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Chapter

Dietary Phytochemicals: As a Natural Source of Antioxidants

Manju Singh Makhaik, Arvind K. Shakya and Raosaheb Kale

Abstract

Since time immemorial, plants are used as the source of food and medicine. It can be traced back to the start of humanity. Bringing plant-based food, such as fruits, vegetables, and whole grains, rich in phytochemicals, with beneficial nutrients, opens the door for healthy living. The health benefits are partly attributed to the compounds which possess antioxidants. Several epidemiological observations have shown an opposite relationship between consumption of plant-based foods, rich in phytochemicals, and many diseases including cancer. The majority of the ailments are related to oxidative stress induced by free radicals. Free radicals are extremely unstable with a very short half-life, highly reactive molecule which leads to oxidative damage to macromolecules such as proteins, DNA, and lipids. Free radical induced cellular inflammation appears to be a major contributing factor to cause aging, and degenerative diseases such as cancer, cardiovascular diseases, diabetes, hepatic diseases, renal ailments, and brain dysfunction. Free radicals have been caught up in the pathogenesis of several diseases. Providentially, free radical formation is controlled naturally by phytochemicals, through their antioxidant potential which plays a key role in preventing many diseases including cancer by suppressing oxidative stress-induced DNA damage. Keeping these facts in mind, an attempt has been made to highlight the oxidative stress, enzymatic and non-enzymatic antioxidant, dietary phytochemicals and their role of in disease prevention and cure.

Keywords: Oxidative stress, antioxidants, reactive oxygen species, antioxidant enzymes, phytochemicals

1. Introduction

Life threatening diseases such as cardiovascular diseases, neurodisorders, diabetes, and cancers are world health problems and account for morbidity and mortality to millions of people. These diseases/disorders are mainly linked to oxidative stress due to free radical induced toxicity. The free radicals (oxidants) are unstable species with a very short half-life, but they are highly reactive metabolites which are harmful to normal functions of the cells and body. They produce oxidative damage toward macromolecules like proteins, DNA, and lipids. In general, the reactive oxygen species circulating in the body tend to react with the electron of other molecules in the body and these also affect various enzyme systems and cause DNA damage which may further contribute to oxidative damage and inflammatory diseases and conditions such as cancer, ischemia, aging, adult respiratory distress syndromes, rheumatoid arthritis, etc. Oxidative stress occurs as result of an imbalance between free radicals and antioxidant defense system. A plant-based diet protects against chronic oxidative stress-related diseases. Many researchers reported that dietary fruits, vegetables, and grains apply a protective effect against the development of these chronic diseases [1–4]. This protective role can be predominantly credited to the phytochemicals in them, which are defined as bioactive non-nutrient compounds in fruits, vegetables, grains, and other parts [5]. Antioxidants or inhibitors of oxidation are compounds that retard or prevent the oxidation in general, and prolong the life of the oxidizable matter.

Plants kingdom contains variable chemical families and amounts of antioxidants. It has been hypothesized that antioxidants from dietary plants may contribute to the beneficial health effects. Among these, routine dietary sources are also easily available and more suitable for dietary interventions.

The need is to identify and generate awareness about these sources, which can be rated from top to down regarding antioxidant potential. The people who are habitual of consuming these vegetables and fruits in their routine diet are proved to be less suffered by various chronic diseases [6], and studies have also endorsed the long-term health impact of consuming these plant based diets. This chapter presents certain information about oxidative stress, antioxidant categories, phytochemicals, and their role in prevention and cure of several diseases.

2. Free radicals and oxidative stress

Free radicals are highly reactive species because they have unpaired electrons which seek an electron to stabilize the molecule. Free radicals can be generated by a variety of sources which can be classified as endogenous (within the body) and exogenous sources (outside the body). They are essential intermediates in natural processes and readily react with other molecules result in oxidative stress. **Figure 1** represents the generation of free radicals. Reactive oxygen species (ROS) is a collective term which include hydroxyl radical (OH•), perhydroxyl radical (HO_2•), hypochlorous acid (HOCl), superoxide anion radical (O_2•$^-$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), nitric oxide radical (NO•), hypochlorite radical (OCl•), peroxynitrite (ONOO),

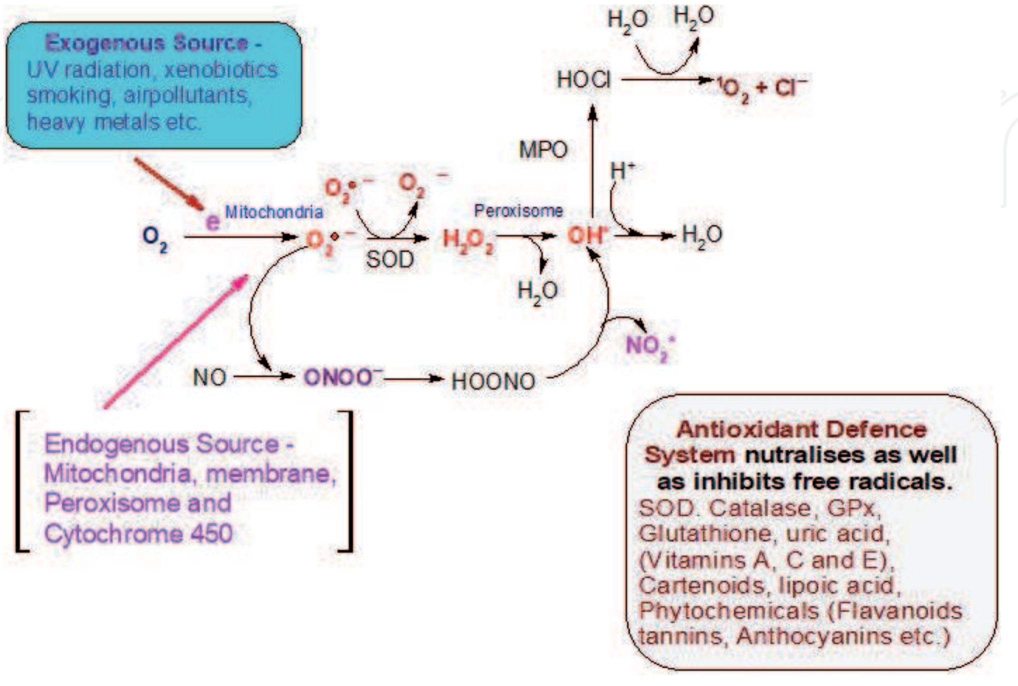


Figure 1.
Overview of generation of reactive oxygen species (free radicals).

and different lipid peroxides. Reactive nitrogen species (RNS) such as $ONOO^-$ and NO• are formed by the reaction of nitric oxide with $O_2•^-$ while RSS are easily produced from thiols through a reaction with ROS [7, 8]. Though, the free radicals are produced naturally by normal process of metabolism and lifestyle also influences their production in the body such as smoking, exposure of toxic chemicals, alcohols and fried foods. Although, cells have antioxidant defense system (antioxidant enzymes) to encounter harmful effects of free radicals. These free radicals are linked to the diseases such as cardiovascular, neurodisorders, diabetes, liver diseases, cancer and aging.

An imbalance between antioxidant defense system and reactive oxygen species result in oxidative stress which further leads to necrosis and cell damage. Cells experience oxidative stress when they are exposed with excess level of free radicals (ROS) as result of depletion of antioxidant level within cells. Free radicals contain uneven number of electrons which can harm biomolecules by producing lipid peroxides, protein carbonyls and various degenerative changes that can cause DNA damage and apoptotic events which lead to damage cell's survival capacity and finally cause cell death. Cells use endogenous and exogenous antioxidants defense mechanism to detoxify these reactive products.

2.1 Oxidative stress and cellular damage

Reactive oxygen species (ROS) are typical by-products of cellular metabolism, playing a role as secondary messengers and influencing different normal physiological functions of the body. In some cases, oxidative stress is also useful for intracellular signaling which is necessary for physiological adaptation of the body.

Furthermore, there is growing evidence supporting the role of ROS in numerous pathological conditions, that is, diseases (**Figure 2**). The paired character of ROS with their beneficial and detrimental characteristics indicates the sophistication of their specific roles at a biological compartment and the difficulties in attaining applicable procedures to treat ROS-related diseases. From basic science research to clinical trials, the biomedical scientific society has promptly progressed toward an improved interpretation of ROS-metabolizing systems and their impact on specific

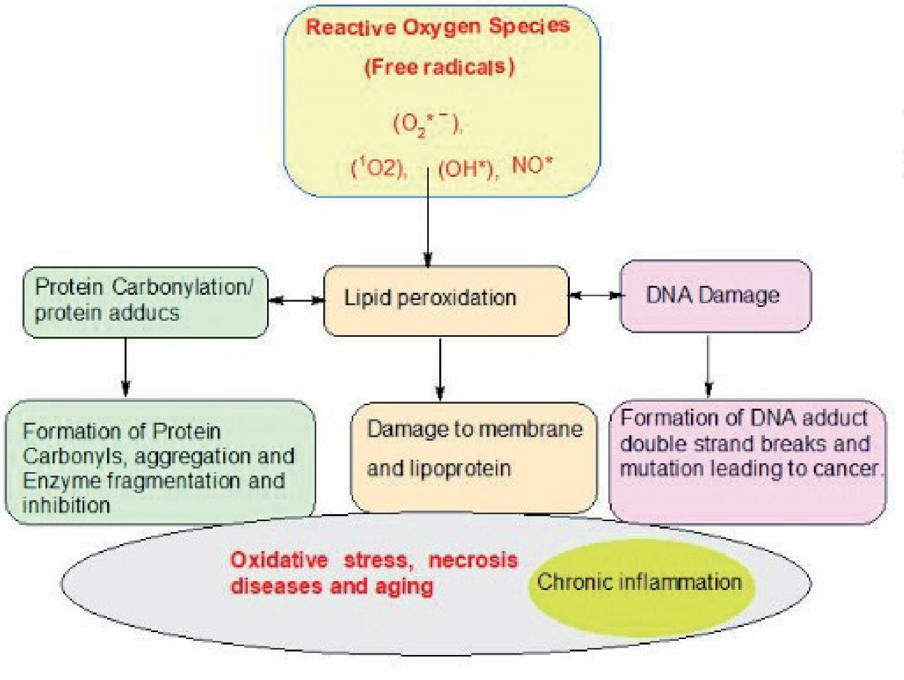


Figure 2.
Impact of free radicals on cellular system.

conditions. The free radicals often involve in cell–cell communication, apoptosis, ion transportation, and gene expression [8].

Oxidation is a normal and necessary process that takes place in the body. Whereas, oxidative stress, on the other hand, takes place when there's an imbalance between oxidants and antioxidants within the body due to lack of antioxidants or increased production of free radicals (ROS) [9, 10]. Free radicals due to unpaired electrons can start oxidation to biomolecules i.e. carbohydrates, proteins, lipids, and nucleic acids. These consequences can lead to heart disease, inflammatory disease, cancer, diabetes mellitus, Alzheimer's disease, autism, and to the aging process [7, 11].

2.2 Antioxidant defense system

Antioxidants are molecule that reduce and prevent the harmful effect of free radicals. Humans have a complex antioxidant protection system, which functions interactively and synergistically to neutralize free radicals. There are several antioxidant enzymes that can neutralize free radicals and ROS. These enzymes form the body's endogenous defense mechanisms from free radicals to protect the cell. Enzymatic defense system mainly includes enzymes such as glutathione peroxidases, superoxide dismutase and catalase, which decrease the concentration of the most harmful ROS whereas non-enzymatic antioxidants are vitamins C and E, β-carotene, uric acid and glutathione.

Antioxidant enzymes are important protein components that offer protection against ROS via removing potential oxidants/transferring ROS/RNS into relatively stable compounds [11]. For optimum catalytic activity, these enzymes require micronutrient cofactors such as Se, Fe, Cu, Zn, and Mn [12]. The following three antioxidant enzymes play significant roles in protecting cells from oxidative stress:

2.2.1 Superoxide dismutases (SOD)

Mc Cord and Fridovich first discovered this enzyme in 1969. Superoxide Dismutase (SOD), is the best known and perhaps most important of the antioxidant enzymes. It converts the harmful free radicals superoxide to the less active peroxide, which then can be further converted by other antioxidant enzyme (catalase) into water. The enzyme dismutase converts two molecules of superoxide radical to form H_2O_2 and O_2. The SOD family consists of four metallo forms which require copper, zinc, one manganese and one iron Cu for their free radical detoxifying activity. ZnSOD is found in the cytosol of most eukaryotic cells [13]. A different form of Cu, ZnSOD is found in extracellular fluids (EC), where it is called EC-SOD [14, 15]. The two superoxide radicals converted into hydrogen peroxide and oxygen during the catalytic reaction of SOD.

$$O_2{\bullet}^- + O_2{\bullet}^- \xrightarrow{\text{SOD}} O_2 + \mathbf{H_2O_2}$$

This is important, because free radicals are highly active and unstable, and will attack any molecule in the body. Organ or tissue damage can occur whenever production of free radicals exceeds to that of scavenger enzymes such as SOD, which are the first-line defense system of the body's tissues.

2.2.2 Catalase (CAT)

Catalase is localized exclusively in peroxisomes and deals with the large amount of H_2O_2 present in them. It requires iron as a cofactor to degrade hydrogen peroxide to water and oxygen. Human CAT composes four identical subunits of 62 kDa [16]. It's optimum pH lies in the alkaline range. At the subcellular level, CAT is found mostly in perxoisomes (80%) and cytosol (20%), and deals with a large amount of hydrogen peroxides (H_2O_2) present in them.

$$2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2$$

2.2.3 Glutathione peroxidase (GPx)

Gutathione peroxidase (GPx) is a group of cytosolic enzymes which contains a single selenocysteine residue, in which selenium is covalently bound in its active site. This selenium dependent enzyme which converts hydroperoxides to H_2O where GSH represent reduced state and GSSH represent the glutathione disulfie (oxidized state) [17].

$$H_2O_2 + 2GSH \xrightarrow{GPx} GSSH + O_2$$

2.2.4 Non-enzymatic antioxidants

The non-enzymatic antioxidants also play important role to neutralize intracellular free radicals which are discussed as follows:

2.2.4.1 Glutathione

Glutathione (GSH) is present in all plant and animal cells and is a tripeptide (glutamyl-cysteinyl-glycine). The cysteine provides an exposed free sulphydryl group (SH) that is highly reactive, providing an abundant target for radical attack. It is mainly synthesized in the liver [18] and exists in several redox forms, among which the most predominant is the reduced glutathione. GSH is a hydrosoluble antioxidant present in high cellular concentrations (1–10 mM) in the nucleus, mitochondria, and cytoplasm. GSH is involved in several lines of defense against ROS. First, the thiol group confers GSH with the ability to protect other thiol functions in proteins against oxidative damage [19]. Thiol groups (-SH) are widespread and highly reactive chemical entities in cells. They make complex with metal ions, participate in oxidation reactions by getting oxidized themselves to sulfonic acids, and form thiol radicals and disulfides [20].

2.2.4.2 Uric acid

Uric acid (UA) is a strong reducing agent (donates electrons) which acts as a powerful antioxidant and scavenge the singlet oxygen and radicals. Normally in humans, one of the main antioxidants in plasma is uric acid.UA is a hydrophilic antioxidant generated during the metabolism of purine nucleotides and accounts nearly for 66% of the total oxygen scavenging activity in the blood serum. Mammals and humans are capable of producing UA, making it the most predominant aqueous antioxidant present in humans [21, 22] with an approximate blood level of 3.5–7.5 mg/dL. UA is an effective metabolite that can stop free radicals produced by xanthine oxidase (XO) in catalysis reaction of xanthine and hypoxanthine [23]. UA gives cellular protection from oxidants, which related to a variety of physiological situation [24, 25].

In addition, there are diverse dietary foods and medicinal plants which are rich sources of vitamins and phytochemicals, provide additional protection to the body against oxidative stress. The major among those antioxidants are vitamin E, Vitamin A, vitamin C and flavonoids, carotenoids, lipoic acids and tannins etc.

2.2.4.3 Vitamin E

Vitamin E is exogenous (lipid-soluble antioxidant) and must be obtained through diet in small amounts since the organism cannot synthesize it. Its biosynthesis is restricted to plants, photosynthetic algae, and certain cyanobacteria. It plays a vital role in protecting membranes from oxidative damage and thus its primary activity is to trap peroxy radicals in cellular membranes. It inhibits the lipid peroxidation induced by free radicals [26]. α-Tocopherol is the most active form of vitamin E that has antioxidant activity and immune functions. It has been revealed to be a more effective free radical scavenging vitamins that prevent peroxynitrite-induced lipid peroxidation and inflammatory reactions [27].

2.2.4.4 Vitamin C

Vitamin C (L-ascorbic acid) is an optically-active hydrosoluble antioxidant which scavenges free radicals from a variety of sources. It bears a highly acidic hydroxyl group (pKa = 4.2) known to be completely ionized at neutral pH [28, 29]. It acts as an antioxidant and reducing agent by donating electrons to various enzymatic and nonenzymatic reactions. It reduces the transition metal ions of several biosynthetic enzymes, thus preventing biological oxidation of macromolecules. Interestingly, it also functions as an enzyme cofactor [23].

2.2.4.5 Vitamin A

Vitamin A, a lipid soluble vitamin, is localization within the lipophilic compartment of membranes and lipoproteins. It has free radicals scavenging feature and thus play important role in human health. It has been shown to be essential for many physiological processes, such as cell metabolism, reproduction, embryonic development, immunity and bone metabolism, in all vertebrates [30–32]. It is essential for vision. The retinal and retinoic acid are the dietary components of vitamin A [33].

2.2.4.6 Carotenoids

Carotenoids are important antioxidants for plants and animals which are present in fruits and vegetables. Carotenoids are known to be very efficient physical and chemical quenchers of singlet oxygen ($^1O_2$), as well as potent scavengers of other reactive oxygen species (ROS) [34–36]. This is of special significance, because the uncontrolled generation and concomitant increase of ROS level in the body results in "oxidative stress", an essential contributor to the pathogenic processes of many diseases. Carotenoids have a protective role against ROS-mediated disorders, such as cardiovascular diseases, cancer as well as photosensitive or eye-related disorders.

2.2.4.7 Lipoic acid

Lipoic acid is one of the most versatile antioxidants known. Aside from its ability to function in both aqueous and lipid media, lipoic acid is capable of neutralizing a wide variety of free radicals: singlet oxygen, superoxides, peroxyl and hydroxyl radicals, hypochlorite, and peroxynitrite [37]. These radicals are believed to play a significant role in disease processes such as hardening of the arteries (atherosclerosis), cancer, cataract formation and diabetes.

2.2.4.8 Flavonoids

Flavonoids are rich source of antioxidants, which are low-molecular-weight phenolic compounds. They are broadly present in fruits, vegetables and certain beverages. They belong to a class of plant secondary metabolites. Flavonoids are, in particular, important antioxidants that can act as reducing agents, free radical scavenger, hydrogen donors, and singlet oxygen quenchers. In addition, they have also metal chelating potential [38]. Their structures and impact on human health is discussed in details in subsequent sections.

2.2.4.9 Tannins

Tannins are naturally found in a variety of edible and inedible plants, including tree bark, leaves, spices, nuts, seeds, fruits, and legumes. They are potentially very important antioxidants. Plants produce them as a natural defense against pests. Tannins also give color and flavor to plant foods. Tannins are phenolics such as flavan-3-ols: (−)-epicatechin and (+)-catechin. Hydrolysable tannins are heterogeneous polymers compound for example phenolic acids and gallic acid (3,4,5trihydroxyl benzoic acid) [23, 39].

3. Phytochemicals: classification and dietary sources

The basic skeleton of polyphenols is made up of 15 carbon chain that arranged in two aromatic rings A and B connected by a unit of carbon–carbon bridge and it can also form ring C. They have conjugated double bonds and functional groups (hydroxyl or other substituents). Flavonoid can occur as a form in aglycones, glycosides and methylated derivatives in plants. They are present in all parts of plant such as stem, root, flower and leaf and seed. The structure of phytochemicals possesses functional groups such as hydroxyl groups (OH), aromatic compounds (CH), Carbonyl and carboxylic groups (CO) and organosulfur groups (SO). The major class of phytochemicals are polyphenols and caratenoids. Based on heterocyclic ring structure, flavonoids are divided into six chemical structures: flavones, flavonols, flavanones, catechins, or flavanols, anthocyanidins and isoflavones (**Figure 3**) [40].

The dietary sources of different phytochemicals are given in **Table 1**. Polyphenols are known for their unique property of activation at multiple levels, through the modulation of A mitogen-activated protein kinase (MAPK), protein kinase B (PKB), and NF-κB signaling pathways, inhibiting the production of inflammatory cytokines and chemokines, suppressing the activity of cyclooxygenase (COX) and Inducible nitric oxide synthase (iNOS) and thus decreasing the production of free radicals. Several phytochemicals including genistein, curcuminoids, and catechins are known to suppress the activation of Akt, thus, inhibiting cancer cell growth. Some phenols like resveratrol, curcumin, and green tea catechins have been shown to suppress COX-2 giving the benefit of decreasing the production of reactive oxygen species (ROS) [41]. The health benefits of functional foods and nutraceuticals fortified with natural polyphenols. Flavonoids exert many biological and pharmacological properties

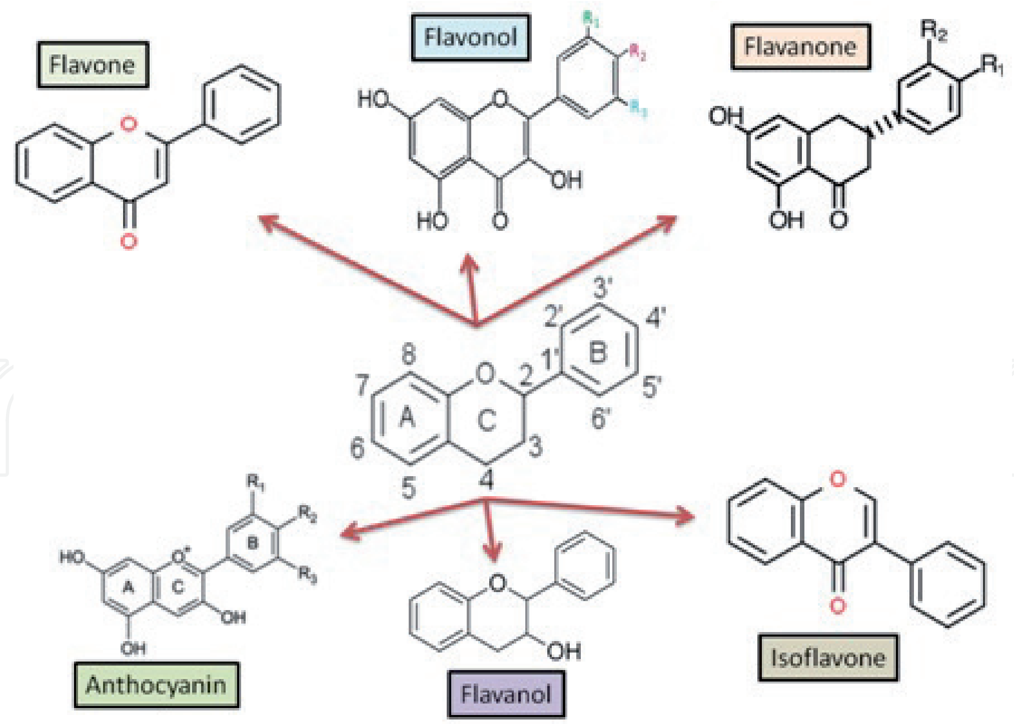


Figure 3.
Basic flavonoid structure.

Phytochemical Class	Phytochemical constituents	Major dietary food sources
Flavones	Luteolin and Apigenine	Celery, chill paper and green vegetables
Flavonols	Quercetin, kaempferol	Garlic, onion, Raw Broccoli, onion, chill paper, Parsely, Blueberries
Flavanones	HesperetinTangeretin	Carrot, Grapefruit juice, citrus fruit,
Isoflavones	Genistein, Daidzein	Soybean, tofu soymilk and black bean
Flavanols	Epicatechinecatechin and epigallocatechin	Tea, fruits and cocoa Chocolate
Anthocyanins	Cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin	Strawberries Green vegetable and fruits

Table 1.
Dietary phytochemicals and their sources.

for instance, cardioprotective inflammatory, antiviral, anti-cancer, anti-diabetic and cytoprotective etc.

4. Biological role of phytochemical antioxidants in prevention and cure of several chronic diseases

Oxidative stress is accountable for pathogenesis of several human diseases, including CVD, certain types of cancers, and aging [42, 43]. Antioxidant phytochemicals play a therapeutic role against chronic diseases caused by oxidative stress [44]. The schematic overview of the therapeutic properties of flavonoid-rich foods is given in **Figure 4**. The phytochemicals are the recent area of drug research to find the promising herbal drug for the treatment of various human diseases such as diabetes, cancer, tuberculosis, malaria and viral diseases etc.

Edible fruits and vegetable have medicinal properties with antioxidant potential. They contain various types of phytochemicals which are proven to reduce the impact of various diseases. The dietary fruits such as strawberries, citrus fruits or green vegetables, cereals are rich source of vitamins and phytochemicals [45]. The medicinal plant rich in flavonoids have been reported to have antioxidant potential [46]. α-tocopherol is good free radicals scavenging vitamins that reduced the oxidative stress in the body and prevents the aging process. Consumption of dietary plants lessens the development of life style related diseases because they are rich in polyphenols an show synergistic effect on metabolic pathway of diseases cells [47]. In addition, polyphenols may enhance the antioxidant defense system against free radical induced toxicity [48]. Many medicinal plant are known to provide defensive role against microbial and viral infections [49, 50]. Pathogens and oxidative stress can cause chronic inflammation that assist in the pathogenesis ofmany chronic diseases including CVD, cancers, neurodegenerative diseases, diabetes [51–53]. Most antioxidant phytochemicals have been scientifically investigated for their anti-inflammatory action, hepatoprotective, cardioprotective, neuro-protective and anticancer and antidiabetes and antimalerial and antiaging effects. Phytochemicals including resveratrol, anthocyanins, and curcumin etc. are known to have medicine like properties that mediate protection via inhibition of lipid peroxidation, lower the prostaglandin production and modulate the nuclear factor-κB activity, enzyme inhibition, as well as improve the immunity [54]. Usually, the phytochemicals have strong antioxidant abilities as well as anti-inflammatory action, which account for other bioactivities with health benefits [55].

Though, the phytochemicals have been reported to exert wide range of biological activities. These include:

4.1 Cardioprotective activity

Cardiovascular disease (CVD) is common health problem in modern society and is the leading cause of morbidity and mortality worldwide. Rising blood pressure

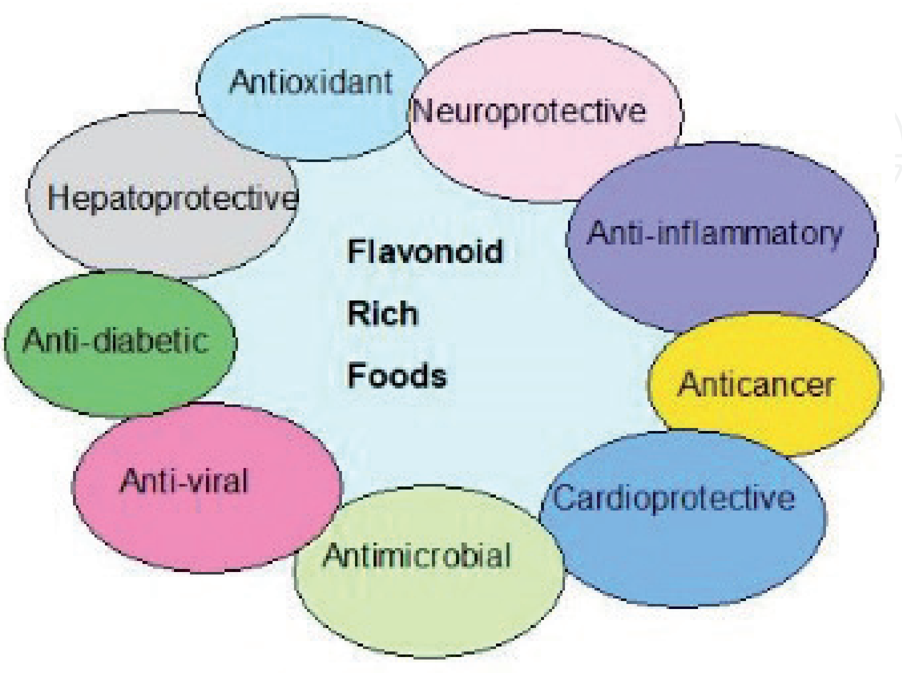
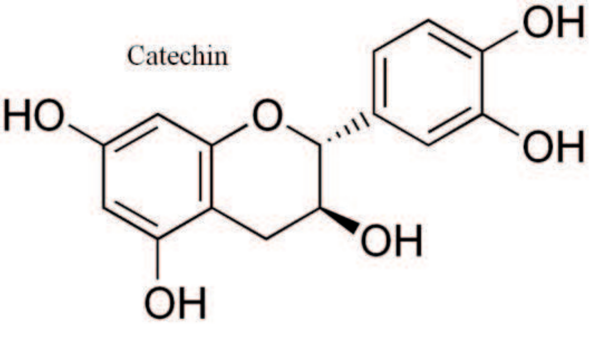


Figure 4.
The schematic overview of the therapeutic properties of flavonoids.

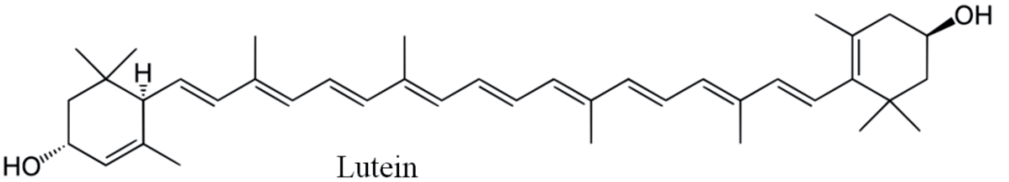
and atherosclerosis diseases are common heart problem in all age group of people. The modern medicine and treatment can reduce the symptoms of the CVD but allopathic treatment sometime produce adverse side effect on the body. The adequate intake of phytochemical rich food can reduce the impact of CVD [56]. The phytochemicals constituents such as Epicatechin, catechin, garlic, Apigenin, luteolin are known to possess cardioprotective properties. Dietary foods containing flavonoids can suppress the cholesterol and lipoproteins to protect the heart.

Catechin is a known flavonoid found in green tea, *Camellia sinensis*. Many experimental and clinical studies have recently reported that catechin has multiple cardiovascular health benefits such as prevention of atherosclerosis, hypertension, endothelial dysfunction, ischemic heart diseases, and cardiomyopathy. It protects normal heart function by decreasing oxidative stress and reducing the inflammatory events [57].

Catechin

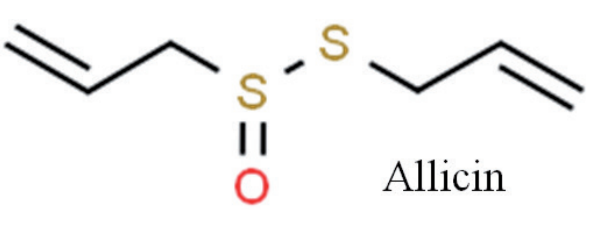


Lutein is a bioactive flavonoid possesses good efficacy as an anti-oxidative, antitumor, and anti-inflammatory properties [58]. Recent scientific studies have reported the lutein has cardiac protective effects *in vitro* and *in vivo*. Epicatechin and procyanidins have been reported to have good cardioprotective health benefits [59].



Lutein

Allicin is one of the key ingredients of *Allium sativum* (Garlic) said to be good regulator of blood pressure and hypertension. It is an organosulfure phytochemical and possesses many medicinal properties such as anticancer, antidiabetic, hepatoprotective and cardioprotective. Many research reports suggested that allicin has shown positive effects on the heart and it can lower high cholesterol levels against atherosclerosis. People use raw garlic to get some relief from blood pressure [60].

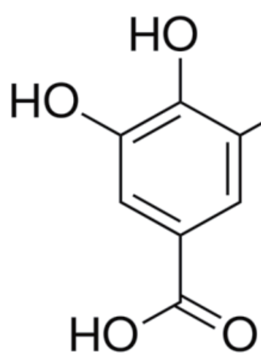


Allicin

4.2 Hepatoprotective activity

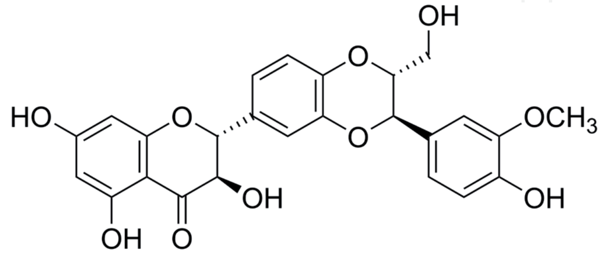
Nowadays, hepatic diseases are common concern in modern societies due to the unhealthy eating habits and over consumption of synthetic medicines, pathogen infection and environmental pollutants. Jaundice and cirrhosis are the most common liver diseases. There are many edible plant and fruits which keep liver healthy against drug induced liver toxicity. The plants contain many hepatoprotective phytochemicals such as resveratrol; saponin, Gallic acid, emodin, and tannin provide protection to liver against free radical induced damage.

Gallic acid well known flavonoid is found in fruits like pomegranates, gooseberry and strawberries and other plant foods, is one of the well-studied phytochemical. It shows antioxidant, anti-inflammatory, hepatoprotective, antimutagenic, and anticancer properties. It has been investigated for its hepatoprotective activity against ethanol, Carbon tetrachloride (CCL_4) and paracetamol-induced hepatotoxicity [61]. Both have shown protection of liver against drug induced hepatotoxicity. Consumption of dietary fruits contain ellagicangallic can cure the liver problems. These flavonoids have restored the normal level of hepatic markers i.e. bilirubin, aminotransferases, lipid peroxides, and improve the antioxidant defense system.



Gallic acid

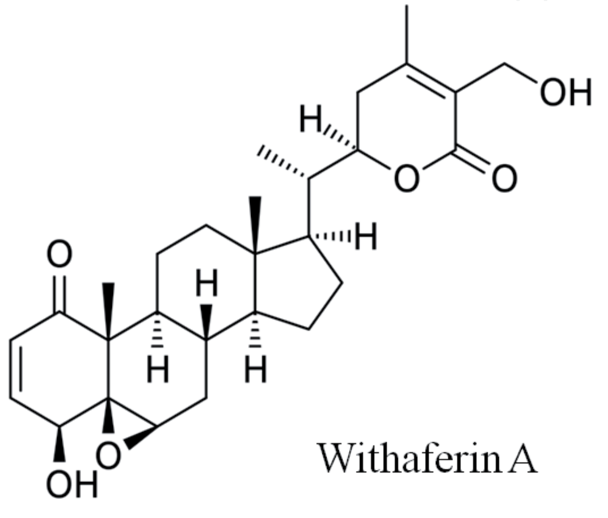
Silymarin is a well-known Hepatoprotective plant having many flavono-lignan. Experimental studies reported that silymarin has improved the level of hepatic enzymes and reversed the normal cellular structure of liver against drug induced hepatotoxicity. It is used for treatment of alcoholic fatty liver, jaundice, viral hepatitis and drug-induced liver diseases. Many researchers across the world reported Hepatoprotective activity of silymarin against the carbon tetrachloride, alcohol, paracetamol, galactosamine and thioacetamide toxicity [62, 63]. Several scientific evidences and clinical studies suggested that Silibinin, is a main bioactive flavonoid which has antioxidant, hepatoprotective and anti-inflammatory properties [64].



Silibinin

4.3 Neuroprotective activity

Alzheimer's disease (AD) is a chronic brain disorder generally seen in the elderly people. Oxidative stress and neuroinflammation can account for neurodegenerative diseases like Alzheimer's and Dementia (memory loss). A dietary food such as walnut is a rich source of many antioxidants (vitamin E and folate), minerals (selenium) and phytochemicals including flavonoids, phenolic acid (ellagic acid), and proanthocyanidins etc. Experimental evidence suggested that walnuts have anti-inflammatory effect which may show the synergistic effect to reduce the risk of neurogenerative disorders and enhance the activeness of neurotransmitter in brain cells. Withaferin A is the main active ingredient of Ayurvedic medicinal plant *Withania somnifera*. It is an oldest medicine used to treat various neurodegenrative diseases [65, 66]. The root extracts of *W. somnifera* has been reported to possess free radical scavenging properties [67] and is associated to induce the Neurons & Glial Cells [68, 69]. The root extract of *W. somnifera* is reported to induce outgrowth in SK-N-SH cells [70].



Withaferin A

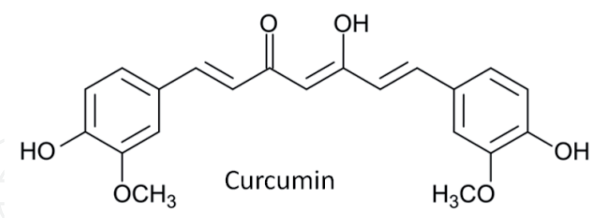
Bacopamonnieri is known as Brahmi an herbal nutraceutical herb which is popular for brain tonic or nootropic agent which is described for use of memory improvement, epilepsy, insomnia, and anxiolytic in Ayurveda. It is rich source of various phytochemicals such as bacoside A, bacoside B, bacopasaponins, D-mannitol, apigenin, luteonin, brahmine, herpestine, hydrocotyline. In addition, sapogeninjujubacogenin, pseudojuju, bacogenin are the major ingredient of B. moneieri. Latest research reports indicated that *B. monnieri* has neuroprotective effect against brain inflammation and Alzheimer's disease [71].

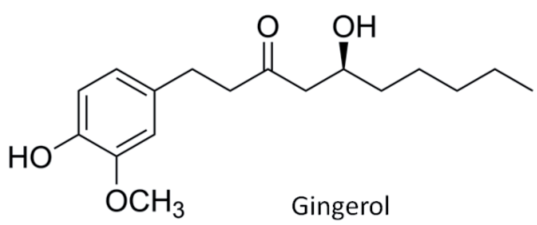
4.4 Anti-inflammatory activity

Inflammation is a normal phenomenon of the body upon pathogen infection. The inflammation is characterized by physical appearance like swelling, redness, heat, pain, and loss of function. It is the series of transformation of infection site as a result of immunological response [72]. Flavonoids intake can inhibit the cyclooxygenase pathway involved in the inflammatory process.

Curcuma longa (turmeric) is popular spice used in making home food. It is the oldest traditional medicine for the treatment of various health problem, joint pain, inflammatory conditions and cancer and diabetes and liver ailments. Its consumption provides healing effect to cure infection and inflammation in the body. The curcumin is main active component of *Curcuma longa* which has various medicinal properties such as hepatoprotecctive, anticancer and antidiabetic and anti-inflammatory. It is the efficient antioxidant that reduces the level of oxidative stress caused by toxic elements [73].

Ginger is a popular edible root of *Zingiberofficinale* plant. It is widely used for treatment of cough and cold due to its anti-inflammatory property. Gingerols is the main bioactive compounds of ginger. It has reduced the level of inflammation markers cytokines and tumor necrosis factors.





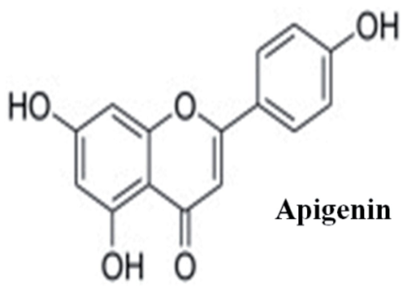
4.5 Anticancer activity

Cancer, a disease is characterized by uncontrolled cell division [74, 75]. Many flavonoids have shown to possess the anticancer properties. There are many dietary flavonoids such as apigenin, karmpferol, quercetin and resveratrol showed the anti-cancer effect against various cancers such as breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach by modulating the signal pathway of apoptosis. The experimental results showed the protective efficacy of flavonoids on cancer cells by modulating the pathway of cell cycles. The molecular mechanism of flavonoid is due their antiproliferation activity, cell cycle arrest, inhibition of P53 protein and down regulation of tyrosin kinases. Flavonoids are evidenced to be effective chemopreventive agents.

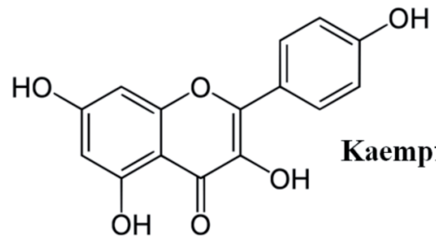
Apigenin is plant derived flavonoid belonging to the flavone structural class. It is found in several edible vegetables and fruits. It has been reported as anticancer molecule *in vitro* and *invivo* experiments. It showed promising antioxidative and antiproliferation effect against cancer disease [76, 77].

Kaempferol is very effective herbal medicine and present in grapes and onion. It has antioxidant and anticarcinogenic activity. It acts as a chemopreventive agent against metastasis and angiogenesis. *In vitro* studies reported that Kaempferol was found to have good cytotoxic effect on cancer cells. It is reported to reduce proliferation of cancer cells by arrest cell cycle events of various cell lines such as glioblastoma leukemia, lung cancer, and breast adenocarcinoma [78].

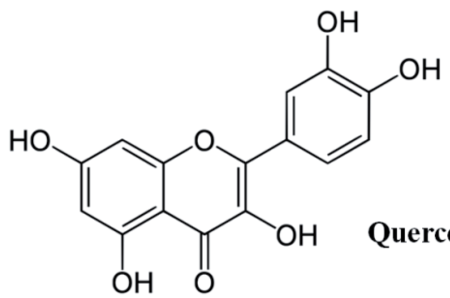
Quercetin is one of the dietary flavonoids, which suppresses tumor growth by inhibiting protein tyrosine kinase (PTK). Fruits and vegetables are having an enormous amount of quercetin, which have been used as cancer chemopreventive agents. The mechanism of action of flavonoids is dues their interphase arrest, heat-shock protein inhibition, tyrosine kinase inhibition, down regulation of p53 protein, inhibition of Ras protein, and expression of Ras protein [79].



Apigenin



Kaempferol



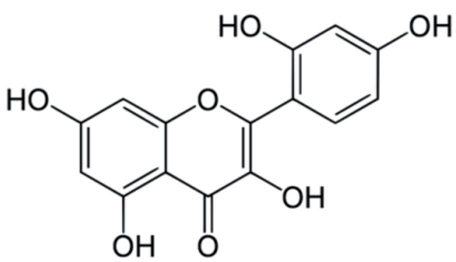
Quercetin

4.6 Antidiabetic activity

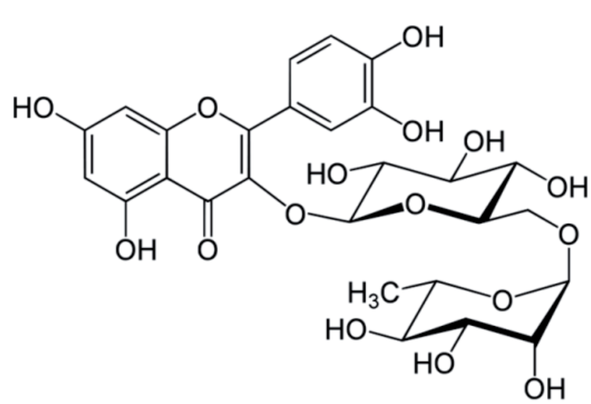
Diabetes is one of the emerging health disease caused by metabolic abnormalities of carbohydrate. The presence of higher blood sugar level in blood and urine is the main the sign of the diabetes. There are many dietary flavonoids such as bitter guard, f*enugreek* leaves and *seeds and* Curry Leaves or KadiPatta that exert anti-diabetic effects by targeting various cellular signaling pathways in pancreas, liver, skeletal muscle, and white adipose tissue sources, that can reduce the higher blood sugar level in diabetic patient. These dietary foods are rich source of phytochemicals that can reverse the abnormal sugar level into normal level.

Morin, a natural flavonoid, is found in the edible plant *Moringaoleifera*. Its oral consumption for 30 days significantly improved the blood sugar level, glucose intolerance, and promotes the pancreas to release sufficient insulin in the body. It also inhibits the insulin resistance [80].

Rutin is a glycosylated flavonoid found in the citrus fruits. The anti-diabetic effects of rutin have been experimentally evaluated and suggested the rutin has good antidiabetic efficacy. It enhances the glucose uptake by the suppression of tissue gluconeogenesis resulting in lowering glucose level in blood. It can activate insulin secretion from β-cells. It also decreases the free radical formation produced due to higher glucose level [81].



Morin



Rutin

4.7 Antiviral activity

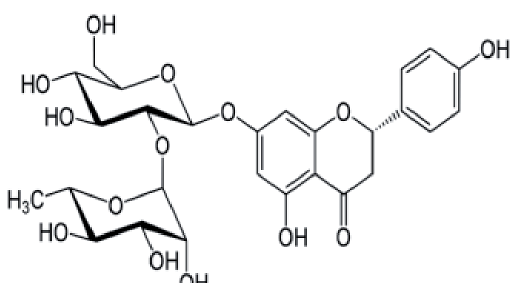
G. glabra or **Licorice** is a traditional remedy for the treatment of liver diseases like jaundice. **Glycyrrhizin** is an active biocompound in the licorice root, that has antioxidant, anti-inflammatory and hepatoprotective and antiviral activity. It also prevents oxidative damage produced by oxidative stress. Scientific studies reported that Glycyrrhizin can inhibit the growth of hepatitis A and hepatitis C virus and effectively control the viral replication [82].

Naringin is a citrus dietary favonoid found in tomatoes, grapefruit and orange and known to have positive biological effect on human health as antioxidant, anti-inflammatory, and antiviral. It was found that **Naringin** can reduce the viral growth in the cell culture. It also investigated to have antiviral effect against HSV-1 and HSV-2 [83].

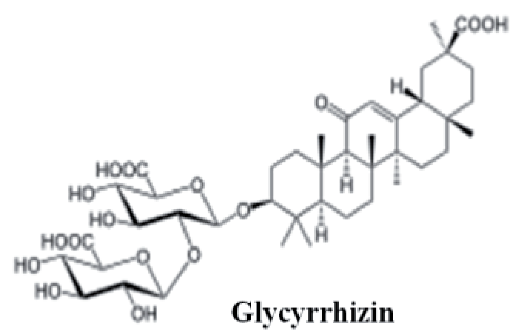
Quercetin, a naturally occurring dietary flavonoid, is well known to ameliorate chronic diseases and aging processes in humans, and its antiviral properties have been investigated in numerous studies. In silico and in vitro studies demonstrated that quercetin can interfere with various growth stages of the coronavirus replication cycle [84].

Epigallocatechin-3-gallate (EGCG), is a principal tea derived catechin which know have many pharmacological properties like cardioprotective, haptoprotective and antiviral. Many research studied confirmed that EGCG has antiviral protective effect against influenza virus [85–87]. It has experimentally shown the protection against DNA and RNA viruses [88].

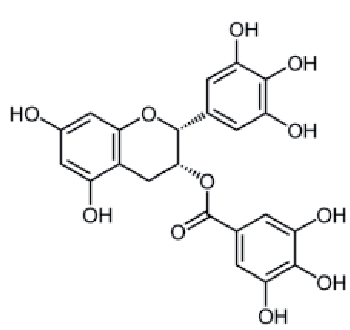
Silymarin has also shown the promising antiviral effect against hepatitis C and B virus [89].



Naringin



Glycyrrhizin



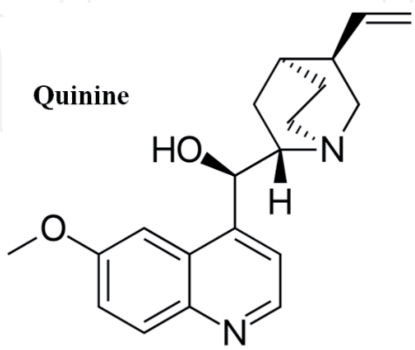
Epigallocatechin-3-gallate

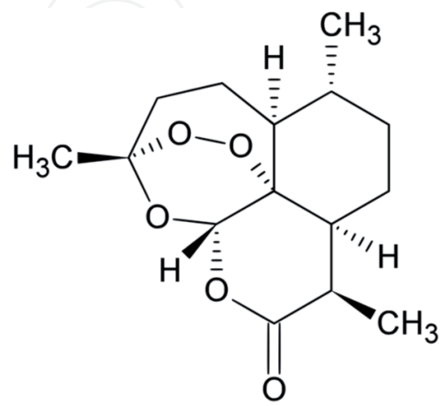
4.8 Antiparasitic activity

Parasites are organism that live in the another organism called host. They use other organism to survive and get food from them. The common parasite that live on or in human body are scabies (skin mites), threadworm (stomach), and hookworm (gut worms). Parasites are microscopic organisms such asprotozoa, helminths, and ectoparasites that cause diseases such as malaria and leishmaniasisin human [90, 91].

Many plant derived phytochemicals have been tested for their antiparasite activity. Quinine is an alkaloid isolated from the Cinchona species is well known effective herbal medicine for its antimalarial properties. It is used to treat malaria disease. Another popular alkaloid, **artemisinin** is a quite useful for the treatment of maleria diseases. Artemisinin is an active component of *Artemisia annua has* been investigated for it antimalarial activity [92].

Quinine





Artemisinin

4.9 Antiaging activity

Aging is a well-established risk factor for a wide range of diseases such as neurodegenerative diseases, and presently, there is no effective treatment for age-related neurodegenerative diseases [93].

Grapes and citrus fruits have a high content of polyphenols which showed free radical scavenging activity [94]. Curcumin and vitamin E are promising antiaging compounds that may delay the symptoms of aging. Vitamin E is lipid soluble antioxidants that scavenges the peroxide radical and stop the chain reaction of free radicals which are involved in aging process [95]. Being a efficient antioxidant and anti-inflammatory molecules, curcumin is modulated cellular senescence involved in aging [96, 97].

4.10 Renoprotective activity

Chronic kidney disorders are common world health problem including India. People with chronic diabetes are at risk of diabetonephropathy. Nephrotoxicity can occur by chemotherapy treatment with cisplatin medicine which causes the oxidative stress and inflammation in kidney [98].

Medicinal plants are used traditionally in ethnomedicine for the treatment of kidney disease. *Bryophyllumpinnatum*, is commonly known as Pattharcaṭṭa, is popular medicine for kidney stone and urinary insufficiency. Some plant derived flavonoids are used in combination as a herbal formulation to cure the kidney diseases [99]. Some antioxidants like kaemferol [100], catechin [101], and quercitrin [102] have been reported to have renoprotective effect.

5. How do phytochemicals work?

Medicinal plants are natural source of phytochemical antioxidants that are known to prevent different diseased states. The medicinal plants contain phytochemical ingredients as source of antioxidants. Phytochemicals are antioxidants compounds that inhibit or delay onset of biological oxidation. They are nitrogenous cyclinphytols compounds which possess functional groups such as hydroxyl groups, ketone groups and aldehyde. Phytochemicals work at different level to provide protection and boost the body defense mechanism against oxidative stress.

5.1 Antioxidant

Antioxidants are such anti molecules which work against oxidation reaction. It means they prevent oxidation of biomolecules caused by free radicals. Many phytochemicals work as antioxidant helping to scavenge free radicals. They donate electron to stabilize the free radicals in order to maintain the imbalance between antioxidant defense system and free radicals. The phytochemicals are subtle molecules or compounds that work like as an antioxidant.

5.2 Hormonal action

Some phytochemical can influence the hormonal activity in the body. Genistein a soy isoflavones, it works like estrogen hormone which inhibit the menopausal hot flushes in some women [103].

5.3 Biological action

Different phytochemicals play different role in the biological system. There are many different groups of phytochemicals which all have different chemical structures which may induce different health benefits. Caroteniods may inhibit the cancer cell growth and reduce the risk of cardiovascular disease and boost immunity. Dietary anthocyanins may help lower the high blood pressure. Phytochemicals as an antioxidant scavenge the free radicals and reduce the oxidative damage.

6. Summary

Oxidative stress has been linked to the various chronic diseases including cardiovascular diseases (CVD), cancer, neurological disorders, hepatic diseases, diabetes and aging. Free radicals (reactive oxygen species and reactive nitrogen species) are accountable for the pathogenesis of such diseases. Free radicals that naturally produced by the normal process of metabolism are generally neutralized by antioxidant enzymes (SOD, catalase and GPx) and non-antioxidants molecules *i.e*. GSH, uric acid and phytochemicals. Sedentary life style factors may accelerate the free radical formation that create imbalance between the antioxidant defense system and oxidative stress which leads to inflammation, necrosis and eventually cell death. Vitamins A, E and C are the primary major antioxidant vitamins which play a significant role in physiological functions of the body. Scientific reports suggested that medicinal plants contain thousands of phytochemicals (alkaloids, flavonoid, carotenoids and tannins, isoflavones and glycosides etc.) that possess antioxidant properties as well as biological activities. Dietary fruits and vegetables provide such vital molecules to our body. Many research studies reported that adequate intake of vegetables and fruits may prevent or reduce the symptoms of chronic diseases caused by oxidative stress or pathogens. Antioxidant phytochemicals are considered to be responsible for these health benefits. They often possess efficient antioxidant properties that neutralize the free radicals as well as anti-inflammatory action. Phytochemicals possess drug like effect and they are considered as therapeutic medicine which are the basis of other bioactivities and health benefits. Flavonoids, alkaloid, carotenoids and anthocyanins are the major groups of phytochemicals that possess many pharmacological properties such as anticancer, anti-aging, anti-diabetic, hepatoprotective, anti-microbial, antiviral and neuroprotective. Due to variety of pharmacological properties, phytochemicals are considered as neutraceuticals. Medicinal plants are rich sources of antioxidants that are known to prevent different diseased states. Phytochemicals are nitrogenous cyclinphytols compound that are rich mostly in functional groups such as hydroxyl groups (OH), aromatic compounds (CH), Carbonyl and carboxylic groups (CO) and organosulfur groups (SO). Their functional group can donate electron to stabilize the free radicals in order to maintain the imbalance between antioxidant defense system and oxidative stress.

There are many different subclasses of phytochemicals which all have different chemical structures responsible for different positive health effects. Scientific communities across the world focusing on the alternative medicinal system in exploring the natural ingredients to be used in the food and food products for the prevention of human diseases. Herbal based medicine can be more safe, convenient and efficient as dietary components for the prevention or treatment of human diseases.

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Conflicts of interest

The authors declare no conflict of interest.

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