatively in various tissues and cells of patients with mitochondrial diseases and elderly subjects.

NON-ENZYMATIC ANTIOXIDANTS

The non-enzymatic antioxidants consist of endogenous molecules and various dietary antioxidants.

ENDOGENOUS MOLECULES

There are a certain number of small molecules, widely distributed in biological systems, which can scavenge oxygen free radicals non-enzymatically. Glutathione (GSH), uric acid, taurine are some of these small molecules. GSH is the most abundant intracellular thiol antioxidant, prevalent in mill molar concentrations in all living aerobic cells. The reduced form of glutathione is GSH, and the oxidized form is GSSG. Generally, the antioxidant capacity of thiol compounds is due to the sulphur atom, which can easily accommodate a single electron from free radicals. GSH takes up an electron from a free radical $R^{\bullet}$ to form a thiyl radical ($GS^{\bullet}$) (Equation 7). The lifetime of sulphur radical species thus generated, i.e. $GS^{\bullet}$, may be significantly longer than many other radicals generated during the oxidative stress.

$$GSH + R^{\bullet} \longrightarrow GS^{\bullet} + RH \qquad \textbf{Equation 7}$$

Thiyl radicals generated may dimerise to form the non-radical product, oxidised glutathione (GSSG) (Reaction 8). Oxidised glutathione GSSG is accumulated inside the cells and the ratio of GSH/GSSG is a good measure of oxidative stress of an organism.

$$GS^{\bullet} + GS^{\bullet} \longrightarrow GSSG \qquad \textbf{Equation 8}$$

GSH plays a protective role against oxidative stress by scavenging hydroxyl radical and singlet oxygen directly, detoxifying hydrogen peroxide and lipid peroxides, regenerating the most important antioxidants, vitamin C and E and by acting as a cofactor of several detoxifying enzymes such as glutathione peroxidase (GPx) [72,73].

DIETARY ANTIOXIDANTS

The nutritious diet contains a large number of substances which act as antioxidants. Among these, the most well known substances are vitamins E and C, β-carotene, phenolic compounds and coenzyme Q.

Vitamin C

Vitamin C (ascorbic acid) is a very important, and powerful, antioxidant that works in aqueous environments of the body. Vitamin C (Figure 11) cooperates with Vitamin E to regenerate □-tocopherol from □-tocopherol radicals in membranes and lipoproteins [74]. In many studies Vitamin C protects against cell death triggered by various stimuli and a major proportion of this protection has been linked with its antioxidant ability. At

physiological pH, 99.9% of Vitamin C is present as ascorbate anion. Ascorbate anion is a donor antioxidant and reacts with radicals to produce the resonance stabilised tricarbonyl ascorbate free radical [75].

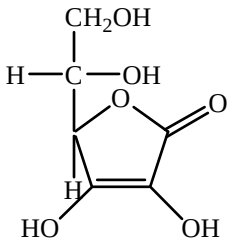


Figure 11: Structure of Vitamin C (ascorbic acid)

Vitamin E

Vitamin E **(**Figure 12**)** is a fat-soluble vitamin that exists in eight different isomeric forms. α-Tocopherol is the most active form of vitamin E in humans and is a powerful biological antioxidant and is considered to be the major membrane bound antioxidant employed by the cell. Its main antioxidant function is protection against lipid peroxidation. During the antioxidant reaction, α-tocopherol is converted to a α- tocopherol radical by the donation of labile hydrogen to a lipid or lipid peroxyl radical [76,77].

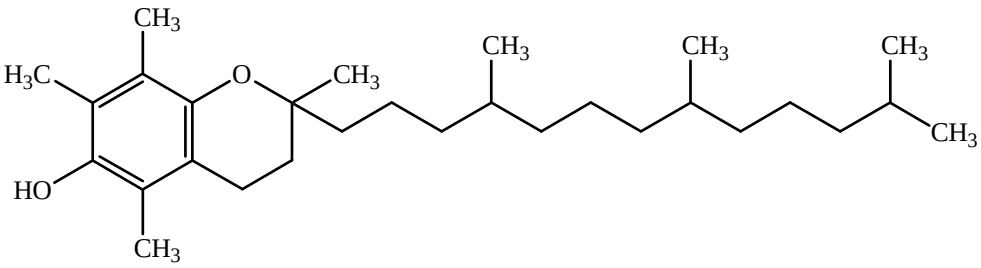


Figure 12: Structure of Vitamin E

CAROTENOIDS

Carotenoids are pigments that are found in plants and microorganisms. There are over 600 carotenoids occurring in nature. Various studies have indicated that carotenoids may prevent or inhibit certain types of cancer, artherosclerosis, age-related muscular degeneration, and other diseases. The antioxidant activity of carotenoids arises primarily as a consequence of the ability of the conjugated double-bonded structure to delocalise unpaired electrons [78]. This is primarily responsible for the excellent ability of β- carotene (Figure 13) to physically quench singlet oxygen, and for its reactivity with free radicals such as $ROO^{\bullet}$, $OH^{\bullet}$ and $O_2^{\bullet -}$. At sufficiently high concentrations, carotenoids can protect lipids from peroxidative damage.

Recently a growing body of evidence has accumulated which suggests that the scavenging of lipid $ROO^{\bullet}$, by β-carotene may not proceed via an electron-transfer mechanism reaction, but rather by adduct formation or hydrogen abstraction. Carotenoids exhibit antioxidant behaviour at low oxygen partial pressures, they may lose antioxidant properties, or even become pro-oxidants, at high pressures of oxygen [79,80].

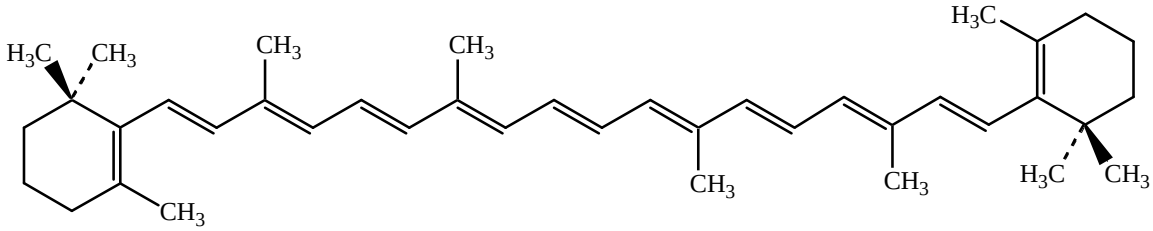


Figure 13: Structure of β-carotene

PHENOLIC COMPOUNDS

Phenolic compounds or polyphenols constitute one of the most numerous and widely distributed group of plant secondary metabolites, with more than 8000 phenolic structures currently known. Natural polyphenols can range from simple molecules (phenolic acids, phenylpropanoids, flavonoids) to highly polymerised compounds (lignins, melanins, tannins), with flavonoids representing the most common and widely distributed sub-group. Phenolics are widely distributed in the plant kingdom and are therefore an integral part of the diet, with significant amounts being reported in vegetables, fruits and beverages. Although the dietary intake of phenolics varies considerably among geographic regions, it is estimated that daily intake range from about 20 mg to 1g, which is higher than that for Vitamin E. Polyphenolics exhibit a wide range of biological effects including antibacterial, anti-inflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, anticarcinogenic and vasodilatory actions many of these biological functions have been attributed to their free radical scavenging and antioxidant activity [81].

Flavonoids constitute the most important group of polyphenol. According to chemical structure, over 4000 flavonoids have been identified and classified into flavanols, flavanones, flavones, isoflavones, catechins, anthocyanins, proanthocyanidins. Their common structural feature is the diphenylpropane moiety, which consists of two aromatic rings linked through three carbon atoms that together usually form an oxygenated heterocyclic. e.g. Quercetin (Figure 14).

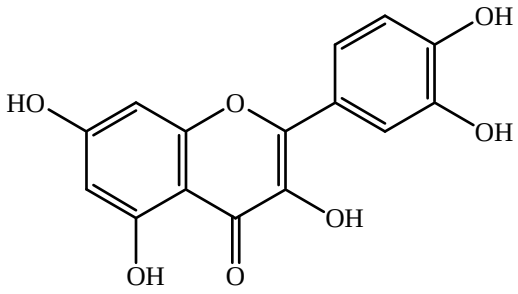


Figure 14: Structure of Quercetin

Phenolic compounds acting as antioxidants may function as terminators of free radical chains and as chelators of redox-active metal ions that are capable of catalysing lipid peroxidation. Phenolic antioxidants (PhOH) interfere with the oxidation of lipids and other molecules by the rapid donation of hydrogen atom to $ROO^{\bullet}$. The phenoxy radical ($PhO^{\bullet}$) intermediates so formed are relatively stable and do not initiate further radical reactions (Equation 9).

$$ROO^{\bullet} + PhOH \longrightarrow ROOH + PhO^{\bullet} \qquad \text{Equation 9}$$

They even act as terminators of the reaction chain by interacting with other free radicals. However, under certain conditions, e.g. a high concentration of PhOH, the presence of redox-active metals (copper, iron) and a high pH, they may behave as pro-oxidants [82].

TRITERPENOIDS

Triterpenoids are natural, biologically active compounds extracted from many plants. They possess antiinflammatory, anticancer, and antioxidant properties. A new multiflorane triterpenoid and two new cucurbitane triterpenoids isolated from the stems of *Momordica charantia* are found to possess antioxidant potential [83]. The triterpenoid monogynol A (Figure 15) isolated from *Salvia macrochlamys* has been reported to possess antioxidant properties [84]. Antioxidant triterpenoids have been isolated from *Olea europaea*, subspecies africana leaves [85].

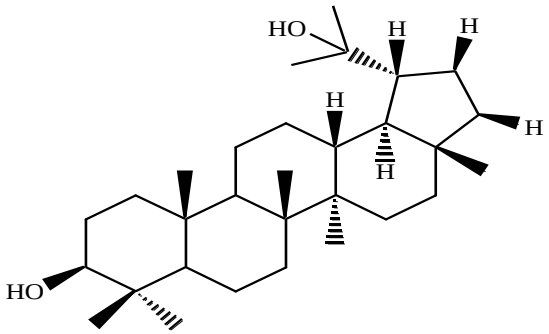


Figure 15: Structure of Monogynol A

CONCLUSION

Ethanobotany is a excellent sources for medicines last thousands of years and have formed the sophisticated traditional medicine systems. The ancient people treated illness by using plants, animal parts, and minerals that were not part of their usual diet. Natural products are staging a comeback and herbal 'renaissance' is happening all over the globe. This present study informed that one third of the plants used in modern system of medicine. It has been noted that Ayurveda, Unani and Siddha system of medicines used the whole or different parts of plants, like leaves, stem, bark, root, flower, seed, for therapeutic activity. The study enlightens on process of development of plants/active constituent like Chloroquine, Arteether, *Emblica officinalis*, *Curcuma longa*, *Momordica charantia*, *Swertia chirata*, *Withania somnifera*, Carotenoids, Triterpenoids shown therapeutic activities like anticancer, antimalarial, anti-inflammatory and antioxidant etc. This study comprised the therapeutic effects, pathways and journey with chemical structures of various medicinal plants.

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