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REVIEW ARTICLE

A REVIEW STUDY ON THE PHARMACOLOGICAL EFFECTS AND MECHANISM OF ACTION OF FLAVONOIDS

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ABSTRACT

Flavonoids are the natural poly phenolic secondary metabolites of plants widely distributed in plant kingdom, which are responsible for the various colors of bark, leaves, flowers, fruits and seeds. Flavonoids are now considered as an indispensable component in a variety of nutraceuticals, pharmaceuticals, medicinal and cosmetic preparations. They possess potentially antioxidant property and versatile fields of the health benefits. Moreover flavonoids have sedative, antidepressant, anticonvulsant, anti-proliferative, anti-inflammatory, anti-microbial, anticancer, cardioprotective, antihypertensive, antiulcerogenic, antidiabetic and hepatoprotective activities. These pharmacological effects are mainly due to their antioxidant property. Also flavonoids have effect on mammalian enzymes like protein kinases, alpha-glucosidase and aldose reductase, and thereby they regulate multiple cellular signaling pathways that are altered during disease conditions. A number of flavonoids are available in the market as pharmaceutical products because of its potent and extended pharmacological activities, higher safety profile, low toxicity and cost effective bulk production. The present review is focused on the pharmacological and biological effects, and mechanism of action of flavonoid compounds along with slightly lighting other significant properties.

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INTRODUCTION

Flavonoids are a diverse group of phytonutrients (plant chemicals) found in almost all fruits, vegetables, tea, coffee, cocoa and certain other beverages. Along with carotenoids, they are responsible for the glowing colors in fruits and vegetables. They have miscellaneous favorable biochemical and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease (AD), atherosclerosis, etc(Burak, 1999; Ovando, 2009; Lee ,2009). Flavonoids are associated with a broad spectrum of health promoting effects and are an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications. This is because of their antioxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme functions. They are also known to be potent inhibitors of several enzymes, such as xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase and phosphoinositide 3-kinase (Metodiewa, 1997; Hayashi T, et al. 1988; Walker E,et al. 2000).

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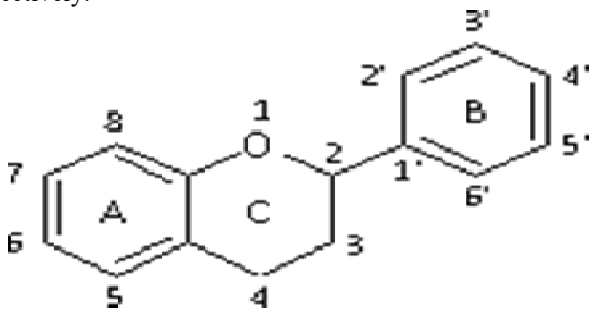
Flavonoids have several subgroups, which include chalcones, flavones, flavonols and isoflavones. These subgroups have unique major sources. For example, onions and tea are major dietary sources of flavonols and flavones. Flavonoids have been ascribed positive effects on human and animal health. Currently there are about 6000 flavonoids that contribute to the colorful pigments of fruits, herbs, vegetables and medicinal plants. Kumar &Pandey (Kelly, 2002) reviewed the protective roles of flavonoids against human diseases as well as their functions in plants. Recently Panche et al.,(Kumar, 2013) while reviewing AD and current therapeutic methods, discussed in detail uses of flavonoids as plant secondary metabolites for the treatment of AD and the mechanisms involved. Flavonoids are the largest group of phytonutrients. In recent years, scientists have turned to various flavonoids to explain some of the health benefits associated with diets rich in fruits and vegetables, according to the Linus Pauling Institute. Diets rich in flavonoid-containing foods are sometimes associated with cancer, neurodegenerative and cardiovascular disease prevention. However, it is not yet clear whether the flavonoids themselves are responsible. Onions, tea, strawberries, kale, grapes, brussels sprouts, citrus fruit, parsley, and many spices are just a few natural foods rich in flavonoids, according to Louis Premkumar, a professor of pharmacology at

Southern Illinois University School of Medicine and author of "Fascinating Facts about Phytonutrients in Spices and Healthy Food". Flavonoids are the most abundant polyphenols in human diet representing about 2/3 of all those once ingested. Like other phytochemicals currently, it is not possible to determine their number precisely, even if over 4000 have been identified. In fruits and vegetables, they are usually found in the form of glycosides and sometimes as acylglycosides, while acylated, methylated and sulfate molecules are less frequent in lower concentrations. They are water-soluble and accumulate in cell vacuoles. This study includes enlisting of the broad spectrum pharmacological and biological activities of different flavonoids,to the point focusing of molecular level mechanisms of action along with slightly insight on composition, classification and physicochemical properties. The entire above studied are arranged in case-specific logics of nature of activities, organs or other significant related parameters.

Basic structure and composition of flavonoids: The flavonoid's basic structure is a skeleton of diphenylpropane namely- two benzene rings (ring A and B, see Figure) linked by a three-carbon chain that forms a closed purine ring (heterocyclic ring containing oxygen, the C ring) with benzene A ring. Therefore, their structure is also referred to as C6-C3-C6. In most cases, B ring is attached to position 2 of C ring but it can also bind in position 3 or 4; together with the structural features of the ring B and the patterns of glycosylation and hydroxylation of the three rings which make the flavonoids one of the larger and more diversified groups of phytochemicals. Polyphenolic flavonoids are found in nature andthey are potent antioxidants depending on both of the structural characteristics and the pattern of glycosylation. Due to this antioxidant property flavonoids can show large spectrum of biological activities. In plants, flavonoids can occur with or without sugar moieties. The biochemical activities of flavonoids and their metabolites depend on their chemical structure and the relative orientation of various moieties on the molecule. A light overview of the classifications of bioactive flavonoids and their structure and examples are arranged below Figure (Fig.- 1) and (Table-1), respectively.



A short insight of physical and chemical properties of different flavonoids: Flavonoids are crystalloid substances with certain melting points such asrutin- 242^0C, quercetin - 316^0C. Cathechins, leucoanthocyanidins, flavanes, isoflavanes, flavanones, flavanonoles are colorless crystals, flavones, flavonoles, chalcones and aurones,which are yellow or vividly yellow. Anthocyanins are sap pigments and the actual colour of the plant organ thatis determined by the pH of the sap. For example, the blue colour of the corn flower and the red of roses are due to the same glycosides and both of these plants upon hydrolysis with hydrochloric acid yield cyanidin hydrochloride.

Changes of anthocyanin color depend on pH; their color is red and bluein acidic and alkaline media, respectively. As a general rule, glycosides are water-soluble as well as soluble in alcohols but flavonoid glycosides are soluble in diluted alcohols and hot water. Aglycones are, for the most part, soluble in polar organic solvents. On the other hand, when they have at least one free phenolic group, they dissolve in alkaline hydroxide solutions. Flavonoid aglycones are soluble in diethyl ether, acetone and alcohols, and almost are insoluble in water. Flavanoles (cathechins) are optically active and among four optical isomers (D- and L- cathechins, D- and L-epicathechins), only L-epicathechin possesses P-vitaminic activity. When flavanones and flavononones are treated with oxidants, they turn into chalcones and leucocyanidins. Flavonoid O-glycosides may be treated with acid, alkaline or fermentative hydrolysis. Rutin occurs as a yellow crystalline powder and soluble in alkali but they are slightly soluble in water. Rutin on hydrolysis yields quercetin, rhamnose and glucose while hesperidin yields hesperetin (or methyl eriodictyol), rhamnose and glucose. C-linkage between aglycone and sugar is very strong. Therefore, hydrolysis of C-glycosides is carried out with Killiani'sreagent of concentrated HCl and acetic acid.

They can be subdivided into different subgroups depending on the carbon of the C ring on which B ring is attached, and the degree of unsaturation and oxidation of the C ring. Flavonoids in which B ring is linked in position 3 of the ring C are called isoflavones; those in which B ring is linked in position 4, neoflavonoids, while those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the basis of the structural features of the C ring. These subgroups are flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins. Finally, flavonoids with open C ring are called chalcones.

Pharmacological and biological activities of flavonoids: The broad spectrum pharmacological and biological activities of flavonoids were first evidenced by Hungarian Physiologist Albert Szent – Gyorgyii in 1938. He reported the citrus peel flavonoid having preventive action against capillary bleeding and fragility tests (Narayana, ,2001). These activities are diversified and include antioxidant, anti-aging, anti-inflammatory, anti-cancer, mutagenic, anti-atherosclerosis, cardio-protective, anti-ulcerogenic, hepato-protective, anti-microbial, anti-viral, anti-allergic, vasodilatory, hypolipidaemic and anti-platelet. They are also used in the treatment of various neurodegenerative diseases and theywere reported to exert their effects by inhibiting various types of enzymes like hydrolases, hyalouronidase, lipase, alkaline phosphatase, cAMPphosphodiesterase, α-glucosidase, kinase and other. The aforementioned effects and the mechanism of actions of flavonoids are illustrated below regarding the nature of the activities, pattern of organ systems or other logical and significant parameters.

Antioxidant Activity: Flavonoids possess many biochemical properties but the best described property of almost every group of flavonoids is their capacity to act as antioxidants. The antioxidant activity of flavonoids is mainly due to their ability to donate hydrogen and depends upon the arrangement of functional groups. The configuration, substitution, and total number of hydroxyl groups substantially influence several mechanisms of antioxidant activity such as radical scavenging and metal ion chelation ability (Pandey, 2012).

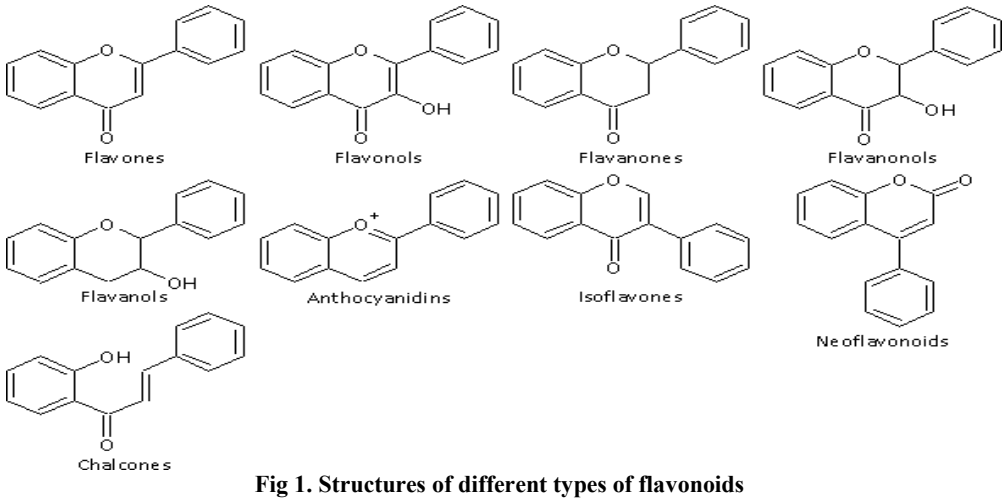


Fig 1. Structures of different types of flavonoids

Table 1. Tabulation of different sub groups of flavonoids with examples and natural sources

Flavonoid sub groups	Examples	Natural Sources
1) Flavones	Luteolin, apigenin and tangeritin .	Celery, Parsley, Red peppers, Chamomile,Mint and ginkgo biloba
2) Flavonols	Kaempferol, Quercetin, Myricetin and Fisetin.	Vegetables (Onions, kale, lettuce, tomatoes) Fruits (apples, grapes, berries) Tea, Red wine.
3) Flavanones	Hesperitin, naringenin and eriodictyol.	Citrus fruits (lemon, oranges and grapes)
4) Flavanonols	Dihydrokaempferol, Taxifolin	Bananas,Apples, Blueberries, Peaches andPears.
5) Flavanols or catechins	(+)-epicatechin and (-)-epicatechin, (+)-catechin and (-)-catechin.	Apples, tea
6) Anthocyanins	Cyanidin, Delphinidin	Cherry, grapes, strawberries
7) Chalcones	Phloretin, glucosidephloridzin (phloretin 2′-0-β-glucopyranoside), and chalconaringenin.	Apples, tomatoes, shallots, bean sprouts, potatoes,licorice
8) Flavonoid Glycosides	Astragalin, Rutin	Archetypal plant
9) Flavonolignans	Silibinin	ChEBI
10) Isoflavones	Genistein, Daidzein	kudzu root, red clover, and alfalfa sprouts.
11) Aurones	Leptosidin, Aureusidin	Snapdragon and cosmos.
12) Leucoanthocyanidins	Teracacidin	Anadenantheraperegrina N. burbidgeae
13) Neoflavonoids	Coutareagenin, Dalbergin	Calophylluminophyllum

Table 2. Antiviral activity of various types of flavonoids

Flavonoid	Virus, against which act	Flavonoid	Virus, against which act
Quercetin	Rabies virus, herpesvirus parainfluenza virus, polio virus, mengo virus, and pseudorabies virus	Naringin	Respiratorysyncytialvirus
Rutin	Parainfluenzavirus, influenzavirus, and potato virus	Morin	Potatovirus
Apigenin	Immunodeficiency virusinfection, Herpes simplex virus type,and Auzesky virus	Galangin	Herpes simplexvirustype

The B ring hydroxyl configuration is the most significant determinant of scavenging of reactive oxygen species (ROS) and RNS because it donates hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, thus stabilizing them and giving rise to a relatively stable flavonoid radicals(Cao, 1997). Antioxidant mechanisms include (1) suppression of ROS formation, (2) scavenging ROS and (3) upregulation or protection of antioxidant defenses (Halliwell,1998;Mishra, 2013). Some of the effects mediated by them may be the combined result of radical scavenging activity and the interaction with enzyme functions. They inhibit the enzymes involved in ROS generation, i.e., microsomal monooxygenase, glutathione S-transferase, mitochondrial succinoxidase, NADH oxidase, and so forth (Brown, 1998).

Hepatoprotective activity: Several flavonoids including catechin, apigenin, quercetin, naringenin, rutin and venoruton are reported for their hepato-protective activities (Tapas, 2008). Different chronic diseases such as diabetes may lead to development of hepatic clinical manifestations. Glutamate-cysteine ligase catalytic subunit (Gclc) expression, glutathione and ROS levels are reported to be decreased in liver of diabetic mice. Anthocyanins have drawn increasing attention because of their preventive effect against various diseases. Zhu et al., demonstrated that anthocyanin cyaniding 3-O-glucoside (C3G) increases hepatic Gclc expression by increasing cAMP levels to activate protein in turn upregulatescAMP response element binding protein (CREB) phosphorylation to promote CREB-DNA binding and increase Gclc transcription. Increased Gclc expression results in a decrease in hepatic ROS levels and proapoptotic signaling. Furthermore, C3G treatment lowers hepatic lipid peroxidation, inhibits the release of proinflammatory cytokines, and protects against the development of hepatic steatosis (Zhu, 2012).

Anti-inflammatory activity: Inflammation is a normal biological feedback response to tissue injury, microbial pathogen infection and chemical irritation. Inflammation is initiated by the migration of immune cells from blood vessels and the release of mediators at the site of damage.

This process is followed by recruitment of inflammatory cells, the release of reactive oxygen species(ROS), RNS, and pro-inflammatory cytokines to eliminate foreign pathogens and repairing injured tissues (Pan, 2010). Some flavonoids significantly affect the function of the immune system and inflammatory cells (Middleton, 1992). A number of flavonoids such as hesperidin, apigenin, luteolin, and quercetin are reported to possess anti-inflammatory and analgesic effects. Flavonoids may affect specifically the function of enzyme systems critically involved in the generation of inflammatory processes, especially tyrosine and serine-threonine protein kinases (Hunter,1995). The inhibition of kinases is due to the competitive binding of flavonoids with ATP at catalytic sites on the enzymes. These enzymes are involved in signal transduction and cell activation processes. It has been reported that flavonoids are able to inhibit the expression of isoforms of inducible nitric oxide synthase, cyclooxygenase and lipooxygenase, which are responsible for the production ofa great amount of nitric oxide, prostanoids, leukotrienes, and other mediators of the inflammatory process such as cytokines, chemokines, or adhesion molecules (Tunon,2009).

Flavonoids also inhibit phosphodiesterases involved in cell activation. Anti-inflammatory effect of flavonoid is on the biosynthesis of protein cytokines that mediates adhesion of circulating leukocytes to sites of injury. Certain flavonoids are potent inhibitors of the production of prostaglandins, a group of powerful pro-inflammatory signaling molecules (Manthey, 2000). Reversal of the carrageenan induced inflammatory changes has been observed with silymarin treatment. Quercetin inhibits mitogen stimulated immunoglobulin secretion of IgG, IgM, and IgA isotypes in vitro22 (Cumella,1987). Several flavonoids are reported to inhibit platelet adhesion, aggregation and secretion significantly at 1–10 mM concentration (Beretz, 1988). The effect of flavonoid on platelets has been related to the inhibition of arachidonic acid metabolism by carbon monoxide (Corvazier,1985). Alternatively, certain flavonoids are potent inhibitors of cyclic AMP phosphodiesterase, and this may in part explain their ability to inhibit platelet function.

Antibacterial Activity: Flavonoid rich plant extracts from different species have been reported to possess broad spectrum antibacterial activity (Mishra, 2011; Pandey,2010). A large number of flavonoids including apigenin, galangin, flavone and flavonol glycosides, isoflavones, flavanones and chalcones have been shown to possess potent anti-bacterial activity .They have multiple cellular targets and in molecular level and they form complex with proteins through nonspecific forces such as hydrogen bonding and hydrophobic effects as well as by covalent bond formation which inactivate microbial adhesions, enzymes, cell envelope transport proteins, and so forth (Mishra,2009).Catechins, the most reduced form, are reported for their *in-vitro* antibacterial activity against *Vibrio cholerae*, *Streptococcus mutans*, Shigella, and other bacteria (Borris,1996;Moerman,1996). They inactivate cholera toxin in *Vibrio cholera* and inhibit isolated bacterial glucosyltransferases in *S. mutans*, perhaps owing to complex activities and epigallocatechin which are known to inhibit DNA synthesis in *Proteus vulgaris.* Mori et al.,(Mori,1987) suggested that the B ring of the flavonoids may intercalate or form hydrogen bond with the stacking of nucleic acid bases and further lead to inhibition of DNA and RNA synthesis in bacteria.

Another study revealed inhibitory activity of quercetin, apigenin, and 3,6,7,3 ,4 - pentahydroxyflavone against *Escherichia coli* DNA gyrase(Ohemeng,1993).

Antifungal Activity: Number of flavonoids isolated from peel of tangerine orange when tested for fungistatic activity towards *Deuterophomatracheiphila* showed promising activity. Chlorflavonin was the first chlorine containing flavonoid type antifungal antibiotic produced by strains of *Aspergilluscandidus* (Tencate,1973).

Antiviral Activity: Flavonoids having antiviral activity have been recognized since the 1940s. Search of available, effective and less side effect drug against human immunodeficiency virus (HIV) is the need of time. Most of the works related with antiviral compounds revolve around inhibition of various enzymes associated with the life cycle of viruses. Structure activity relationship between flavonoids and their enzyme inhibitory activity has been observed. Gerdin and Srensso(Gerdin,1983) demonstrated that flavan-3-o1 was more effective than flavones and flavonones in selective inhibition of HIV-1, HIV- 2 and similar immunodeficiency virus infections. Baicalin, a flavonoid isolated from *Scutellariabaicalensis* (Lamieaceae) inhibits HIV-1 infection and replication. Baicalein and other flavonoids such as robustaflavone and hinokiflavone have also been shown to inhibit HIV-1 reverse transcriptase (Cushnie,2005). Antiviral activity of various types of flavonoids isillustrated in the table below (Table- 2).

Anticancer activity: Dietary factors, fruits and vegetables having flavonoids play an important role in the prevention of cancers (Ho, 1994). Flavonolquercetin, is inversely associated with the incidence of cancer of the prostate, lung, stomach and breast. Numerous anticancer mechanisms have been proposed of flavonoids including i) down regulation of mutant p53 protein, ii) cell cycle arrest, iii) tyrosine kinase inhibition, iv) inhibition of heat shock proteins, v) estrogen receptor binding capacity and vi) inhibition of expression of Ras proteins. Flavonoids regulate the expression of mutant p53 protein to nearly undetectable levels in human breast cancer cell lines (Davis,2000).Quercetin was the first tyrosine kinase inhibiting compound tested in a human phase I trial (Ferry,1996). Heat shock proteins form a complex with mutant p53, which allows tumor cells to bypass normal mechanisms of cell cycle arrest. These proteins also allow for improved cancer cell survival under different bodily stresses. Flavonoids are known to inhibit the production of heat shock proteins in several malignant cell lines including breast cancer, leukemia and colon cancer. Recently, it has been shown that the flavanolepigallocate-chin-3-gallate inhibited fatty acid synthase (FAS) activity and lipogenesis in prostate cancer cells, an effect strongly associated with growth arrest and cell death (Brusselmans,2003).Quercetin is known to produce cell cycle arrest in proliferating lymphoid cells. In addition to antineoplastic activity, quercetin exerted growth-inhibitory effects on several malignant tumor cell lines in vitro such as P-388 leukemia cells, gastric cancer cells (HGC-27, NUGC-2, NKN-7, and MKN-28) and colon cancer cells (COLON 320 DM).

Effects on Central Nervous System: Flavonoids are stated to produce sedation, anxiolytic, anti-cholinesterase and anti-convulsanteffects by binding with the benzodiazepine site on the GABA (A) receptor.

It possesses anti-depressant and anti-parkinsonism effects which happen by the inhibition of monoamine oxidase A or B. These substances also exert neuro-protective effect in vitro cells and animal models by weakening of oxidative stress, regulation of kinase signal cascade and apoptotic neuronal death. Baicalein is a flavonoid protects neuronal tissue damage and facilitates cognitive behavioral performance by inhibitory action on MMP-9.

Effects on Cardiovascular System: Flavonoid antioxidants have been stated to increases the endothelial nitric oxide release and relax blood vessels in conditions like hypertension and stroke. It is revealed that hesperidin and naringin are effective in age related increases in blood pressure. Similarly,epicatechin, quercetin and avicularin are reported to have effect in cardio protective activity.

Effects on Dyslipidemia: Flavonoids are reported to be preventive in hepatic steatosis and dyslipidemia in experimental models by either decreasing fatty acid synthesis or by increasing fatty acid oxidation. Quercetin, Isoquercitrin, biochanin- A and formononetin are reported to have effective action against controlling cholesterol in experimental models.

Effects on Diabetes: Many flavonoids are reported to have anti-diabetic action. They exert anti-diabetic effect by acting on the biological targets including aldose reducatse and α-glycosidase involved in the occurrence of diabetes mellitus type –2. Diabetic complications like neuropathy, retinopathy and nephropathy are caused by an increase of polyol pathway flux, activation of protein kinase C isomers, advanced glycation end-products (AGEs) formation, increase in hexosamine pathway flux. In insulin-dependent diabetes mellitus, Quercetin reported to increase the insulin release by improving the regeneration of pancreatic islets cell. In non-insulin-dependent diabetes mellitus, Fiestin was shown to increase calcium uptake from islets cells.

Effects on Respiratory Tract: The antioxidant, anti-inflammatory, anti-allergic and antispasmodic actions of Flavonoids account for its beneficial effect in respiratory tract disease. Many flavonoids including apigenin, silibinin and wogonin are reported to have airway mucus secretion modulation activity.

Effects on Digestive Tract: Flavonoids are recounted to have beneficial effect in treating digestive tract problem.Many researches reveal that flavnoids are having anti-ulcer and anti-diarrheal action and exhibit antiulcer activity by inhibiting cAMP, Protein Kinase, COX and protein phosphorylation.

Conclusion

Flavonoids are important class of secondary metabolites which have been found to exhibit many important pharmacological and biological activities including antioxidant, anti- aging, antinflammatory, anticancer, mutagenic, antiatherosclerosis, cardioprotective, antiulcerogenic, hepatoprotective, antimicrobial, antiviral, antiallergic, vasodilatory, hypolipidaemic and antiplatelet activities and they are also used in the treatment of various neurodegenerative diseases. They were reported to exert their effects by inhibiting various types of enzymes like hydrolases, hyalouronidase, lipase, alkaline phosphatase, cAMPphosphodiesterase, α-glucosidase and kinase. Some examples of such significant flavonoids are Luteolin, apigenin, tangeritin, Kaempferol, Quercetin, Myricetin , Fisetin, hesperitin, naringenin , eriodictyol, Dihydrokaempferol, Taxifolin, (+)-epicatechin , (-)-epicatechin, (+)-catechin and (-)-catechin, Cyanidin, Delphinidin, Astragalin, Rutin, Silibinin, Genistein, Daidzein etc. These compounds are used for the curative purposes and are helpful for the mankind. With the advancements in the field of science and technology, flavonoids are being exploited for various purposes. Mechanism of actions of flavonoids is antioxidant activity due to their ability of the electron donation and dependent upon the arrangement of functional groups. Flavonoids also have biochemical effects, which inhibit a number of enzymes such as aldose reductase, xanthine oxidase, phosphodiesterase, Ca(+2)-ATPase, lipoxygenase and cycloxygenase. In addition, they also have a regulatory role on different hormones like estrogens, androgens and thyroid hormones. We would like to conclude that flavonoids are useful for plants, human as well as animals. They can be employed for pharmaceuticals purposes due to its presence in almost all the vegetables and medicinal plants. Therefore, more attention is required in testing those compounds for the exploration of expanded era of curative poses ofthe human diseases.

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