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An updated review on flavonoids

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Abstract
Flavonoids, a group of natural substances with variable phenolic structures, are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. Flavonoids are now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is attributed to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme function. Flavonoid constitute one of the largest class of naturally occurring plant products mostly phenols either in the Free State or as their respective glycosides. The main constituent of flavonoid drugs are 2-phenyl-γ-benzopyrones. The family includes monomeric flavanols, flavanones, anthocyanidins, flavones, Isoflavonoid and Neoflavanoids. It is very probable that a number of herbal remedies, whose constituents are yet unknown, will be shown to contain active flavonoids, quercetin and rutin in plant Trigonella foenum seed, they are known for its anti-inflammatory properties. Most flavonoids have anti-tumor properties. Flavonoids are powerful antioxidant. Extract from onion contain quercetin which induce the cellular antioxidant system.
The main aim of this review was to give an overview of the research in the field of flavonoids. The potential valuable working mechanisms of flavonoids are discussed, followed by present knowledge on the absorption, conjugation, and toxicity of these substances. The potential clinical applications of flavonoids are also discussed.

Keywords: Flavonoids, phenols, benzopyrones, quercetin, isoflavonoid

Introduction
Flavonoids are secondary metabolites, which mainly consists of a benzopyrone ring bearing a phenolic or poly-phenolic groups at different positions. They are most commonly found in fruits, herbs, stems, cereals, nuts, vegetables, flowers and seeds. The presence of bioactive phytochemical constituents present in these different plants parts gives them their medicinal value and biological activities. So far, over 10,000 flavonoid compounds have been isolated and identified. Most of the flavonoids are widely accepted as therapeutic agents. These are naturally synthesized through the phenylpropanoid pathway with bioactivity dependent on its absorption mechanism and bioavailability. The Flavonoids have been used in natural dyes, in cosmetics and skin care products, and anti-wrinkle skin agents. The most pronounced applications of these polyphenols, however, are in the field of medicine. Flavonoids have been used extensively as anticancer, antimicrobial, antiviral, antiangiogenic, antimalarial, antioxidant, neuroprotective, antitumor, and anti-proliferative agents. Apple peel extracts rich in flavonoids inhibits acetylcholinesterase (ACE) *in vitro* and is an effective antihypertensive agent. It also prevents cardio-metabolic disorders and displays better preservation of cognitive performance with aging. Population studies have shown that flavonoid intake is inversely correlated with mortality from cardiovascular disease.
Flavonoids are found ubiquitously in plants, which contribute to the orange, blue, and purple color of fruits, flowers, and leaves. Flavonoids belong to a broad polyphenol family, water soluble, group of natural substances with not consistent phenolic structures. They are available in all dietary plants, fruit, vegetables, grains, bark, roots, stems, flowers, tea and wine. These natural products were known for their beneficial effects on health since many years and they were isolated as the effective compounds. More than 8000 varieties of flavonoids have been identified. After the discovery of the French paradox, i.e., the low cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake, research in the field of flavonoids has increased. Flavonoids in red wine responsible for it. Against coronary heart disease, epidemiologic studies suggest a protective role of dietary flavonoids. The association between flavonoid intake and the long-term effects on the number of deaths in a given area or period, or from a particular cause (mortality) was

studied subsequently and it was suggested that flavonoid intake is inversely correlated with mortality due to coronary heart disease. *In vitro* experimental systems also showed that flavonoids possess anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties. Until 60 years ago, information on the working mechanisms of flavonoids was scarce. However, it has been widely known for centuries that derivatives of plant origin possess a broad spectrum of biological activity. From oranges in 1930 a new substance was isolated, which is believed to be a member of a new class of vitamins, and was designated as vitamin P. When it became clear that this substance was a flavonoid (rutin), research began in an attempt to isolate the various individual flavonoids and to study the mechanism by which flavonoids act.

There are several subclasses of flavonoids: flavanols, flavanones, flavones, isoflavones, anthocyanidins, and flavonols. The divisions in flavonoid subclasses are based on structural properties. The flavanols are found in red grapes and red wine (example:- catechins), flavanones are found in citrus foods (example:- narigenin), flavones (example :- apigenin) are found in green leafy spices, isoflavones are found in soya foods, and in almost all foods flavonols are found{3}. Catechins origin flavonoids are mainly found in green and black tea and in red wine, whereas anthocyanins are found in strawberries and other berries, grape, wine and tea.

Classification

Flavonoids chemical class are divided into six classes, such as;

1) Flavonol
2) Flavonones
3) Flavones
4) Isoflavones
5) Neoflavonoids

Table 1: Classification of Flavonoids and their Sources

Chemical Class	Examples	Major Source (Dietary)
Flavonol	Quercetin, Rutin, Kaempherol, Myricetin, Isoquercitrin	Apple, Tea, Tomato, Red wine, Cherry, Onion, Broccoli, Fruit peels, Lettuce, Olives, Citrus fruits, Mango
Flavanones	Naringenin, Hesperidin, Fisetin, Naringin	Grapefruit, orange
Flavones	Apigenin, Chrysin, Luteolin	Parsley, Thyme
Isoflavonoids	Daidzein, Formononetin, Genistein, Glycitein	Soya bean, legumes
Neoflavonoids	Calophyllolide	Green tea, apricots, cherries
Anthocyanins	Cyanidin, Malvidin, Delphinidin, Peonidin	Pomegranate, Egg plant, purple corn, cherries, plums.

I. Flavonol

Flavonols are flavonoids with a ketone group. They are building blocks of proanthocyanins. Flavonols occur abundantly in a variety of fruits and vegetables. The most studied flavonols are kaempferol, quercetin, myricetin and fisetin. And in Onions, kale, lettuce, tomatoes, apples, grapes and berries are rich sources of flavonols. Apart from fruits and vegetables, tea and red wine are also sources of flavonols. Intake of flavonols is found to be associated with a wide range of health benefits which includes antioxidant potential and reduced risk of vascular disease. Compared with flavones, flavonols have a hydroxyl group in position 3 of the C ring, which may also be glycosylated. Like flavones, flavonols are very diverse in methylation and hydroxylation patterns as well and, considering the different glycosylation patterns, they are perhaps the most common and largest subgroup of flavonoids in fruits and vegetables. For example, quercetin is present in many plant foods.

II. Flavanones

Flavanones are another important class which is generally present in all citrus fruits such as oranges, lemons and grapes. Hesperitin, naringenin and eriodictyol are examples of this class of flavonoids. Flavonones are associated with a number of health benefits because of their free radical-scavenging properties. These compounds are responsible for the bitter taste of the juice and peel of citrus fruits. Citrus flavonoids exert interesting pharmacological effects as antioxidant, anti-inflammatory, blood lipid-lowering and cholesterol-lowering agents. Flavanones, also called dihydroflavones, have the C ring saturated; therefore, unlike flavones, the double bond between positions 2 and 3 is saturated and this is the only structural difference between the two subgroups of flavonoids. Over the past 15 years, the number of flavanones has significantly increased.

III. Flavones

Flavones are the most important flavonoid subclass. Flavones may be found as glucosides in large quantities in flowers, leaves, and fruits. Flavones may be found in *Ginkgo biloba*, celery, parsley, red peppers, chamomile, and mint. This set of flavonoids comprises luteolin, apigenin, and tangeritin. The polymethoxylated flavones tageretin, nobiletin, and sinensetin are abundant in citrus fruit coverings.

IV. Isoflavonoids

Isoflavonoids are a large and very distinctive subgroup of flavonoids. Isoflavonoids enjoy only a limited distribution in the plant kingdom and are predominantly found in soyabeans and other leguminous plants. Some isoflavonoids have also been reported to be present in microbes. They are also found to play an important role as precursors for the development of phytoalexins during plant microbe interactions. Isoflavonoids exhibit tremendous potential to fight a number of diseases. Isoflavonoids such as genistein and daidzein are commonly regarded to be phyto-oestrogens because of their oestrogenic activity in certain animal models. Szkudelska & Nogowski reviewed the effect of genistein inducing hormonal and metabolic changes, by virtue of which they can influence various disease pathways.

V. Neoflavanoids

Neoflavonoids are a class of polyphenolic compounds. The first neoflavone isolated from natural sources in 1951 was calophyllolide from *Calophyllum inophyllum* seeds. It is also found in the bark and timber of the Sri Lankan endemic plant *Mesua thwaitesii*.

VI. Anthocyanins

Anthocyanins are pigments responsible for colours in plants, flowers and fruits. Cyanidin, delphinidin, malvidin, pelargonidin and peonidin are the most commonly studied anthocyanins. They occur predominantly in the outer cell layers of various fruits such as cranberries, black currants, red grapes, merlot grapes, raspberries, strawberries, blueberries, bilberries and blackberries. Stability coupled with health benefits of these compounds facilitate them to be used in the food industry in a variety of applications . The colour of the anthocyanin depends on the pH and also by methylation or acylation at the hydroxyl groups.

Mechanism of Flavonoids

Flavonoids have a GRASS (Generally Recognized as Safe) status and do not require toxicological testing. In various ways, flavonoids can prevent injury caused by free radicals. One way is the direct scavenging of free radicals. Flavonoids are oxidized by radicals, resulting in a more stable, less-reactive radical. In other words, flavonoids stabilize the reactive oxygen species by reacting with the reactive compound of the radical. Because of the high reactivity of the hydroxyl group of the flavonoids, radicals are made inactive, according to the following equation:

Flavonoid (OH) + R - Flavonoid (O-) + RH

Where R- is a free radical and O- is an oxygen free radical. Selected flavonoids can directly scavenge superoxides, whereas other flavonoids can scavenge the highly reactive oxygen-derived radical called peroxynitrite. Epicatechin and rutin are also powerful radical scavengers. The scavenging ability of rutin may be due to its inhibitory activity on the enzyme xanthine oxidase. By scavenging radicals, flavonoids can inhibit LDL oxidation *in vitro*. This action protects the LDL particles and, theoretically, flavonoids may have preventive action against atherosclerosis. Several flavonoids, including quercetin, result in a reduction in ischemia-reperfusion injury by interfering with inducible nitric-oxide synthase activity. Nitric oxide is produced by several different types of cells, including endothelial cells and macrophages. Although the early release of nitric oxide through the activity of constitutive nitric-oxide synthase is important in maintaining the dilation of blood vessels, the much higher concentrations of nitric oxide produced by inducible nitric-oxide synthase in macrophages can result in oxidative damage. In these circumstances, activated macrophages greatly increase their simultaneous production of both nitric oxide and superoxide anions. Nitric oxide reacts with free radicals, thereby producing the highly damaging peroxynitrite. Nitric oxide injury takes place for the most part through the peroxynitrite route because peroxynitrite can directly oxidize LDL, resulting in irreversible damage to the cell membrane. When flavonoids are used as antioxidants, free radicals are scavenged and therefore can no longer react with nitric oxide, resulting in less damage. Interestingly, nitric oxide can be viewed as a radical itself, and it is was reported that nitric oxide molecules are directly scavenged by flavonoids. Therefore, it has been speculated that nitric oxide scavenging plays a role in the therapeutic effects of flavonoids. Silibin is a flavonoid that has been reported to inhibit nitric oxide dose dependently.

Specific flavonoids are known to chelate iron, thereby removing a causal factor for the development of free radicals. Quercetin in particular is known for its iron-chelating and iron-stabilizing properties. Direct inhibition of lipid peroxidation is another protective measure Selected flavonoids can reduce complement activation, thereby decreasing the adhesion of inflammatory cells to the endothelium and in general resulting in a diminished inflammatory response. Another feature of flavonoids is a reduction in the release of peroxidase. This reduction inhibits the production of reactive oxygen species by neutrophils by interfering with α1-antitrypsin activation. A progressive inactivation of proteolytic enzymes was described in neutrophils. Another interesting effect of flavonoids on enzyme systems is the inhibition of the metabolism of arachidonic acid. This feature gives flavonoids anti-inflammatory and antithrombogenic properties. The release of arachidonic acid is a starting point for a general inflammatory response. Neutrophils containing lipoxygenase create chemotactic compounds from arachidonic acid. They also provoke the release of cytokines.

Mechanism of cardio protective effects

On the cardio protective potential of flavonoids in several *in vitro* systems many experimental studies are conducted by researchers. In CHD there is increasing experimental and epidemiological evidence of cardioprotective effect of red wine. For cardio vascular benefits polyphenolic constituents of wine have been thought to be responsible. Cardioprotective properties of proanthocyanidins (polyphenolic constituents derived from grape seeds) against ischemia / reperfusion injury in perfused hearts may be attributed to their ability to directly scavenge peroxyl and hydroxyl radicals and to reduce oxidative stress developed during ischemia/ reperfusion. Quercetin significantly reduced tissue factor activity induced by an agonist in a dose dependent manner that may be responsible for their cardioprotective action. Tissue factor (the cellular receptor that initiates blood coagulation), plays a primary role both in haemostasis following tissue injury and in the pathogenesis of atherosclerosis that predispose to thrombosis. Reactive oxygen species (ROS) induced oxidative stress, a pathological determinant, is involved in the development and progression of various cardiovascular diseases. ROS production results in deleterious effects on both cardiac structure and function. ROS generated intracellularly causes membrane lipid peroxidation and oxidative damage to nucleic acids, carbohydrates and proteins, potentially leading to myocardial cell damage and death. Flavonoids have free radical scavenger activity; they serve as antioxidant by scavenging superoxide anion, singlet oxygen and lipid peroxy radicals. Flavonoids possess the potential to stabilized ROS involved in oxidative processes through hydrogenation or complexing with oxidizing species. Thus flavonoids may be cardioprotective through prevention or retardation of damaging oxidative reactions in cells, which may predispose to the development of cardiovascular disease.

Mechanism of neuroprotective effects

Dietary flavonoids exhibit neuroprotective properties that involve several effects on the brain, including the protection of neurons against injury and promotion of memory, learning and cognitive function. Flavonoid compounds benefited humans in overcoming oxidative damage - related diseases like Parkinson's disease and Alzheimer's disease. Quercetin

acts as a neuroprotective agent to reduce white matter damage in chronic cerebral ischemia models, improving memory and learning abilities and protects cognitive functions in a amyloidosis model based on improved performance on a memory test. In fact, the flavonol quercetin exerts antidepressant and/or anxiolytic effects based on several studies of oral administration of quercetin to both rats. Furthermore, quercetin has been demonstrated to act as a monoamine oxidase inhibitor. Rutin is a promising agent for Alzheimer's disease treatment because of its antioxidant, anti-inflammatory, and reducing Aβ Oligomer activity. The vulnerability of brain lipid membranes to lipid peroxidation is thought to lead to neurodegenerative disease, such as Alzheimer's and Parkinson's disease. It is found that oxidative stress occurring in the brain membrane lipids is associated with the extracellular accumulation of amyloid beta-peptide, which precedes neural losses in Alzheimer's patients. Yet, formation of amyloid plaques can be prevented by taking antioxidants. In this condition; quercetin does not only stop the propagation of lipid peroxidation, but also increases glutathione (GSH) levels. GSH is part of the neuron's defense against oxidative damage. GSH can convert hydrogen peroxide to oxygen and water, preventing the formation of free radicals.

Mechanism of anti-inflammatory activity

Anti-inflammatory effects Cyclooxygenase and lipoxygenase play an important role as inflammatory mediators. They are involved in the release of arachidonic acid, which is a starting point for a general inflammatory response. Neutrophils containing lipoxygenase create chemotactic compounds from arachidonic acid. They also provoke the release of cytokines. Selected phenolic compounds were shown to inhibit both the cyclooxygenase and 5-lipoxygenase pathways. This inhibition reduces the release of arachidonic acid. The exact mechanism by which flavonoids inhibit these enzymes is not clear. Quercetin, in particular, inhibits both cyclooxygenase and lipoxygenase activities, thus diminishing the formation of these inflammatory metabolites. Flavonoid exhibits anti-inflammatory characters. Another anti-inflammatory feature is the ability of flavonoids to inhibit eicosanoid biosynthesis. Eicosanoids, such as prostaglandins, are involved in various immunologic responses and are the end products of the cyclooxygenase and lipoxygenase pathways. Flavonoids also inhibit both cytosolic and membranal tyrosine kinase. Integral membrane proteins, such as tyrosine 3-monooxygenase kinase, are involved in a variety of functions, such as enzyme catalysis, transport across membranes, and transduction of signals that function as receptors of hormones and growth factors, and energy transfer in ATP synthesis. Inhibition of these proteins results in inhibition of uncontrolled cell growth and proliferation. Tyrosine kinase substrates seem to play key roles in the signal transduction pathway that regulates cell proliferation. Another anti-inflammatory property of flavonoids is their suggested ability to inhibit neutrophil degranulation. This is a direct way to diminish the release of arachidonic acid by neutrophils and other immune cells.

Mechanism of anti-tumor activity

The antitumor activity of flavonoids is still a point of discussion. Antioxidant systems are frequently inadequate, and damage from reactive oxygen species is proposed to be involved in carcinogenesis. Reactive oxygen species can damage DNA, and division of cells with unrepaired or misrepaired damage leads to mutations. If these changes appear in critical genes, such as oncogenes or tumor suppressor genes, initiation or progression may result. Reactive oxygen species can interfere directly with cell signaling and growth. The cellular damage caused by reactive oxygen species can induce mitosis, increasing the risk that damaged DNA will lead to mutations, and can increase the exposure of DNA to mutagens. It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis. Some flavonoids such as fisetin, apigenin, and luteolin are stated to be potent inhibitors of cell proliferation. A large clinical study suggested the presence of an inverse association between flavonoid intake and the subsequent incidence of lung cancer. Quercetin and apigenin inhibited melanoma growth and influenced the invasive and metastatic potential in mice. This finding may offer new insights about possible therapies for metastatic disease. It has been speculated that flavonoids can inhibit angiogenesis. Angiogenesis is normally a strictly controlled process in the human body. The process of angiogenesis is regulated by a variety of endogenous angiogenic and angiostatic factors. It is switched on, for example, during wound healing. Pathologic, unregulated angiogenesis occurs in cancer. Angiogenesis inhibitors can interfere with various steps in angiogenesis, such as the proliferation and migration of endothelial cells and lumen formation. Among the known angiogenesis inhibitors, flavonoids seem to play an important role. However, the mechanism behind the antiangiogenetic effect of flavonoids is unclear. A possible mechanism could be inhibition of protein kinases. These enzymes are implicated to play an important role in signal transduction and are known for their effects on angiogenesis.

Mechanism of anti-cancer activity

The ability of flavonoids to scavenge free radicals, regulate cellular metabolism, and prevent oxidative stress–related diseases have been demonstrated in numerous studies. There is accumulating evidence that many flavonoids exert anticancer activity, however, the molecular mechanisms responsible for this effect have not been fully elucidated yet. Cancer is a heterogeneous disease characterized by uncontrolled proliferation and impaired cell cycle leading to the growth of abnormal cells that invade and metastasize to other parts of the body. Oxidative stress, hypoxia, genetic mutations and lack of apoptotic function are the main internal causes of cancer, whereas the external causes are related to increased exposure to stress, pollution, smoking, radiation and ultraviolet rays. Altered metabolism, impaired cell cycles, frequent mutations, resistance to immune response, chronic inflammation, formation of metastasis, and induction of angiogenesis are the main characteristics of the cancer cells. There is emerging evidence that cancer is a metabolic disease determined by various degrees of mitochondrial dysfunctions and metabolic alterations. Mitochondria play essential roles in cellular energy supply, regulation of metabolism, cell death signaling and reactive oxygen species (ROS) generation. The main metabolic alterations of the tumor cells involve increased aerobic glycolysis, deregulated pH, impaired lipid metabolism, increased generation of ROS, and compromised enzyme activities. As a direct consequence, the extracellular environment becomes acidic and more favourable to inflammation, glutamine-driven lipid biosynthesis increases

and upregulates the pathways involved in tumorigenesis initiation and metastasis, cardiolipin levels decrease in membranes causing impaired enzyme activities, mitochondria are hyperpolarised, and this effect correlates with the malignancy and invasiveness of cancer cells. Flavonoids exert a wide variety of anticancer effects: they modulate ROS-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, autophagy, and suppress cancer cell proliferation and invasiveness.

Mechanism of anti-oxidant activity

Almost every group of flavonoids has a capacity to act as antioxidants. It has been reported that the flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species. Body cells and tissues are continuously threatened by the damage caused by free radicals and reactive oxygen species, which are produced during normal oxygen metabolism or are induced by exogenous damage. The mechanisms and the sequence of events by which free radicals interfere with cellular functions are not fully understood, but one of the most important events seems to be lipid peroxidation, which results in cellular membrane damage. This cellular damage causes a shift in the net charge of the cell, changing the osmotic pressure, leading to swelling and eventually cell death. Free radicals can attract various inflammatory mediators, contributing to a general inflammatory response and tissue damage. To protect themselves from reactive oxygen species, living organisms have developed several effective mechanisms. The antioxidant defence mechanisms of the body include not only the enzymes such as superoxide dismutase, catalase and glutathione peroxidase, but also non-enzymic counterparts such as glutathione, ascorbic acid and α-tocopherol. The increased production of reactive oxygen species during injury results in consumption and depletion of the endogenous scavenging compounds. Flavonoids may have an additive effect to the endogenous scavenging compounds. Codorniu-Hernández . carried out docking studies to understand flavonoid–protein interactions. The results indicated that hydrophilic amino acid residues demonstrate high-affinity interactions with flavonoid molecules, as was predicted by the theoretical affinity order. The docking modes among catechin molecules and four proteins (human serum albumin, transthyretin, elastase and renin) are also supporting this information. The theoretical affinity order among flavonoids and amino acid residues seems to have great applications in the theoretical predictions of flavonoid–protein interactions as a high-quality approach to understand the biological activity of flavonoids.

Mechanism of atherosclerotic activity

Oxygen radicals can oxidize low density lipoprotein, which injures the endothelial wall and thereby promotes atherosclerotic changes. Because of their antioxidative properties, flavonoids are likely to have a major influence on the vascular system. A few clinical studies have pointed out that flavonoid intakes protect against coronary heart disease. The flavonoids in regularly consumed foods might reduce the risk of death from coronary heart disease in elderly men. Furthermore, a Japanese study reported an inverse correlation between flavonoid intake and total plasma cholesterol concentrations. Oxidative stress and vascular damage are postulated to play a key role in dementia, and the intake of red wine is reported to prevent the development of dementia. The intake of flavonoids was reported to be inversely related to the risk of incident dementia.

Mechanism of anti-hypertensive activity

Flavonoids inhibit angiotensin converting enzyme (ACE) which may account for their anti- hypertensive effect. Anti-hypertensive effect of flavonoids is due to their vasodilatory properties. Such kind of vasodilatory effect of flavonoids can also be mediated by their superoxide anion scavenging activity thereby preventing nitric oxide degradation by free radicals. Some other proposed mechanisms for their anti-hypertensive effect is decrease in endothelin levels possibly via activation of tetraethyl ammonium-sensitive K+ channels.

Mechanism of anti-viral activity

Flavonoids exhibits antiviral properties. Some of the viruses reported to be affected by flavonoids are herpes simplex virus, respiratory syncytial virus, parainfluenza virus, and adenovirus. The antiviral activity of flavonoids was carried out and quercetin was reported to exhibit both anti-infective and anti-replicative abilities. The interaction of flavonoids with the different stages in the replication cycle of viruses was studied. For example, some flavonoids work on the intracellular replication of viruses, whereas others inhibit the infectious properties of the viruses. By far, most studies of the effects on viruses were performed *in vitro* and little is known about the antiviral effect of flavonoids *in vivo*. There is some evidence that flavonoids in their glycone form seem to be more inhibitory on rotavirus infectivity than are flavonoids in their aglycone form. Investigations of the antiviral activity of flavonoids have mainly focused on HIV because of the worldwide spread of HIV since the 1980. Many natural products can inhibit various stages of the replication cycle of the virus. The discovery and development of flavonoids as anti-HIV agents has expanded in the past few decades. Most of these studies focused on the inhibitory activity of reverse transcriptase, or RNA-directed DNA polymerase, but anti-integrase and antiprotease activities were also described. Again, flavonoids have mainly been studied in *in vitro* experiments; therefore, no clear contribution of flavonoids to the treatment of HIV-infected patients has yet been shown.

Mechanism of anti-obesity activity

Coronary heart disease, type 2 diabetes, cancer (specifically breast and colon), hypertension, dyslipidemia, stroke, liver and gallbladder disease, sleep apnea, osteoarthritis, and gynecological complications has been linked to obesity. Quercetin has recently been implicated as an AMP-activated protein kinase (AMPK) activator. AMPK is the major metabolic regulator of the cell, and a major target for obesity related conditions because of its ability to induce fatty acid oxidation. Flavonoid quercetin is of great interest because of its suggested ability to alleviate obesity-related conditions. Thus flavonoid has ability to remove obesity.

Mechanism of anti-thrombogenic activity

In Antithrombogenic effects, Flavonols are particularly antithrombotic because they directly scavenge free radicals, thereby maintaining proper concentrations of endothelial prostacyclin and nitric oxide. Thrombosis plays a critical role in the development, progression and clinical sequelae of atherosclerosis and CHD. Several flavonoids significantly

inhibited the platelet adhesion, aggregation and secretion. Proposed mechanisms for their activity in reducing platelet aggregation includes inhibition of synthesis of TXA2 in platelets and leukotrienes in neutrophils, regulation of expression and activity of adhesion molecules, inhibition of cyclic AMP phosphodiesterase and NADPH. Selected flavonoids, such as quercetin, kaempferol, and myricetin were shown to be effective inhibitors of platelet aggregation in dogs and monkeys. One study showed that flavonoids are powerful antithrombotic agents *in vitro* and *in vivo* because of their inhibition of the activity of cyclooxygenase and lipoxygenase pathways. Platelet aggregation contributes to both the development of atherosclerosis and acute platelet thrombus formation, followed by embolization of stenosed arteries. Activated platelets adhering to vascular endothelium generate lipid peroxides and oxygen free radicals, which inhibit the endothelial formation of prostacyclin and nitrous oxide. It was shown that tea pigment can reduce blood coagulability, increase fibrinolysis, and prevent platelet adhesion and aggregation. It is well known that arachidonic acid, which is released in inflammatory conditions, is metabolized by platelets to form prostaglandin, endoperoxides, and thromboxane A2, leading to platelet activation and aggregation. The main antiaggregatory effect of flavonoids is thought to be by inhibition of thromboxane A2 formation. Flavonoids affect arachidonic acid metabolism in different ways. Some flavonoids specifically block cyclooxygenase or lipoxygenase, whereas others block both enzymes. *In vitro* studies showed that flavonoids bind to platelet membranes and may therefore have an accumulative effect over time.

Mechanism of anti-apoptotic activity

The significant cardioprotective effect of flavonoids may be partly imparted to their anti-apoptotic properties. Apoptosis is a cell - autonomous mechanism (suicide) consisting of a complex series of ordered biochemical events regulated by a set of genes. Myocardial infarction arises from diverse causes, including cumulative injury from ischemic episodes, which ultimately leads to cell death, much of which is accomplished through apoptosis. Flavonoids inhibit apoptosis in the myocardial tissues and salvage normal cells. Further it is comprehensible that flavonoids inhibit apoptosis, the mechanism behind this remains obscure.

Mechanism of anti-microbial activity

The antibacterial activity of flavonoids is being increasingly documented. Crude extracts from plants with a history of use in folk medicine have been screened *in vitro* for antibacterial activity by many research groups. Flavonoid-rich plant extracts from species of *Hypericum*, *Capsella* and *Chromolaena* have been reported to possess antibacterial activity. Many other phytochemical preparations with high flavonoid content have also been reported to exhibit antibacterial activity. Propolis has been analysed on many occasions too, and samples containing high concentrations of flavonoids are frequently reported to show antibacterial activity.

Mechanism of anti-angiogenic activity

Naringenin is a type of flavonoid which is abundantly found in tomatoes and oranges. Naringenin has possessed some biological activities like hypolipidemic, hypocholesterolemic, and antagonistic to estrogenic; antihypertensive; and anti-inflammatory exercises. Qunyi *et al*. reported the antiangiogenic role of naringenin in HUVEC cell lines. And later it was revealed that naringenin slowed down a few stages in cell expansion, migration, cell cycle arrest, apoptosis, and tube development of endothelial cells. These impacts were joined by the VEGF inhibition initiated by the intervening of the VEGF/KDR pathway. Afterward, Chen *et al*. reported the antiangiogenic activity of naringenin in HUVEEC and zebrafish. They revealed that naringenin showed potential antiangiogenic activity by inhibiting SIV formation in zebrafish embryos.

The availability within food of flavonoids

1. From various foods researchers have begun to identify and quantify flavonoids.
2. When flavonoid content in the flesh and peel of apples are compared then it is find out that peel contains more concentration of flavonoids.
3. Quercetin is one of the best-described flavonoid and the Quercetin is found in numerous fruits and vegetables but the major dietary sources include onion, red apples, red wine, tea, cranberry, kale, hot peppers and broccoli{38} .
4. United States Department of Agriculture gives a list of quercetin aglycone content in foods based on High-Performance liquid chromatography (HPLC). Studies on green and black tea shows that they both contained approximately 200 mg/cup for a typical brew.
5. Flavonoid content in various vegetables, fruits, and beverages was found.

When glycoside form extracted from plants was hydrolyzed to determine the parent compound, and performed high-performance liquid chromatography (HPLC) to separate and quantify the flavonols, the highest concentrations of flavonols were found in vegetables like onions and broccoli, fruits like apples, cherries, and berries, and drinks such as tea and red wine.

Table 2: Quercetin content in foods

Food source	Quercetin content
Dry Green Tea Leaves	255.55 mg/100 gm
Dry Black Tea Leaves	204.66 mg/gm
Raw onions	13.2 7mg/gm
Raw spinach	4.86 mg/gm
Apple with skin	4.42 mg/gm
Raw broccoli	3.21 mg/gm
Red wine	0.84 mg/gm

Future research and development Programmes

Flavonoids have received much attention in the literature over the past 10 years and a variety of potential beneficial effects have been elucidated. However, a number of studies carried out involved *in vitro* and *in silico* studies. Therefore, further studies are needed so that the usefulness of flavonoids in the diet could be improved for better human health. The study of flavonoids is complex because of the heterogeneity of the different molecular structures and the scarcity of data on bioavailability. Furthermore, insufficient methods are available to measure oxidative damage *in vivo* and the measurement of objective end points remains difficult. There is a need to improve analytic techniques to allow the collection of more data on absorption and excretion. Data on

the long-term consequences of chronic flavonoid ingestion are especially scarce. A number of reports have emphasised that molecular docking studies are required to identify the potential molecules of flavonoids for their usage in the treatment of various ailments in the human health system. The interactions of flavonoids with receptor molecules during the treatment of acute and chronic diseases are an important area of future research. More and more research is needed to discover new flavonoids from nature's bounty so that this will replace the use of synthetic medicines which are harmful to the body. In this context there is a need of research and development programmes involving *in vivo* studies which will give a hopeful and safe picture for the future. Currently, the intake of fruit, vegetables and beverages containing flavonoids is recommended, although it is too early to make recommendations on daily flavonoid intakes.

Conclusion

Some epidemiologic studies suggest a cardioprotective role of flavonoids against coronary heart disease. One large clinical study indicated that flavonoids may reduce mortality from coronary heart disease. Various cohort studies indicated an inverse association between flavonoid intakes and coronary heart disease mortality. Recent studies have shown the ability of flavonoids to alter transport of vitamin C, as well as to alter function of an enzyme called ascorbate oxidase, which converts vitamin C into a non-vitamin form (monodehydroascorbate). While we do not yet know the full meaning of these relationships, it is clear that the transport and cycling of vitamin C is flavonoid related. This association makes sense to us, since so many foods high in vitamin C (such as our top five W H foods for vitamin C are papaya, bell peppers, broccoli, brussels sprouts, and strawberries) are also high in flavonoids. Flavonoids act as powerful antioxidants, and have often proven so *in vitro*. Flavonoids being a major constituent of the dietary intake could be key in fighting several chronic degenerative diseases. However, the degree to which flavonoids are absorbed, and thus its bioavailability, leaves some doubt as to whether flavonoids can exert an antioxidant effect *in vivo*. Further study is needed to elucidate the effects of flavonoids within the body and the degree and rate of absorption, but in particular, the primary forms of flavonoids found in human plasma, its metabolites, need to be used in the studies. The study of flavonoids is complex because of the heterogeneity of the different molecular structures and the scarcity of data on bioavailability. Furthermore, insufficient methods are available to measure oxidative damage *in vivo* and the measurement of objective endpoints remains difficult. There is a need to improve analytic techniques to allow collection of more data on absorption and excretion. Data on the long-term consequences of chronic flavonoid ingestion are especially scarce. Procyanidins have been considered antinutritional compounds because they can interact with proteins and inhibit certain enzymes. It is necessary to have more information to evaluate the adverse effects of these compounds. In conclusion, the *in vivo* studies that have been performed do give a hopeful picture for the future. Currently, the intake of fruits and vegetables containing flavonoids is recommended.

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