Chemistry Research Journal, 2017, 2(4):59-72

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Flavonoids: The Bioactive Phytochemical Agent–A Review

Hamidu Usman*[1], Fanna I. Abdulrahman[1], Haruna A. Kaita[2], Irfan Z. Khan[1], Muhammad A. Tijjani[1]

[1]Department of Chemistry, Faculty of Science, University of Maiduguri, P.M.B. 1069, Maiduguri, Nigeria.
[2]Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria.

Abstract Plant, being the major source of medicine is fundamental to the well being of mankind. Today, approximately 80% of world's population relies on plants-based medicines as their primary source of medications. Therefore, it is evident that "*there is a plant for every disease condition on every continent"*. Being a bioactive natural products, phytochemicals [*fight-o-chemicals*] fight to protect ones health through numerous mechanisms including the antioxidants properties. Phenolic is one of the major and important groups of phytochemicals known amongst the alkaloids, carotenoids, nitrogen containing compounds and organo-sulphur compounds. Flavonoids chemically called benzo-γ-pyrone are ubiquitous in the plant kingdom (gymnosperms and angiosperms) and their use in the treatment of many infectious diseases such as cardiotonic, CNS, lipid lowering and hepatoprotective effects; others are anti-ulcer, anti-microbial, anti-inflammatory, anti-cancer, anti-oxidant have been related to their polyphenolic nature. The damaging effects of free radicals have been attributed to many ailments including the neurodegenerative diseases, cancer, aging, atherosclerosis, inflammation among others. The exposure route to free radicals had been through: *tobacco smoke, alcohol, radiation, excess sunlight, strenuous exercise and high fat or spicy fried foods.* The mechanism of action of most flavonoids as potent anti-oxidants had been counteracting the damaging effects of reactive oxygen species in tissues/cells through its scavenging properties, through metal chelation or generating balanced redox reactions. Therefore, it is timely to kick-off the trapped reactive oxygen species by eating natural fruits and vegetables - *Natural Phytotherapy.*

Keywords flavonoids, review, bioactive, phytochemicals, phytotherapy

Introduction

Plant, being the major source of medicine is fundamental to the well being of mankind. Not only is man absolutely dependent on plants for medicine but it also provide food, fodder, fuel, gum, clothing, paper, timber and many other constructive and useful materials. Throughout history trees have been featured in religion and folklore and have been reported to be an integral part of African ethics. More so, plants have come to bear an affectionate kinship with man, not shared by many other things [1].

Plants have formed the basis for traditional medicinal systems for thousands of years; with the first records dating from about 2600 BC is the Mesopotamia. They had used oils from Cedar and Cypress, Liquorices, Myrrh and Poppy juice amongst other things - substances that are still in use today for the treatment of a variety of illnesses and infections. Ancient Egyptians, Chinese and Indian documents show that the medicine in these societies included numerous plants based remedies and preventives. The Greeks and Arabs contributed substantially to the assimilation, codification and development of plants based remedies. Today, approximately 80% of world's population relies on traditional plants based medicines for primary source of medication [2, 3, 1]. It is then evident that "*There is a plant for every disease condition on every continent"* [3].

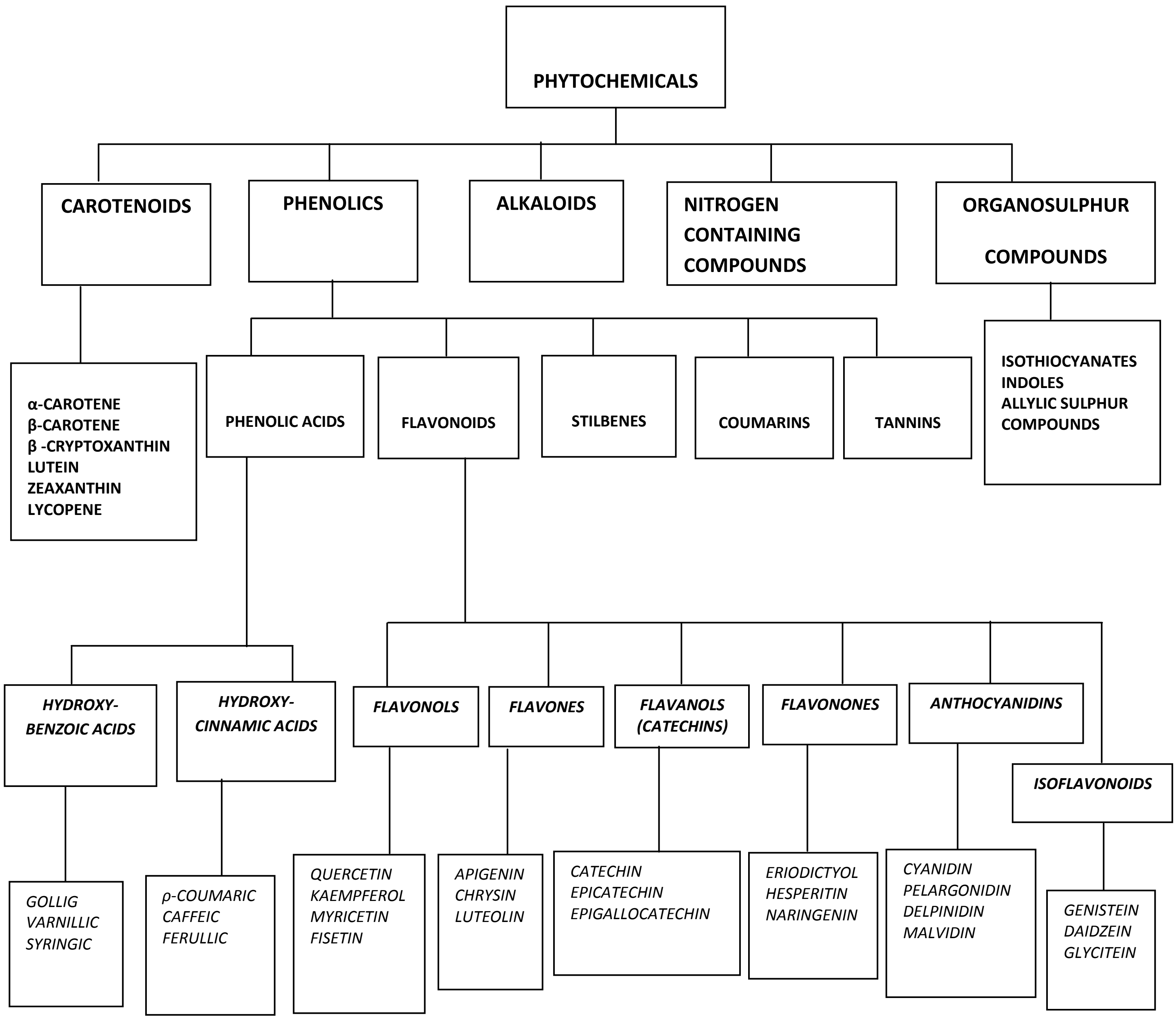


Figure 1: Classification of Phytochemicals [9].

The remaining 20% of the world's population also depends on plant products for health care. About 25% of prescription drugs dispensed in USA contain plant extracts or active ingredients derived from plants. Out of a total of 520 new drugs approved for commercial use between 1983 to1994, 30 were new natural products and 127 were chemically modified natural products [1]. Plants vary within and among species in the types and concentrations of phytochemicals due to variables in plant growth, soil, weather conditions and the age of the plant. Phenolic phytochemicals are the largest category of phytochemicals and the most widely distributed in the plant kingdom; flavonoids, appeared to be the largest group of plant phenols and most studied. The functions of polyphenols in plants include antioxidants (protection from UV light), protection from insects, fungi, viruses and bacteria, visual attention- pollinator attraction, feed repellent and plant hormone controllers. Due to their activity as antioxidants, flavonoids found in botanical dietary supplements may play a role in the prevention of heart disease and cancer [4].

This review deals with the structural properties as well as therapeutic importance including some cellular and metabolic efficacies of flavonoids groups of compounds against many human and animal diseases.

Phytochemicals

Bioactive substances are present in plants for a reason; many influence the colour and flavour of plant foods, or the structure and function, and others such as glucosinolates are part of the plant's defense system. In particular, phytochemicals may be consumed via leaves, stems, roots, tubers, buds, fruits, seeds and flowers, and plant derived foods and drinks {such as tea, coffee, alcoholic beverages}[5].

A phytochemical is a natural bioactive compound found in plant foods that works with nutrients and dietary fibre for protection against disease. Research suggests that phytochemicals, working together with nutrients found in fruits, vegetables and nuts, may help slow the aging process and reduce the risk of many diseases, including cancer, heart disease, stroke, high blood pressure, cataracts, osteoporosis and urinary tract infections. Phytochemicals pronounced *"fight-o-chemicals"*, fight to protect ones health. They can have complementary and overlapping mechanisms of action in the body, including antioxidant effects, modulation of detoxification enzymes, stimulation of the immune system, modulation of hormone metabolism, antibacterial and antiviral effects. "*Phyto*" is Greek word which stands for plant and phytochemicals are usually related to plant pigments. So, fruits and vegetables that are bright coloured – yellow, orange, red, green, blue, and purple – generally contained the most phytochemicals and nutrients.

More than 900 different phytochemicals have been found in plant foods and more will be discovered [6]. It is estimated that more than 5000 individual phytochemicals have been identified in fruits, vegetables, and grains, but a large percentage still remain unknown and need to be identified before the health benefits of phytochemicals can be fully understood in whole foods [7]. However, more and more convincing evidence suggests that the benefits of phytochemicals in fruits and vegetables may be even greater than is currently understood, because the oxidative stress induced by free radicals is involved in the etiology of a wide range of chronic diseases [8].

Phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds as shown in figure 1 below. The most studied of the phytochemicals are the phenolics and carotenoids [9]**.**

Categories of Phytochemicals of Biological Importance

Phyto-oestrogens

These are naturally occurring plant compounds that structurally resemble mammalian oestrogen. They copy or counteract the effect of oestrogen in the body. Consumption of Isoflavone (a phyto-oestrogen), is associated with cancer prevention, improved cardiovascular health and improved bone health. Isoflavones contained in soy are believed to be helpful in the treatment of menopausal symptoms while isoflavones isolated from the roots of the *Kudzu* plant may be used to treat alcoholism by lowering a person's tolerance for alcohol and thus reduce the pleasure response to drinking [9].

Phytosterols

Phytosterols are plant sterols that occur in most plant species but appear to be most abundant in the seeds of green and yellow vegetables. They are important in the human diet because they help to reduce the amount of dietary cholesterol absorbed by the body by blocking uptake in the intestine. They also facilitate cholesterol excretion from the body. This is especially important as cholesterol is a well established risk factor for heart disease [9].

Carotenoids

These are plant pigments found in bright yellow, orange and red fruits and vegetables. They are responsible for the pink colour of flamingoes and shellfish and the colour of egg yolk. There are more than 600 carotenoidal compounds known [9].

Naturally occurring carotenoids are divided into two distinct types: carotenes and xanthophylls. Carotenoids are generally well known as vitamin A precursors, meaning that once ingested, the body converts the compounds into vitamin A. However, less than 10% of carotenoids function in this way. In the carotene group only alpha, beta and epsilon carotene function as vitamin A precursors. Beta carotene is the most active of the three. Xanthophylls protect vitamin A, other carotenoids and vitamin E from oxidation. The vitamin A precursors as well as other carotenoids such as gamma carotene, lycopene and lutein have been shown to be protective against lung, breast, uterine, colorectal and prostate cancer. Zeaxanthin and lutein may help to prevent loss of sight in persons over fifty years. Since xanthophyll protects the skin from sunlight; it was once popular as a tanning product. Another xanthophylls called cryptoxanthin is thought to have a protective effect on the female reproductive tissues, namely vaginal, uterine and cervical tissues [9].

Food Sources of Phytochemicals

Phytochemicals are found in all plant products. It is advised that we consume a wide variety of fruits and vegetables in order to gain maximum benefit from the nutrients and phytochemicals they contain. Preferably, intake of phytochemicals should be from dietary sources rather than from supplements or pills. These can only provide a few of the thousands of phytochemicals available to us and are thus less effective than a serving of fruits and vegetables. Additionally, phytochemicals work in synergy, that is, they work together and the effect together is stronger than the sum of the parts. Some good food sources of phytochemicals across the world include: broccoli, cauliflower, cabbage, brussel sprouts, pakchoi, lettuce, other cruciferous vegetables, spinach, tomatoes & tomato products, bell/sweet peppers, carrots; watermelon, citrus fruits (including pink grapefruit), mangoes, pawpaw, grapes, apples, cantaloupe, red grape juice, pears; soybeans; oats, barley, brown rice, sweet potatoes, whole wheat, corn; ginger, mint, rosemary, thyme, garlic, oregano, sage basil, tumeri, celery, cilantro, onions, parsley; red wine, green tea. Among the foods widely eaten the amount of phytochemicals present and consumed as food are not known to be harmful. Harmful forms are generally found in plants already identified as not being safe for human consumption and are not usually eaten. Remember, use foods rather than supplements as your source of nutrients since these chemicals may be harmful in high dosages present in supplemental form [10].

Intake of phytochemicals

To increase consumption of the phytochemicals from fruits and vegetables:

- ✓ Keep fruits and vegetables available and in sight so that you can remember to use them.
- ✓ Drink fruit juice, instead of soft drinks and other fruit-based beverages.
- ✓ Add chopped fruit to cereal, porridge, milkshakes, pancakes, muffins, cakes.
- ✓ Use fruits and vegetables as snacks for example carrots, raw pumpkin, sweet peppers.
- ✓ Use dried fruits such as raisins and prunes as tasty sweet treats instead of candy.
- ✓ In place of salt, use fresh herbs such as chive, thyme and garlic to season food.

The Flavonoids

Flavonoids pronounced *(Fláyvə nòyd)* comprise a large group of secondary plant metabolites that occur throughout the entire plant kingdom (gymnosperm and angiosperm). Presently more than 5000 individual flavonoids compounds are known many of which occur in fruits, vegetables and beverages (tea, coffee, beer, wine and fruit drinks), which are based on very few core structures. Their multitude derives mainly from the various hydroxylation patterns (up to six hydroxyl groups) and ether substitution by simple methylation or diverse mono-and disaccharides [11]. Their function in plants themselves most likely involves screening of UV light, *in situ* radical scavenging, antifeeding effects (astringency). The distinct occurrence of flavonoids makes them good candidates for taxonomic studies. Flavonoids constitute one of the most characteristic classes of compounds in higher plants. Many flavonoids are easily recognized as flower pigments in most angiosperm families (flowering plants). However, their occurrence is not restricted to flowers but include all parts of the plant. Availability through microorganisms had been reported through a number of recent research articles which demonstrated the efficient production of flavonoids molecules from genetically-engineered microorganisms [12, 13].

Flavonoids occur widely in fruits and vegetables and their principal function appears to protect these plants from disease and the damage which may be caused to them by extremes of light or heat. It has long been suspected, however, that the well established health protecting and curative properties of the many plants commonly used in folk remedies for humans may also be due to flavonoids. And there is now abundant evidence to support the idea that certain flavonoids, particularly those of the polyphenol type, possess potent anti-inflammatory and anti-oxidant properties [14].

The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health-they have been reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory, anti-tumour and antioxidant activities. The flavonoids are pigments responsible for the autumnal burst and hues and the many shades of yellow, orange and red flowers [15]. The flavones and their close relations are often yellow in colour and the extent of colour intensity increases with the number of hydroxyl group. Flavonoids are most frequently found in nature as conjugates in glycosylated or esterified forms but can occur as aglycones, especially as a result of the effects of food processing. Many different glycosides can be found in nature; >80 different sugars have been discovered bound to flavonoids. Anthocyanidins give the red and blue colours in some fruits and vegetables. Their glycosides are generally soluble in water and alcohol, but insoluble in organic solvents. The genins are only soluble in water but insoluble in ether [16] and compose of the largest group of naturally occurring polyphenols present in fruits, vegetables, grains, bark, root, stem, flowers appearing either in free state, as glycosides, methylated derivatives or both; with their glycosides mostly as O-glycosides; though, few occur as C-glycosides [17].

Chemistry of flavonoids

Flavonoids are polyphenolic compounds that are ubiquitous in nature and are categorized, according to their chemical structure, into flavonols, flavones, flavanones, isoflavones, neoflavones, isoflavonoids, catechins, anthocyanidins, aurones and chalcones.

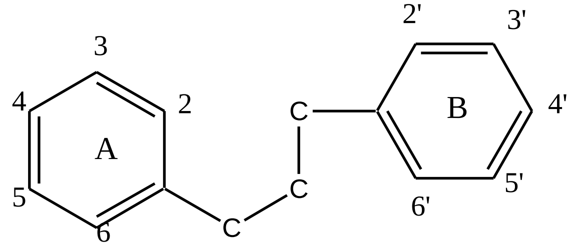
According to the IUPAC nomenclature, flavonoids can be chemically classified into:

- *flavonoids*, derived from 2-phenylchromen-4-one (2-phenyl-1,4-benzopyrone) structure
- *isoflavonoids*, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure
- *neoflavonoids*, derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone) structure [18].

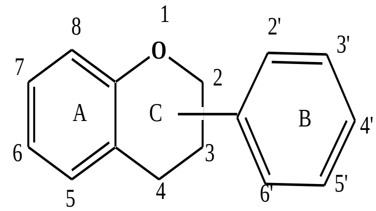
Flavonoids are often hydroxylated in position 3, 5 and 7; and frequently at positions 3′, 4′ and 5′. Positions 5, 7, and 4′ are generally methylated. When flavonoids occur as glycosides, the glycosidic linkages are normally located in position 3 or 7 and the sugars can be L-Rhamnose, D- Glucose, Gluco-Rhamnose, Galactose or Arabinose [19, 20].

Structure and classification of flavonoids

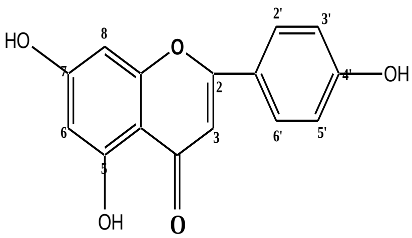
The flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a linear three carbon chain and refer to as the C_6 - C_3 - C_6 skeleton system as shown below:

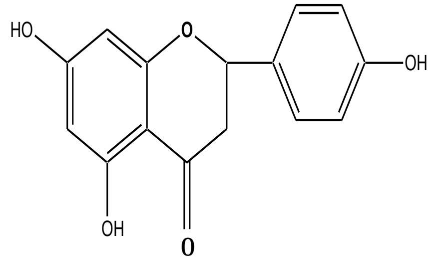


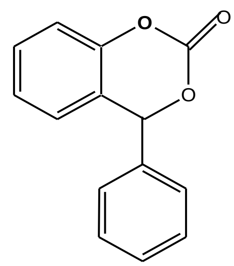
The chemical structure of flavonoids are based on a C_{15} skeleton with a CHROMANE ring bearing a second aromatic ring B in position 2, 3 or 4.



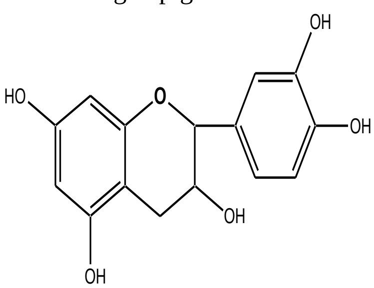
Benzo-γ-pyrone

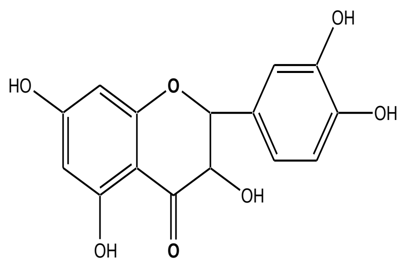


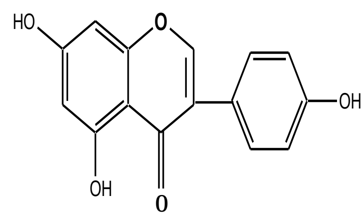




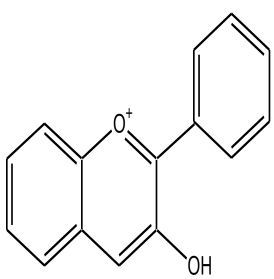
Flavone e.g. Apigenin Flavanone e.g. Naringenin Neoflavone e.g. 4-phenylcoumarone

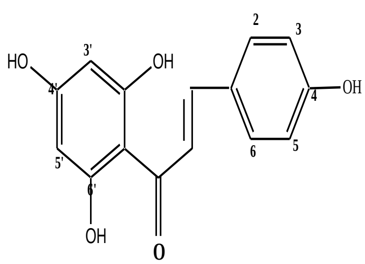


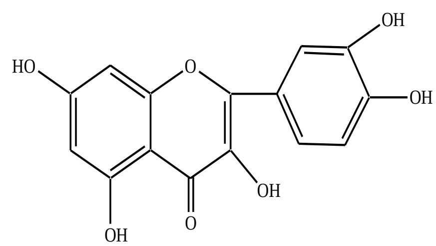




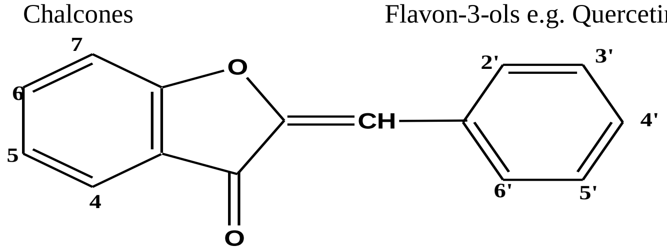
Flavan-3-ols e.g. Catechin Dihydroflavonoid e.g. Taxifolin Isoflavones e.g. Genistein



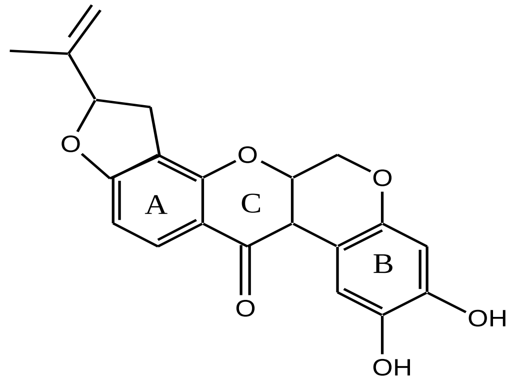




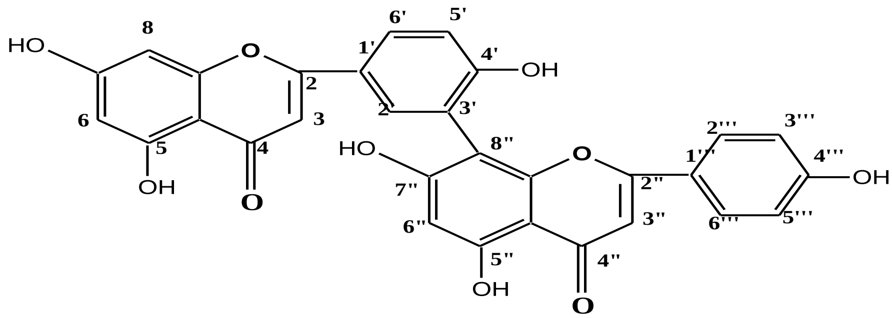
Anthocyanidin Chalcones Flavon-3-ols e.g. Quercetin



Aurone (2-benzyl coumarone) e.g. Aureusidin



Isoflavonoids e.g. Rotenone

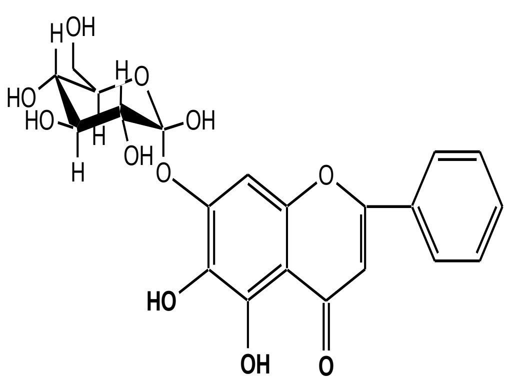


Bisflavonoid e.g. Amentoflavone-(3'–8"- bisapigenin)

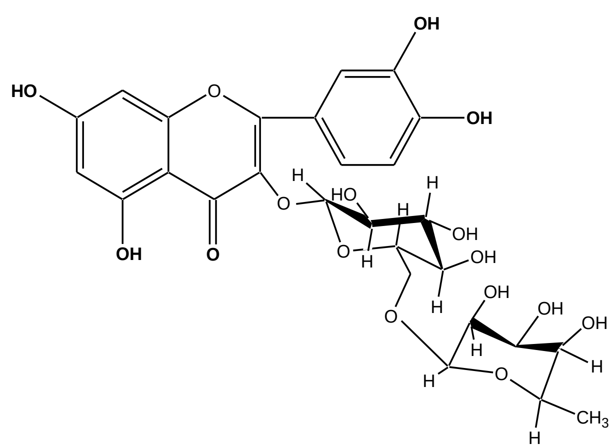
Figure 2: Structures of some flavonoids [19]

The Isoflavonoids and the Neoflavonoids can be regarded as *abnormal flavonoids*. In few cases, the six-membered heterocyclic ring C occurs in an isomeric open form or is replaced by a five - membered ring. In the aurones (2-benzyl-coumarone), the oxygen bridge involving the central carbon atom (C_2) of the 3C - chain occurs in a rather limited number of cases, where the resulting heterocyclic is of the *furan* type. Various subgroups of flavonoids are classified according to the substitution patterns of ring C. Both the oxidation state of the heterocyclic ring and the position of ring B are important in the classification.

Flavonoids may also exist as glycosides; typical examples are the baicalin (I) a flavone glycoside and rutin (II)- flavonols glycoside.



(I)



(II)

Figure 3: Structures of some flavonoids glycosides [19].

Functions of Flavonoids

***Hesperidin* -** Raises blood levels of the "good" cholesterol and lowers the “bad” cholesterol. It also prevents inflammation and is a pain reliever.

***Quercetin* -** Reduces inflammation associated with allergies; can inhibit the growth of head and neck cancers; can stop reverse transcriptase, the enzyme that HIV uses to replicate itself and quercetin protects the lungs from the harmful effects of pollutants and cigarette smoke.

***Tangeretin* -** Induces programmed cell death in cancer cells (leukemia) but does not affect normal healthy cells.

***Resveratol* -** May reduce the risk of blood clots, cancer, heart disease and stroke.

***Anthocyanins (also known as flavanols)* -** Potent antioxidants: They have been shown to improve balance coordination and short term memory in the elderly.

There are a range of other phytochemicals that have been found to boost cancer-fighting enzymes (e.g., organo sulphur compounds); promote growth of beneficial bacteria (e.g., organic acids and polysaccharides); and help in blood clotting (e.g., phytosterols and fatty acids) [9].

Therapeutic and Pharmacological Effects of Flavonoids

Central Nervous System Activity

Synthetic flavonoids like 6-bromoflavone and 6-bromo-3′-nitro-flavones were shown to displace [3H] flumazenil binding to membranes from rat cerebellum but not from spinal cord, indicating selectivity for BZ-Omega receptor subtype, but later was very potent than 6-bromoflavone. Results from two conflicts tests in rats showed that these synthetic flavonoids possess anxiolytic like properties similar to that of diazepam [21].

Cardiotonic Activity

Flavonoids have been reported to have action on the heart. The unsubstituted parent flavone exerts coronary dilatory activity and was commercially available under the name “Chromocor” and its combination with routine and isoquercetin was also available with brand name ‘Flavoce’ useful in the treatment of atherosclerosis. 3-methyl quercetin has positive chronotropic effect on guinea pig right atrium and antiarrhythmic effect on left atrium [22]. The glycosides of luteolin, apigenin and genistein produced antihypertensive activity even more than the reference drug *papaverine*. Three flavonoids showed vasorelaxant effect in order of potency, luteolin>eriodictyl>naringenin on rat thoracic aorta.

Lipid Lowering Activity

Oxidative modification of low-density lipoproteins (LDL) by free radicals is an early event in the pathogenesis of atherosclerosis. The rapid uptake of oxidatively modified LDL via a scavenger receptor leads to the formation of foam cells. Oxidative LDL also has a number of other atherogenic properties. A number of mechanisms are likely to contribute to inhibition of LDL oxidation by flavonoids. Flavonoids may directly scavenge some radical species by acting as chain-breaking antioxidants [23]. In addition, they may recycle other chain-breaking antioxidants such as α-tocopherol by donating a hydrogen atom to the tocopheryl radical [24]. Transition metals such as iron and copper are important pro-oxidants, and some flavonoids can chelate divalent metal ions, hence preventing free radical formation. The ability of quercetin and quercetin glycosides, to protect LDL against oxidative modification has shown a significant protective effect [25].

Effect on Git

Anti-ulcer activity

Recent reports have shown that many flavonoids possess anti-ulcerogenic activity. Oral treatment with the ether fraction of the flavonoid extract demonstrated a good level of gastric protection. Quercetin, rutin and kaempferol administered intraperitoneally (25-100 mg/kg) inhibited dose-dependent gastric damage produced by the acidified ethanol in rats. Flavone was inactive while naringin was active at a higher dose (200 mg/kg). Quercetin, morin, myricetin, rutin and kaempferol were found to inhibit the mucosal content of platelet activating factor (PAF) in a dose dependent manner suggesting that the protective role of these substances may be mediated by endogenous PAF [26].

Hepatoprotective

In a study carried out to investigate many flavonoids against hepatoprotective activity, silymarin, apigenin, quercetin and naringenin were shown to contain putative therapeutic agents against microcrysin LR-induced hepatotoxicity in animal models.

Antioxidant Activity

Free radical production in animal cells can either be accidental or deliberate. With the increasing acceptance of free radicals as common place and important biochemical intermediates, they have been implicated in a large number of human diseases [27]. Quercetin, morin, myricetin, rutin and kaempferol by acting as antioxidants exhibited several beneficial effects, such as anti-inflammatory, anti-allergic, anti-viral as well as anti-cancer activity. Quercetin and silybin acting as free radical scavengers were shown to exert a protective effect in reperfusion ischemic tissue damage [28, 29]. The scavenging effects of flavonoids have been reported in the order:
myricetin>quercetin>rhamnetin>morin>naringenin>apigenin>catechin>kaempferol>flavones [30].

Anti-Inflammatory Activity

A number of flavonoids are reported to possess anti-inflammatory activity. Hesperidin, a citrus flavonoid possesses significant anti-inflammatory and analgesic effects. Recently, apigenin, luteolin and quercetin have been reported to exhibit anti-inflammatory activity [30].

Antineoplastic Activity

Numerous flavonoids have exhibited anti-neoplastic activity. Recent reviews have highlighted this activity [31]. Detailed studies have revealed that quercetin exerted a dose-dependent inhibition of cell growth and colony formation.

Antimicrobial Activity

Flavonoids and esters of phenolic acids have been shown to exhibit antibacterial, antifungal and antiviral activity.

Antibacterial activity

Antibacterial activity has been displayed by a number of flavonoids. Twenty five (25) out of one hundred and eighty two (182) flavonoid studied were found to be active against many bacteria. Most of the flavonones having no sugar moiety showed antibacterial activities where as none of the flavonols and flavono-lignans tested showed inhibitory activity on the microorganisms [32].

Antifungal activity

Various flavonoids isolated from peel of tangerine orange, when tested for fungistatic activity towards *Deuterophoma trachelphilia* showed promising activity. Chlo-flvonin was the first chlorine-containing flavonoid type antifungal antibiotic produced by strains of *Aspergillus candidus* [21].

Antiviral activity

Flavonoids also displayed antiviral, including anti-HIV activity. It has been found that flavonols are more active than flavones against herpes simplex virus type 1 and the order of importance was galangin>kaempferol>quercetin. Recently, a natural plant flavonoid polymer of molecular weight 2100 D was found to have antiviral activity on two strains of type-1 herpes simplex virus [21]. Out of twenty eight (28) flavonoids tested, flavan-3-ols were more effective than flavones and flavonones in selective inhibition of HIV-1, HIV-2 and similar immunodeficiency virus infections [33].

Flavonoids and Antioxidant Property

An antioxidant is a chemical that reduces the rate of particular oxidation reactions in a specific context, where oxidation reactions are chemical reactions that involve the transfer of electrons from a substance to an oxidizing agents, this generally results in different chemicals to the original ones. Antioxidants are particularly important in the context of organic chemistry and biology [34]. It can also be said to be molecules/compounds ingested or made by our bodies to neutralize free radical damage that protect cells against the damaging effects of reactive oxygen species. Antioxidant can also be an enzyme or other organic molecule that can counteract the damaging effects of oxygen in tissues. Although the term technically applies to molecules reacting with oxygen, it is often applied to molecules that protect one from any free radical-molecule with unpaired electron [34].

Two of the biggest premature killers in the affluent Western world, as well as major causes of disability and early loss of independence, are stroke and heart disease. Both frequently follow on the development of the cardiovascular disease, atherosclerosis, otherwise known as hardening of the arteries, and it is known that the oxidation of low density lipids (LDL), the blood fats known as "bad cholesterol", is one of the major causes of this condition. The prevention of LDL oxidation is one of the key functions of vitamin E, the body's most important fat-soluble anti-oxidant, but anti-oxidant flavonoids are also known to play a significant role in this case [14].

Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's). Flavonoids may help provide protection against these diseases by contributing, along with antioxidant vitamins and enzymes, to the total antioxidant defense system of the human body. It is important to note that, epidemiological studies have shown that flavonoid intake is inversely related to mortality from coronary heart disease and to the incidence of heart attacks.

The contribution of flavonoids to the antioxidant defense system may be substantial considering that the total daily intake of flavonoids can range from 50 to 800 mg. This intake is high compared to the average daily intake of other dietary antioxidants like vitamin C (70 mg), vitamin E (7-10 mg) or carotenoids (2-3 mg). Flavonoid intake depends upon the consumption of fruits, vegetables, and certain beverages such as red wine, tea and beer. The high consumption of tea and wine may be most influential on total flavonoid intake in certain groups of people [35].

The oxidation of low-density lipoprotein (LDL) has been recognized to play an important role in atherosclerosis. Immune system cells called macrophages recognize and engulf oxidized LDL, a process that leads to the formation of atherosclerotic plaques in the arterial wall. LDL oxidation can be induced by macrophages and can also be catalyzed by metal ions like copper. Several studies have shown that certain flavonoids can protect LDL from being oxidized by these two mechanisms [35]. The capacity of flavonoids to act as antioxidants depends upon their molecular structure. The position of hydroxyl groups and other features in the chemical structure of flavonoids are important for their antioxidant and free radical scavenging activities. Quercetin, the most abundant dietary flavonol, is a potent antioxidant because it has all the right structural features for free radical scavenging activity [35].

Natural Sources of Antioxidants

There has been an upsurge of interest in the therapeutic potentials of medicinal plants as antioxidants in reducing such free radical induced tissue injury. Some of the antioxidants are from tea, wine, fruits, vegetables and spices, some natural antioxidant (e.g. rosemary and sage) are already exploited commercially either as antioxidant additives or a nutritional supplements [36]. It has been mentioned the antioxidant activity of plants might be due to their phenolic compounds [37].

Antioxidants include some vitamins (such as Vitamins A, C and E), some minerals (such as selenium, zinc, carotenoids), flavonoids and hundreds of other plant compounds—that neutralize the cell-damaging oxidative agents called free radicals.The best sources of antioxidants are fruits and vegetables; also found in fruits, red wine and some teas (hundreds of other plant compounds—that neutralize the cell-damaging oxidative agents called free radicals [38, 34].

Category of Antioxidants

Antioxidants can be categorized into two subgroups: dietary antioxidants (Vitamins A, C, D, zinc, selenium, carotenoids and flavonoids from foods) and endogenous antioxidants—sometimes called *antioxidant enzymes*—which are produced in the body or manufactured synthetically. These include glutathione (GSH), superoxide dismutase (SOD), alpha lipoic acid (ALA), catalase, and N-acetyl-cysteine (NAC). Endogenous antioxidants are not found in the diet or most supplements: they are made by the body in small amounts, or manufactured in the laboratory [38]. There also many different types of free radicals: superoxide anion, hydroxyl radicals, hydrogen peroxide, to name but few. It is important to note that, no single antioxidant protects against all types of free radicals: each antioxidant is specific for a different type of free radical [38].

Free Radicals

A free radical is defined as any molecule with at least one unpaired electron such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. Free radicals are a common bye-product of the normal chemical reactions that occur in cells. Free radicals are involved in many disorders like neurodegenerative diseases (Parkinson's, Alzheimer's), cancer and AIDS. Antioxidants through their scavenging power are useful for the management of those diseases [39].

Free radicals contribute to more than one hundred disorders in humans including atherosclerosis, arthritis, ischemia and reperfusion injury of many tissues, central nervous system injury, gastritis, cancer and AIDS [40, 37]. Free radicals due to environmental pollutants, radiation, chemicals, toxins, deep fried and spicy foods as well as physical stress, cause depletion of immune system antioxidants, change in gene expression and induce abnormal proteins. Oxidation process is one of the most important routes for producing free radicals in food, drugs and even living systems.

One is exposed to free radicals [34]:

- *through by-products of normal processes that take place in the body*
- *when the body breaks down certain medications*
- *through pollutants*
- *tobacco smoke*
- *alcohol*
- *insecticides*
- *radiation*
- *chemicals in the home or at work*
- *excessive amounts of sunlight*
- *high fat diet or eating fried foods*
- *strenuous exercise*

Radical scavenger in chemistry is a chemical substance added to a mixture in order to remove or inactivate impurities or unwanted reaction products. Their use is wide-ranged: Hydrazine and ascorbic acid are used as oxygen scavenger corrosion inhibitors; tocopherol and naringenin are bioactive free radical scavengers and synthetic catalytic scavengers [their synthetic counterparts] [41].

Superoxide Ion (O_2^-)

Superoxide is the anion O_2^- which is important as the product of the one-electron reduction of dioxygen, which occurs widely in nature [42]. With one unpaired electron, the superoxide ion is a free radical and like dioxygen, it is paramagnetic in effects.

Properties and basic reactions of superoxide

Superoxides are compounds in which the oxidation number of oxygen is -½. The O-O bond distance in O_2^- is 1.33 Å, vs. 1.21 Å in O_2 and 1.49 Å in O_2^{2-}. The salts CsO_2, RbO_2, KO_2, and NaO_2 are prepared by the direct reaction of O_2 with the respective alkali metal [42]. The overall trend corresponds to a reduction in the bond order from 2 (O_2), to 1.5 (O_2^-), to 1 (O_2^{2-}). The alkali salts of O_2^- are orange-yellow in color and quite stable, provided they are kept dry. Upon dissolution of these salts in water, however, the dissolved O_2^- undergoes disproportionation (dismutation) extremely rapidly:

$$2O_2^- + 2H_2O \rightarrow O_2 + H_2O_2 + 2OH^-$$

In this process O_2^- acts as a strong Brønsted base, initially forming HO2. The pKa of its conjugate acid, hydrogen superoxide (HO2, also known as "hydroperoxyl" or "perhydroxy radical"), is 4.88 so that at neutral pH 7 the vast majority of superoxide is in the anionic form, O_2^- [43].

Superoxide is biologically quite toxic and is deployed by the immune system to kill invading microorganisms. In phagocytes, superoxide is produced in large quantities by the enzyme NADPH oxidase for use in oxygen-dependent killing mechanisms of invading pathogens. Mutations in the gene coding for the NADPH oxidase cause an immunodeficiency syndrome called chronic granulomatous disease, characterized by extreme susceptibility to infection. Superoxide is also deleteriously produced as a byproduct of mitochondrial respiration (most notably by Complex I and Complex III), as well as several other enzymes, for example xanthine oxidase [43]. The biological toxicity of superoxide is due to its capacity to inactivate iron-sulfur cluster containing enzymes (which are critical in a wide variety of metabolic pathways), thereby liberating free iron in the cell, which can undergo Fenton chemistry and generate the highly reactive hydroxyl radical. In its HO_2 form (hydroperoxyl radical); superoxide can also initiate lipid peroxidation of polyunsaturated fatty acids. It also reacts with carbonyl compounds and halogenated carbons to create toxic peroxy radicals. Superoxide can also react with nitric oxide (NO) to form $ONOO^-$. As such, superoxide is one of the main causes of oxidative stress [43]. Because superoxide is toxic, nearly all organisms living in the presence of oxygen contain isoforms of the superoxide scavenging enzyme, superoxide dismutase (SOD). SOD is an extremely efficient enzyme; it catalyzes the neutralization of superoxide nearly as fast as the two can diffuse together spontaneously in solution. Superoxide may contribute to the pathogenesis of many diseases, and perhaps also to aging via the oxidative damage that it inflicts on cells.

Mechanism of Action of Antioxidants

Our body constantly maintains a balance between pro-oxidants and anti-oxidants. This balance is called Redox (for "reduction" and "oxidation"). If the balance shifts toward excessive free radicals (oxidation), we experience elevated cell damage. If antioxidants are excessive, our immune function is impaired (immune cells use free radicals to attack viruses and bacteria) and we feel fatigued (oxidation is required to burn our foods to create energy). Antioxidant nutrients are tissue specific: in other words, *"each antioxidant has an affinity for certain places in the body and are found in these organs in high concentrations but in other locations in much smaller amounts if at all"*. For example, lycopene accumulates in the breast, prostate and pancreas. Vitamin C accumulates in the eye and adrenal gland, but has no storage in any other region of the body. Some antioxidants work in the space between cells, while others work on the interior of a cell. Antioxidants that accumulate in the heart or brain, for example, they may help to reduce the cardio toxicity and neurotoxicity [38].

Conclusion

Flavonoid being so ubiquitous in nature is very unique in the management of diseases through phytotherapy. From the aforesaid biotherapeutic importance of flavonoids; especially being a good remediation against the principal agent (*free radical*) implicated in most diseases condition among races. It is noteworthy to conclude that, as a simple precautionary measure against the neurodegenerative diseases; one should adopt the habit of eating phytochemicals [natural fruits and vegetables] as part of one's diets. The exposure route of free radicals should be extremely minimized to the lesser level and if possible avoided; in order to avert their damaging and fatal effects.

Acknowledgements

The authors wish to acknowledge the Management of University of Maiduguri for the provision of Study fellowship.

References

1. Seshadri, M. (2008). Flavonoids- Where do we find these magic supplements? Department of Chemistry, Pharmaceutical Chemistry unit, Vellore Institute of Technology, Vellore-632 014, India. Retrieved from the webpage on 19th February.
2. Farnsworth, N.R. and Soejarto, D.D. (1991). *Global Importance of Medicinal Plants. In: Conservation of Medicinal Plants*. (Akerele, A.O. Ed.) Cambridge Univ. Press publication NY pp. 25-51.
3. Cordell, G.A. (2000). Biodiversity and Drug discovery – a Symbiotic Relationship. *Phytochemisrty.* 55: 463-480.
4. Natural Remedies (2008). Natural Remedies Flavonoids and Health.htm. Retrieved Mar., 15th.
5. EuroFIR *(2008). Bioactive Compounds.* Retrieved Feb. 19th.

http://www.nutrition.org.uk/EuroFIR/bioactivecompounds

6. Phytochemicals (2008). http//:www.search.com/farmfreshllc/phytochemicals. Retrieved Feb., 19th.
7. Liu, R. H. (2003). Health benefits of fruits and vegetables are from additive and synergistic combination of phytochemicals. *American Journal of Clinical Nutrition*. 78:517S-520S.
8. Ames, B. N. and Gold, L. S. (1991) Endogenous mutagens and the causes of aging and cancer. *Mutation Research.* 250:3-16.
9. Liu, R.H. (2004). Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action Journal of Nutrition. 134:3479S-3485S
10. Phytochemicals Nyamnews (2005). Phytochemicals Nyamnews Dec. #1&2. http://www.paho/cfni.org Retrieved March, 15th.
11. Harborne, J.B. (1993). *The flavonoids: advances in research since 1986*. Chapman and Hall Publication, London.
12. Hwang, E.I., Kaneko, M., Ohnishi, Y. & Horinouchi, S. (2003). Production of Plant-Specific Flavanones by *Escherichia coli* Containing an Artificial Gene Cluster. *Applied Environmental Microbiology*. 69(5): PMID
13. *Ververidis F., Trantas, E., Douglas, C., Vollmer, G., Kretzschmar, G. & Panopoulos, N. (*2007*). Biotechnology of Flavonoids and Other Phenylpropanoid-Derived Natural Products. Part II: Reconstruction of Multi-enzyme Pathways in Plants and Microbes". Biotechnology Journal. 2(10): 108-120.*
14. Smith, S. (2008). Powerful-Antioxidant-Flavonoids http://www.articlesbase.com/health-articles/powerful-antioxidant-flavonoids-found-in-red-wine-and-chocolate-326687.html Retrieved February, 19th.
15. Timberlake, C.F. & Henry, B.S. (1986). *Endeavour.* 10: 31-36.
16. Trease, G.E. & Evans, M.C. (1997). *Textbook of pharmacognosy*, 14th edition. W B Saunders Company Ltd., 24-28 Oval Road, London NW1 7DX, UK and Printed by Harcourt Brace & Company Asia Pte. Ltd. 583 Orchard Road No. 09-01 Forum Singapore 238884. pp. 13-53, 117-139, 293-334, 471-511.
17. Harborne, J.B. & Williams, C.A. (2000). Advances in research since 1992 – A Review. *Phytochemistry.* 55: 481-504.
18. IUPAC (2008). Flavonoids (isoflavonoids and neoflavonoids), Compendium of Chemical Terminology. Retrieved February, 19th.
19. Middleton, E. (1984). The Flavonoids Trends. *Pharmacology Science*. 5: 335 – 338.
20. Finar, I.L. (1999). *Organic Chemistry: stereochemistry and the chemistry of natural products* (Vol. 2) 5th Edition. Pearson Education (Singapore) Pte. Ltd., Indian Branch, 482 F.I.E. Patparganj, Delhi 110 092, India.
21. Thomas, P.R.S., Nash, G.B. & Dormandly, J.A. (1988). White Cell Accumulation in Dependent Legs of Patients with Venous Hypertension: A Possible Mechanism for Tropic Changes in the Skin. *British Medical Journal*. 296: 1673-1695
22. Lackeman G.M., Claeys, M., Rwangabo, P.C, Herman, A.G. & Vlietinck, A. (1986). Chronotropic Effect Quercetin on Guinea pig Right Atrium. *Journal Planta Medica*. 52: 433-439.
23. De-Whalley, C., Rankin, S.M., Houct, J.R.S., Jessup, W. & Leake, D.S. (1990). Flavonoids inhibit the oxidative modification of low density lipoproteins by microphages. *Biochemical Pharmacology.* 39: 1743-1750.
24. Francel, E.N., Kanner, J., German, J.B., Packs, E. & Kinsella, J.E. (1993). Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 341: 454-457.
25. Fuhrman, B., Lavy, A. & Aviram, M. (1995). Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoproteins to lipid peroxidation. *American Society of Clinical Nutrition.* 61: 549-554.
26. Parmar N.S. & Parmar, S. (1998). Anti-ulcer potential of flavonoids. *Indian Journal of Physiology and Pharmacology*. 42: 343-351.

27. Wegener, T. & Fintelman, V. (1999). Flavonoids and Bioactivity. *Wein. Med. Wochem. Schr.*149: 241-247.
28. Hilwell, B. (1994). Free radicals, antioxidants and human disease: curiosity, cause or constipation? *Lancet* **344:** 721-724.
29. Fraga, C.G., Mactino, U.S., Ferraro, G.E., Coussio, J.F. & Boveris, A. (1987). Flavonoids as antioxidants evaluated by *in vitro* and *in situ* liver Chemiluminescence. *Biochemical Medicine and Metabolic Biology.* 36: 717-720.
30. Rajnarayana, K., Spiralreddy, M., Chaluvadi, M.R. & Krishna, D.R. (2001). Bioflavonoids Classification, Pharmacological, Biochemical Effects and Therapeutic Potential. *Indian Journal of Pharmacology* 33: 2-16.
31. Izzo, AA., Dicarlo, G., Mascolo, N., Capasso, F. & Autore, G.(1991). Anti-ulcer effects of flavonoids. Role of Endogenous PAF. *Phytotherapy Research.* **8:** 179-181.
32. Wild, C. & Fassel, J. (1969). Effects of a Flavonoid on the Capillary Resistance of the Rectal Mucosa in Hepatic Cirrhosis. *American Journal of Proct.* **20**: 60 – 62.
33. Gerdin, B. & Strensso, E. (1983). Inhibitory effect of the Flavonoid on Increased Micro Vascular Permeability Induced by Various Agents in Rat Skin. *International Journal of Microbiology and Clinical Experiments.* 2: 39-46.
34. Antioxidant- Cancer and Chemotherapy, 2008. http://www.Yahoo.health.htm.(Antioxidant- Cancer and Chemotherapy, 2008) Retrieved February 19th.
35. Miranda, C. & Buhler, R.D. (2008). Antioxidant Activities of Flavonoids Department of Environmental and Molecular Toxicology Oregon State University.
36. Schuler, P. (1990). Natural antioxidants exploited commercially, In *Food Antioxidants*, Hudson BJF (Ed.). Elsevier, London, pp. 99-170.
37. Cook, N.C. & Samman, S. (1996). Flavonoids-Chemistry, Metabolism, Cardio-protective Effects, and Dietary Sources. *Nutritional Biochemistry*. **7:** 66-76.
38. Wallace, J.M. (2004). Nutritional Solutions: Comments for Your Consideration on Antioxidants & Chemotherapy. Retrieved March 17th 2008.
39. Pourmorad, F., Hosseinimehr, S. J. & Shahabimajd, N. (2006). Antioxidant activity, phenol and flavonoid contents of some selected Iranian medicinal plants *African Journal of Biotechnology.* 5 (11): 1142-1145.
40. Kumpulainen, J.T. & Salonen, J.T. (1999). Natural Antioxidants and Anticarcinogens in Nutrition, Health and Disease. The Royal Society of Chemistry, UK. pp. 178-187.
41. Wikipedia (2008a). http://en..org/wiki/Scavenger_(chemistry). Retrieved 17th Mar.
42. Sawyer, D. T. (2008) Superoxide Chemistry, McGraw-Hill, doi:10.1036/1097-8542.669650 Retrieved 16th March.
43. Wikipedia (2008b). http://en.wikipedia.org/wiki/Superoxide Retrieved 15th Mar.