IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2018 Vol.:12, Issue:3

Review of Flavonoids: A Medical Boon in Various Disease

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

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Submission: 27 May 2018
Accepted: 2 June 2018
Published: 30 June 2018

Keywords: Flavonoids, Solvent extraction, pharmacological action

ABSTRACT

Flavonoids are the secondary metabolites of the plant. Chemically they are polyphenolic. They are synthesized by the polypropanoid pathway. Capers, apples, tea plant, onions, red grapes, citrus fruits, curly kale, broccoli, cherries, raspberry, cranberry, and blueberry etc. are the richest source of flavonoids. Flavonoids are classified into six groups which are flavones, flavonols, flavanones, flavan-3-ols, isoflavones, and anthocyanidins. Extraction of flavonoids can be done by techniques like sequential solvent extraction, microwave assisted extraction (MAE), Supercritical fluids extraction etc. Flavonoids show various pharmacological action likes cardiotonic activity, hepatoprotective activity, antiulcer activity etc. Flavonoid derivatives such as silymarin, apigenin was found to be effective against microcystin LR-induced hepatotoxicity. Some flavanoid acts as free radical scavengers such as quercetin and silybin. Significant anti-inflammatory and analgesic effects were observed in Hesperidin, a citrus flavonoid. Cell growth was suppressed by flavonoids such as kaempferol, catechin, taxifolin, and fisetin thus found effective in tumors. Antiviral activity against two strains of type 1 and type 2 Herpes simplex virus was found to be effective by flavonoid polymer of molecular weight 2,100 daltons. Flavones and Flavonones are the class of flavonoids which are found to be effective in the selective inhibition of HIV-1 and HIV-2. A number of enzymes such as *aldose reductase, lipooxygenase, adenosine deaminase* etc can be inhibited by flavonoids. Flavonoids regulate estrogen, androgen levels in humans.

INTRODUCTION

Flavonoids are secondary metabolites. Chemically they are polyphenol. They are synthesized by the polypropanoid pathway with phenylalanine as starting molecule. Flavonoids exhibit several biological effects such as [1,2]. They also inhibit enzymes such as *aldose reductase* and *xanthine oxidase* etc. They found to be potent antioxidants and have free radical scavenging abilities. Many have antiallergic, antiviral actions and some provide protection against cardiovascular mortality[3,4]. Capers, apples, tea plant, onions, red grapes, citrus fruits, curly kale, broccoli, cherries, raspberry, cranberry, and blueberry etc. are the richest source of flavonoids out of which citrus fruit has high concentrations of flavanoid. They are involved in the synthesis of pigmentation in flowers. For example, blue color results from the presence of anthocyanin (delphinidin-based) in petals. Anthocyanins are, also, responsible for the autumn's colors in many plant species and photoprotection of leaf's cells. Their ability to act as natural UV filters comes from their absorption in 280-315 nm regions. Different plant flavonoids have the role in protection from microbes and insects. Some of them (isoflavones, flavones, and flavanones) are recognized as constitutive antifungal plant agents. Others (flavonoids, tannins, etc) play role in plant's protection from insects and mammalian herbivor.[5] Besides, many flavonoids have an ability to alter enzymatic and chemical reactions, and thus impact on human health positively or negatively.[6]

FLAVONOIDS STRUCTURE AND CLASSIFICATION:

They are classified as followed :

1. Flavones

2. Flavonols

3. Flavanones

4. Flavan-3-ols

5. Isoflavones

6. Anthocyanidins[7,8].

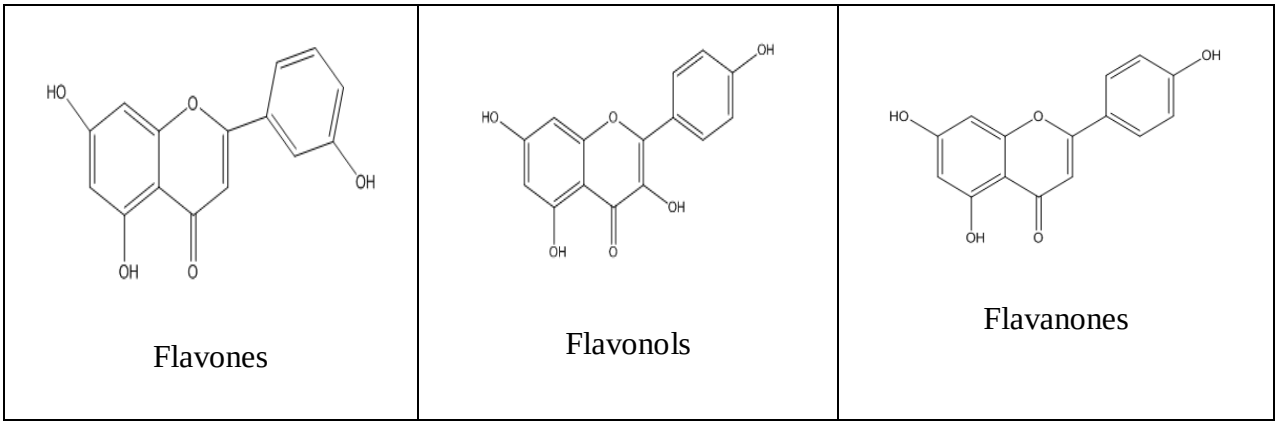

Figure 1: Chemical structure of flavones,flavonols,and flavanones

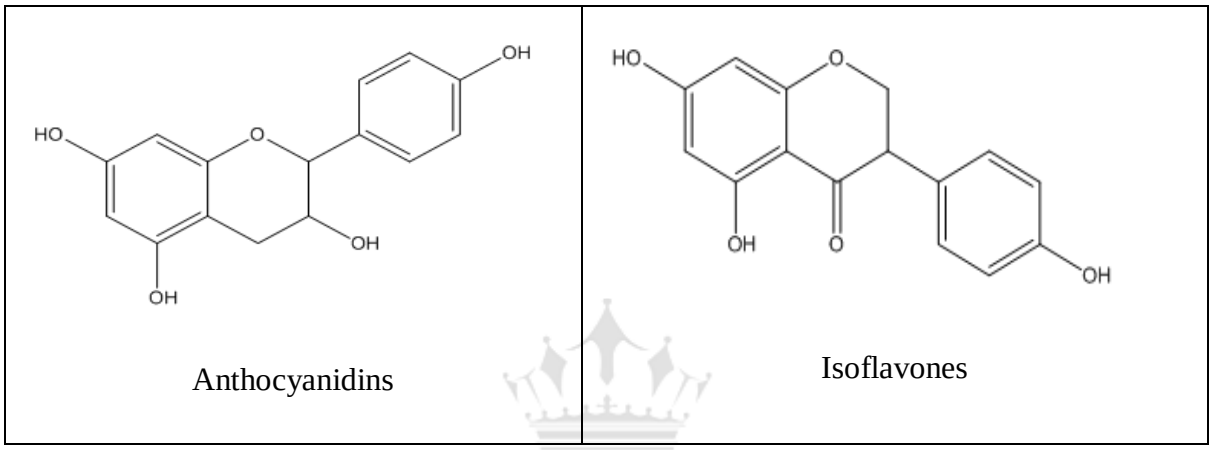

Figure 2: Chemical structure of anthrocyanidins and isoflavonones

Flavonoids occur as glycosides and methylated derivatives. Aglycone part of flavonoid consists of a benzene ring condensed with a six-membered ring, this six-membered ring carries a phenyl ring as a substituent at 2-position. This Six-member ring condensed with the benzene ring is either α-pyrone or its dihydro derivative (flavanols and flavanones). The substituent at the second position of benzenoid divides the flavonoid class into flavonoids and at the third position of benzenoid divides the flavonoid class into isoflavonoids. Flavonols differ from flavonones by hydroxyl group at the 3-position and a C2=C3.[7] It is also found as Methyl ethers and acetyl esters of the alcohol group. The glycosidic linkage is normally located at 3 or 7 positions. Glycones can either be L-rhamnose, D-glucose, glucor-rhamnose, galactose or arabinose. [9]

BIOSYNTHESIS OF FLAVONOIDS:

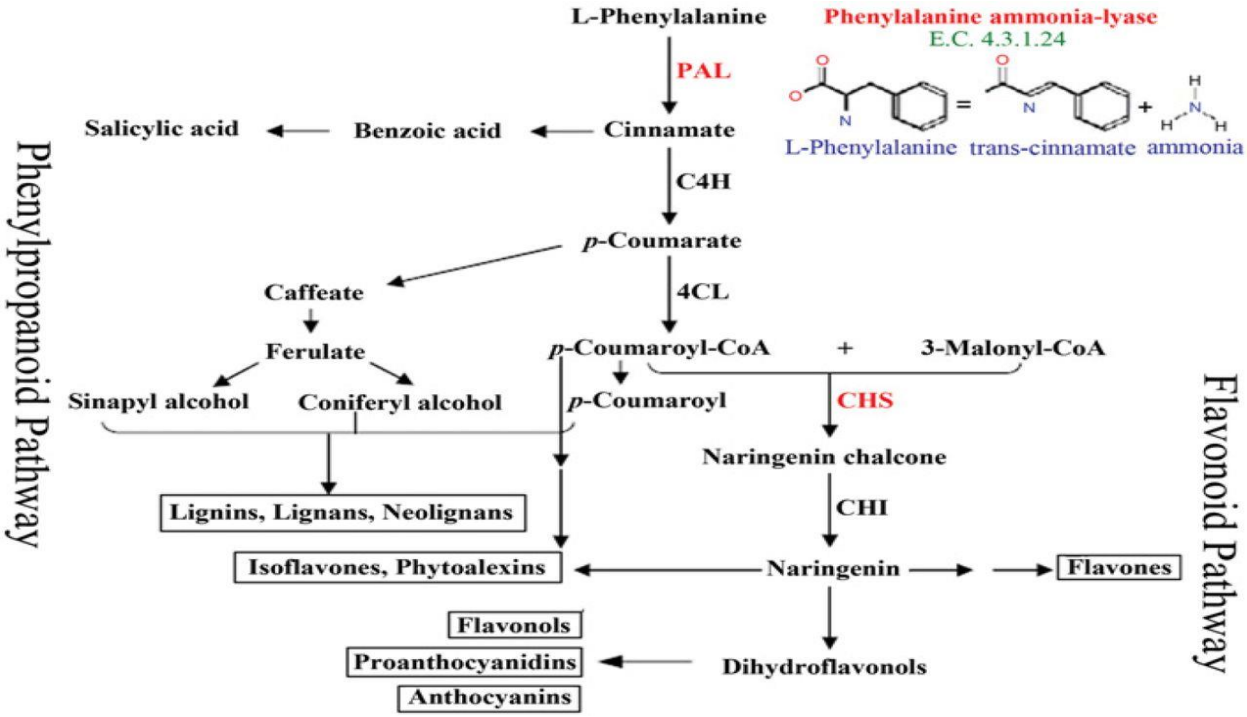

Figure 3 Biosynthesis of flavonoids

EXTRACTION:

- When Flavonoids are collected from plant material in fresh or nondried form; It (particularly glycosides) can be degraded by enzyme action.

- When dry plant material is used it is ground into a powder.

- For extraction, the solvent is chosen based on the function of the type of flavonoid required and polarity.

- Less polar flavonoids are extracted either by using chloroform, dichloromethane, diethyl ether, or ethyl acetates such as isoflavones, flavanones, methylated flavones, and flavonols and more polar aglycones with alcohols or alcohol-water mixtures.

- If the content of flavonoid is more in plant material then it is extracted by simple direct solvent extraction. It is generally first extracted with hexane, to remove lipids and then extracted with ethyl acetate or ethanol to get flavanoid.

- Sequential solvent extraction is a convenient and frequently used procedure. For example, in this, it is first extracted with dichloromethane which will extract flavonoid aglycones and less polar material and then with alcohol which will extract flavonoid glycosides and polar constituents.

- Flavan-3-ols generally extracted directly with water or alcohol-water mixture such as catechins, proanthocyanidins.

- Supercritical fluid extraction (SFE) can also be used. Due to fewer viscosities and high diffusion rates of supercritical fluids, it is ideal for the extraction of flavanoid. It has advantages such as less solvent consumption, selectivity, and less thermal or chemical degradation over the other method.[11,12]

- Ultrasound-assisted extraction can also be used with mixtures of immiscible solvents: such as hexane with methanol-water (9:1), For example, extraction of Brazilian plant Lychnophora ericoides (Asteraceae). In this hexane and aqueous alcohol is used. In hexane phase less polar sesquiterpene lactones and hydrocarbons are concentrated and in aqueous alcohol phase flavonoids and more polar sesquiterpene lactones are concentrated.[13]

- Microwave-assisted extraction (MAE) can also be used for the extraction of various compounds from different matrices.[14] It is the simplest technique which can be completed in a few minutes. In this sample suspended in the solvent, by using either closed vessel or open cell and to this Microwave energy is applied.[15]

PHARMACOLOGICAL EFFECTS OF FLAVONOIDS:

1. CNS Activity: Synthetic flavonoids displace[3H] flumazenil binding to membranes from rat cerebellum for examples 6-bromoflavone and 6-Bromo-3'-nitro- flavones, which indicates they are selectivity for the BZ-Omega receptor subtype. Results indicate these flavonoids shows anxiolytic properties which are either similar or superior to that of diazepam .[16]

2. Cardiotonic activity: Isoquercetin was available with the brand name ‘flavoce’, useful in the treatment of atherosclerosis and Flavone dilate coronary artery was available under the brand name ‘Chromocor'. 3-methyl quercetin shows a positive chronotropic effect on guinea pig right atrium and shows the antiarrhythmic effect on left atrium.[17]

3. Hepatoprotective activity: By using several substances including phalloidin (toxic obtained from mushroom, *Amanita phalloides*), CCl_4, galactosamine, ethanol, and other compounds, Acute and potentially lethal injury are developed in the liver. Flavonoids hepatoprotective activity possesses. In a study, the flavonoid derivatives like silymarin, apigenin, quercetin, and naringenin, found to be effective on microcystin LR-induced hepatotoxicity, silymarin was most effective among them.[18] The flavonoid such as rutin and venoruton tested on experimental cirrhosis, showed regenerative and hepatoprotective effects.[19]

4. Antiulcer activity: Flavonoid glycosides of *Ocimum basilicum* (Labiatae) decreased ulcer index; in aspirin-induced ulcers in rats and inhibited gastric acid and pepsin secretions.[20] Dose-dependent gastric damage produced by acidified ethanol in rats has been inhibited by quercetin, rutin, and kaempferol when they are administered intraperitoneally (25-100 mg/kg).[21]

5. Antioxidant activity: In animal cells accidental or deliberate free radical is produced. The release of free radical leads to a lot of human diseases[22,23]. Flavonoids such as quercetin, kaempferol, morin, myricetin and rutin show antioxidants activity hence, found to be effective against inflammation, allergy, viral infection, cancer etc. In reperfusion ischemic tissue damage, quercetin and silybin show the protective effect by acting as free radical scavenger [24-26.] Flavonoids shows the scavenging activity in the following order: myricetin > quercetin > rhamnetin > morin > diosmetin > naringenin > apigenin > catechin > 5,7- dihydroxy-3',4',5'-trimethoxy flavone > robinin > kaempferol > flavone. [27]

6. Effect on heat shock proteins: Against physiological stress such as heat shock, heavy metals and glucose starvation Heat shock proteins (HSP) have been recognized. Recent progress has revealed the role of HSPs in various diseases. HSP27 involved in acquiring resistance against tumor cells, hyperthermic and chemotherapeutic treatment. Aberrant expression of HSP causes various autoimmune diseases. The expression of HSP27, HSP47, and HSP72/73 was inhibited by flavonoids.[28]

7. Anti-inflammatory activity. A number of reports show that flavonoids can inhibit *cyclo-oxygenase* (COX) and *lipoxygenase* activity (LO) thus can modulate arachidonic acid metabolism.[29] Among flavones/flavonols kaempferol, quercetin, myricetin, fisetin was reported to possess LO and COX inhibitory activities.[30] Hesperidin, a citrus flavonoid, possesses significant anti-inflammatory and analgesic effects [31]. Recently apigenin, luteolin, and quercetin have been reported to exhibit anti-inflammatory activity .[32]

8. Antineoplastic activity: Number of flavonoids shows antineoplastic activity. Detailed studies have revealed that quercetin exerted a dose-dependent inhibition of cell growth and colony formation. The flavonoids kaempferol, catechin, taxifolin and fisetin also suppressed cell growth[33-35, 36, 37] On screening antileukemic efficacy on human promyelocytic leukemia HL-60 cells of genistein, an isoflavone was found to have the strong effect than other 28 naturally occurring and synthetic flavonoids. Out of the 14 flavonoids tested 2',6'-diacetoxy -4,4' –dimethoxy dihydrochalcone found most potent against murine and human cancer cell lines. [39- 43]

9. Effects on blood vessels: Quercetin and rutin used in several pharmaceuticals which are used for the treatment of capillary fragility and phlebosclerosis. The activities of certain flavonoids in inhibiting capillary permeability and Arthus phenomenon were found to be in the following order, hesperetin > rutin > quercetin > naringenin > kaempferol > isoquercitol [44- 47]. Beneficial physiological effects on capillaries of Flavonoids is due to free hydroxyl groups at 3, 3' and 4' positions. Quercetin, 3-methyl quercetin, troxerutin, fisetin, dihydroquercetin and flavone inhibit aggregation of platelets. Nobeletin and sinensetin might be useful in the dietary control of high blood viscosity syndrome as *In vitro* they decreased erythrocyte aggregation and sedimentation [44-51]. Orally administered flavonoids weakly inhibit the vascular permeability and prevent pulmonary hemorrhage. Capillary fragility in mice is reduced by Acacetin at 25-100 mg/kg oral dose and Acacetin reduced vascular permeability at 50-100 mg/kg [50,51].

10. Antimicrobial activity: Flavonoids and esters of phenolic acids were investigated for their antibacterial, antifungal and antiviral activities. All samples were active against the fungal and gram-positive bacterial test strains and most showed antiviral activity [52].

i) Antibacterial Activity*:* Number of flavonoids shows antibacterial activity. 25 out of 182 flavonoid studies were found to be active against many bacteria. [52]. Quercetin has been reported to completely inhibit the growth of *Staphylococcus aureus.* [53].

ii) Antifungal Activity**:** Fungistatic activity towards Deutero phoma tracheiphila was shown by flavonoids isolated from the peel of a tangerine orange. Antifungal antibiotic activity against *Aspergillus candidus* was shown by Chlorflavonin; the first chlorine-containing flavonoid [54].

iii) Antiviral Activity**:** Antiviral activity against 11 types of viruses possess by Quercetin, morin, rutin, dihydroquercetin (taxifolin), apigenin, catechin, and hesperidin etc[55]. The

antiviral activity appears to be associated with the non-glycosidic compounds, and hydroxylation at the 3-position is apparently a prerequisite for antiviral activity. It has been observed that against *Herpes simplex* virus type 1 flavonols are more active than flavones.The order of importance of such flavones was galangin>kaempferol>quercetin [56.] Antiviral activity against two strains of type 1 and type 2 Herpes simplex virus was found to be effective by flavonoid polymer of molecular weight 2,100 daltons. Flavones and Flavonones are the class of flavonoids which are found to be effective in the selective inhibition of HIV-1 and HIV-2.[57-59]

11.Antidiabetic effects: Regeneration of pancreatic islets and probably increases insulin release in streptozotocin-induced diabetic rats is showed by Flavonoids, especially quercetin.[60] It is also revealed that quercetin stimulate insulin release and enhanced Ca^{2+} uptake from isolated islets cell which suggests a place for flavonoids in non-insulin-dependent diabetes.[61,62]

12. Anti-Atherosclerotic effects: Foam cells formation takes place due to the rapid uptake of oxidatively-modified LDL via a scavenger receptor. Some radical species are directly scavenged by flavonoids as it is acting as a chain-breaking antioxidant. [63] The ability of quercetin is to protect LDL against oxidative modification has shown a significant protective effect.[64] A Japanese study reported that flavonoid intake and total plasma cholesterol concentrations are inverse correlated.[65]

13. Anti-thrombogenic effects: Endothelial formation of prostacyclin and nitrous oxide is inhibited by lipid peroxides and oxygen free radicals generate by platelets adhering to vascular endothelium. It was shown in the 1960s that tea pigment can reduce blood coagulability, increase fibrinolysis, and prevent platelet adhesion and aggregation [66]. Flavonoids such as quercetin, kaempferol, and myricetin were tested in dogs and monkey and were found to be effective inhibitors of platelet aggregation[67]. Flavonols maintaining the proper concentration of endothelial prostacyclin and nitric oxide because they directly scavenge free radicals [68]. *In vitro* and *in vivo* study it is reported that flavonoids inhibit the activity of *cyclooxygenase* and *lipoxygenase* pathways hence it is a powerful antithrombotic agent. [69]

14. Cardioprotective effects: Recent show flavonoids show potential health benefits arising from the antioxidant activity. Due to the antioxidant activity, it results in the high propensity to transfer electrons, chelate ferrous ions, and scavenge reactive oxygen species[70]. Due to these properties, flavonoids are potential protectors against chronic cardiotoxicity caused by the

cytostatic drug doxorubicin. Doxorubicin is a very effective antitumor agent but its clinical use is limited by the occurrence of a cumulative dose-related cardiotoxicity, resulting in, for example, congestive heart failure (negative inotropic effect). In a recent report, the cardiotoxicity of doxorubicin on the mouse left atrium has been inhibited by flavonoids, 7-monohydroxyethylrutoside and 7',3',4'- trihydroxyethylrutoside[71-73].

BIOCHEMICAL EFFECTS OF FLAVONOIDS:

(i) On enzymes:

Flavonoids inhibit a number of enzymes such as aldose reductase[74], xanthine oxidase[75], Phosphodiesterase[76], Ca^{2+} A TPase[77], lipo-oxygenase[78], and cyclooxygenase[79]. Flavonols like quercetin, myricetin and kaempferol inhibit the activity of the adenosine deaminase of endothelial cells, while flavones are inactive [80]. Flavonoids inhibit intracellular Ca^{2+}elevation by reducing phospholipase-C activity [81].

(ii) On hormones:

Hormones activity is regulated by flavonoids, as it binds to 17 beta-hydroxysteroid dehydrogenases, which further regulates estrogen and androgen levels in humans and by binding to 3 beta-hydroxysteroid dehydrogenase, which further regulates progestin and androgen levels in humans [82]. Quercetin, myricetin, rutin, kaempferol affect the transport, metabolism, and action of thyroid hormones. [83].

EXAMPLES OF FLAVONOIDS:

1) Onion: *Allium cepa* (Onion) possess a high content of flavonoid compounds (mainly quercetin and its conjugates) and sulfur compounds (i.e. thiosulphinates) [84] *Allium cepa* has many pharmacological properties such as Anti-microbial activity, Antioxidant activity, Anti-carcinogenic activity, Anti-mutagenic activity, Anti-diabetic potential etc. [85]

2) Berries: Cyanidin is anthocyanin pigment found in many berries (grapes, blackberry, blueberry, cherry, cranberry, raspberry etc.), apples, plums and red cabbage. It exerts antioxidant, anti-inflammatory and anticancer effects. It may have an important role in future cancer treatment[86].

3) Mandarin: Mandarin (*Citrus reticulata* Blanco) is very popular Citrus fruit and its production constantly increases throughout the world flavonoids, especially polymethyl avones and flavanones (hesperidin, narirutin and naringin) are identified in Citrus pulp as well as in peel [87,88].

4) Tea: A cup of brewed black tea contains approximately 268 mg of flavonoids, and a cup of green tea contains around 316 mg of flavonoids The best effective polyphenol in tea is a compound noted as epigallocatechin gallate and catechin [89-91]

5) Apple: Apples contain flavonoids like quercetin which inhibits enzymes like alpha-amylase and *alpha-glucosidase*. Since these enzymes are involved in the breakdown of complex carbohydrates into simple sugars, your blood sugar has fewer simple sugars to deal with when these enzymes are inhibited. Apple and wine is inversely associated with death from coronary heart disease in postmenopausal women in a study of nearly 35,000 women in Iowa[92].

CONCLUSION

Flavonoids are the secondary metabolites of a plant. Chemically they are polyphenol. They can be synthesized by the polypropanoids pathway. Capers, apples, tea plant, onions, red grapes, citrus fruits, curly kale, broccoli, cherries, raspberry, cranberry, and blueberry etc. are the richest source of flavonoids. Flavonoids are broadly classified into six class such as flavones, flavonol, flavaones etc. It can be extracted by various different extraction techniques. Flavonoids possess various activity like anti-inflammatory, antihepatotoxic, cardiotonic activity, antioxidant, anti-ulcer actions etc. Flavones and Flavonones are the class of flavonoids which are found to be effective in the selective inhibition of HIV-1 and HIV-2. Thus flavonoids found to be a medical boon in various disease.

ACKNOWLEDGMENT

We authors would like to thank our principal Dr. Mohan Kale. Our college member like the librarian, computer experts, and all other persons who help us in the direct or indirect way to whom we fail to notice. Our sincere thanks to almighty God for their continuous monitoring of our work till its completion.

REFERENCES

1. Bors W, Heller W, Michel C, Saran M, Flavonoids as antioxidants: Determination of radical scavenging efficiencies.Methods Enzymol., 1990;186:343-55.
2. Colerige Smith PO, Thomas P, Scurr JH, Dormandy JA.Causes of various ulceration, a new hypothesis. *Br Med J* 1980;296:1726-7.
3. Clack W, Mackay E. Effect of flavonoid substances on histamine toxicity, anaphylactic shock and histamine enhanced capacity to dye. *J Allergy* 1950;21:133-147.
4. Hertog MGL, Hollman PCH, Katan MB, KIomhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. *Nutr Cancer*1993;20:21-9.
5. Harborne J., Williams C. (2000): Advances in flavonoid research since 1992. Phytochemistry55: 481-504
6. Beecher G. (2003): Overview of dietary flavonoids: Nomenclature, Occurrence and Intake1. J. Nutr. 133.
7. Manach C., Scalbert A., Morand C., Rémésy C., Jiménez L. (2004): Polyphenols: food sources and bioavailability. American Journal of Clinical Nutrition 79 (5): 727-747
8. Dahan A., Altman H. (2004): Food-drug interaction: grapefruit juice augments drug Bio- availability mechanism, extent, and relevance. European Journal of Clinical Nutrition 58: 1-9
9.Hansteen B, Flavonoids. A class of natural products of high pharmacological potency *Biochem Pharmacol* 1983;32: 1141-8.
10. Ali, M., Chaudhary, A., and Ramachandran, R., New pterocarpans from Oroxylum Indicum stem bark, Indian Journal of Chemistry, 1999;38B, 950.
11. Bevan, C.D., and Marshall, P.S., The use of supercritical fluids in the isolation of natural products, Nat. Prod. Rep., 1994;11, 451.
12. Jarvis, A.P. and Morgan, E.D., Isolation of plant products by supercritical fluid extraction, Phytochem. Anal., 1997;8, 217.
13. Sargenti, S.R. and Vichnewski, W., Sonication and liquid chromatography as a rapid technique for extraction and fractionation of plant material, Phytochem. Anal., 2000;11, 69.
14. Ganzler, K., Szinai, I., and Salgo, A., Effective sample preparation method for extracting biologically active compounds from different matrices by a microwave technique, J. Chromatogr., 1990.520,257.
15. Kaufmann, B. and Christen, P., Recent extraction techniques for natural products: microwave-assisted extraction and pressurized solvent extraction, Phytochem. Anal., 2002;13, 105.
16. Griebel G, Perrault G, Tan S, Schoemarker H, Sanger DJ.Pharmacological studies on synthetic flavonoids: comparison with diazepam. *Neuropharmacology* 1999;38:965-77.
17. Lackeman GM, Claeys M, Rwangabo PC, Herman AG, V lietinck A. Chronotropic effect of quercetin on guinea pig right atrium. *J Planta Med* 1986;52:433-9.
18. Carlo GD, Autore G, Izzoaa et al. Inhibition of intestinal motility and secretion by flavonoids in mice and rats; structure-activity relationships. J Pharm Pharmcol 1993; 45:1045-1059.
19. Lorenz W, Kusche J, Barth H, Mathias CH. An action of several flavonoids on the enzyme of histidine metabolism in vivo. In: Cz Maslinski (ed). Histamine. Pennsylvania: Hutchinson and Ross; 1994; 265-269.
20. Alarcon DL, Martin MJ, Locasa C, Motilva V. Antiulcerogenic activity of flavonoids and gastric protection. Ethnopharmacol 1994; 42:161-170.
21. Izzo AA, Carlo GD, Mascolo N, Capasso F, Autore G. Effect of quercetin on the gastrointestinal tract. Phyto Ther Res 1994; 8:179-185.
22. Wegener T, Fintelmann V. Flavonoids and Bioactivity. *Wein Med Wochem Schr* 1999;149:241-7.
23. Ares JJ, Outt PE. Gastroprotective agents for the prevention of NSAID- induced gastropathy. *Curr Pharm Des* 1998; 4:7-36.
24. Santos AC, Vyemura SA, Lopes JL, Bazon JN, Mingatto FE, Curtic. Effect of naturally occurring flavonoids on lipid peroxidation and membrane permeability transition in mitochondria. *Free Radic Biol Med* 1998;24:1455-61.
25. Hillwell B. Free radicals, antioxidants and human disease: curiosity, cause or constipation? *Lancet* 1994;344:721-4.
26. Fraga CG, Mactino US, Ferraro GE, Coussio JF, Boveris A. Flavonoids as antioxidants evaluated by *in Vitro* and *in situ* liver chemiluminescence. *Biochem Med Metabol BioI* 1987;36:717-20.

27.Ratty AK. Effects of flavonoids on nonenzymatic lipid peroxidation: structure-activity relationship. *Biochem Med Metabol BioI* 1988;39:67-79.
28. Laughton MJ, Halliwell B, Evans PJ, Hoult JRS. Antioxidant and pro-oxidant actions of the plant phenolics quercetin, morin, glossypol and myricetin effects on lipid peroxidation, hydroxyl radical generation and bleomycin dependent damage to DNA. *Biochem Pharmacol* 1989;38: 2859-65.
29. Ferrandiz ML, Alcaraz MJ. Anti-inflammatory activity and inhibition of arachidonic acid metabolism by flavonoids. Agent and Actions 1991; 32(3/4):283-288.
30. Kim HP, Mani I, Iversen L, Ziboh VA. Effects of naturally occurring flavonoids and bioflavonoids on epidermal cycloxygenase and lipoxygenase from guinea pigs. Prostag Leukot Essent Fatty acids 1998; 58:17- 24.
31. Jachak SM. Natural products: Potential source of COX inhibitors. CRIPS 2001; 2(1):12-15.
32. Shahid F, Yang Z, Saleemi ZO. Natural flavonoids as stabilizers. J Food Lipids 1998; 1:69-75.
33. Kontruck SJ, Radecki T, Brozozowski T, Drozdowicz D, Piastucki I, Muramatsu M, Tanaka M, Aihara H. Anti-ulcer and gastroprotective effects of solon, a synthetic flavonoid derivative of sophorandin. Role of endogenous prostaglandins.*Bur J Pharmac* 1986;125:185-92.
34. Izzo AA, Dicarlo G, Mascolo N, Capasso F, Autore G. Antiulcer effects of flavonoids. Role of Endogenous PAF. *Phytotherapy Res* 1991;8:179-81.
35. Murakami S, Muramatsu M, Otomo S. Gastric H+/K+ATPase inhibition by catechins. *J Pharm Pharmacol* 1992; 44:926-8.
36. Kim HK, Namgoong SY, Kim HP. Biological actions of flavonoids-I. *Arch Pharmacol Res* 1993;16:18-27.
37. Gill B, Sanz MJ, Terencio MC, Ferrandiz ML, Bustos G, Paya M. The flavonoids. *Life Sci* 1994;54:333-9.
38. Hirano T, Gotoh M, Oak K. Natural flavonoids and lignans are plant cytostatic agents against Human Leukemic HL- 60 cells. *Life Sci* 1994;55:1061-9.
39. Wei H, Tye L, Bresnick E, Birt DF. Inhibitory effect of Apigenin, a plant flavonoid on epidermal ornithine decarboxylase skin tumour promotion in mice. *Cancer Res*1990;50:499-502.
40. Block G, Patterson B,Sufai A. Fruits, vegetables and cancer prevention: A review of the epidemiological evidence. *Nutr Cancer* 1992;18:1-29.
41. Hirose M, Hoshiya T, Akagi T, Takalashi S, Hara Y. Effect of green tea catechin in a rat multi-organ carcinogenesis model. *Carcinogenesis* 1993;14:1549-53.
42. Hertog MGL, Hollman PCH, Katan MB, Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. *Nutr Cancer* 1993;20:21-29.
43. Hirano T, Oka K, Akiba M. Antiproliferative effects of synthetic and naturally occurring flavonoids on turner cells of the human breast carcinoma cell line, 2R- 75-1. *ResCommun Chem Pahol Pharmacal* 1989;64:69-78.
44. Felicia VS, Najla G, Ann PC, Madeleine M, Keneeth KC. Inhibition of Human Breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices. *Nutr Cancer* 1996;26:167-81.
45. Catherine C, Malc S, Esther HL, Vadimir A, Krutorslaikh, *et al*. Lack of tumour-Promoting effects of flavonoids: studies on rat liver preneostatic foci and on *In vivo* and *In vitro* gap junctional intercellular communication. *Nutr Cancer* 1996;26:251-63.
46. Paul P, Ritra J, Ritva S, Mackku H, Lyly T, Eero P, Arpo A. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *Am J Epidemiology* 1997;146:223-30.
47. Fritz B, Tobias S, Albrecht K, Chaelotte B, Kent C, *et al*. Selected novel flavones inhibit the DNA binding or the DNA religation step of eukaryotic topoisomerase-I. *J BioI Chem* 1996;271:2262-70.
48. Versantvoort CH, Schuurhuis GJ, Pinedo HM, Bekman CA, Kuiper CM, *et al*. Genistein modulates the decreased drug accumulation in non-p-glycoprotein-mediated multidrug-resistant tumor cells. *Br J Cancer* 1993;68:939-46.
49. Griffith LA, Ballow A. The fate of orally and parenterally administered flavonoids in the mammal, the significance of biliary excretion. *Angiologica* 1972;9:162-74.
50. Mc Ewan AJ, Mc Ardle CS. Effect of Hydroxyethylrutosides on blood oxygen levels and venous insufficiency symptoms in varicose veins. *Br Med J* 1971;2:138-41.
51. Wenner A, Leu HJ, Spycher M, Brunner U. Ultrastructural changes of capillaries in chronic venous insufficiency. *Exp Cell BioI* 1980;48:1-14.
52. Wild C, Fasel J. Effect of a flavonoid on the capillary resistance of the rectal mucosa in hepatic cirrhosis. *Am J Product* 1969;20:60-2

53.Havsteen B. Flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol 1983; 32(7):1141-1148.
54. Tencate JW, Van Haeringen NJ, Gerritsen J, Glasius E. Biological activity of a semisynthetic flavonoid, Rutosine: Light- scattering and metabolic studies of human red cells and platelets. *Clin Chem* 1973; 19:31-5.
55. Selway JWT. Antiviral activity of flavones and flavans. In: Cody V, Middleton E, Harborne JB (eds). Plant flavonoids in biology and medicine: Biochemical, pharmacological and structure-activity relationships. New York:Alan R Liss, Inc; 1986; 521-536.
56. Thomas PRS, Nash GB, Dormandly JA. White cells accumulation independent legs of patients with venous hypertension: A possible mechanism for trophic changes in the skin. Br Med J 1988; 296:1673-1695.
57. Loewenstein WR. Junctional Intercellular communication and the control of growth. Biochem Biophys Acta 1979; 560:1-65.
58. Ng TB, Huang B, Fong WP, Yeung HW. Anti-human immunodeficiency virus (anti-HIV) natural products with special emphasis on HIV transcriptase inhibitors. Life Sci 1997; 61:933- 949.
59. Gerdin B, Srensso E. Inhibitory effect of flavonoids on increased microvascular permeability induced by various agents in rat skin. Int J Micro Cir Clin Exp 1983; 2:39-46.
60. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C 2003; 135:357- 364.
61. Hif CS, Howell SL. Effects of epicatechin on rat islets of langerhans. Diabetes 1984; 33:291-296.
62. Hif CS, Howell SL. Effects of flavonoids on insulin secretion and 45Ca+2 handling in rat islets of langerhans. J Endocrinol 1985; 107:1-8.
63. De-whallely C, Rankin SM, Houct JRS et al. Flavonoids inhibit the oxidative modification of low density lipoprotein by macrophages. Biochem Pharmacol 1990; 39:1743-1750.
64. Fuhrman B, Lavy A, Aviram M. Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoproteins to lipid peroxidation. Am Soc Nutr 1995; 61:549- 554.
65.Arai Y, Watanabe S, Kimira M et al. Dietary intake of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr 2000; 130:2243-2250.
66. Lou FQ, Zhang MF, Zhang XG, Liu JM, Yuan WL. A study on tea pigment in prevention of atherosclerosis. Chin Med J (Engl) 1989;102:579-583.
67. Osman HE, Maalej N, Shanmuganayagam D, Folts JD. Grape juice but not orange or grapefruit juice inhibits plate activity in dogs and monkeys. J Nutr 1998; 128:2307-2312.Tapas et Trop J Pharm Res September 1099 2008; 7 (3)
68. Gryglewski RJ, Korbut R, Robak J, Swips J. On the mechanism of antithrombotic action of flavonoids. Biochem Pharmacol 1987; 36:317-322.
69. Alcaraz MJ, Ferrandiz ML. Modification of arachidonic metabolism by flavonoids. J Ethnopharmacol 1987; 21:209-229.
70. Kandaswami C, Middleton E. Free radical scavenging and antioxidant activity of plant flavonoids. In: Armstrong D ed. Free radicals in diagnostic medicine. Ed 2. New York: PlenumPress; 1994. 351-376.
71. Lackeman GM, Claeys M, Rwanagabo PC, Herman AG, Vlietinck A. Chronotropic effect of quercetin on guinea pig right atrium. J Planta Med 1986;52:433-439.
72. Huesken BCP, Dejong J, Beekman B, OnderwaterRCA. Flavonoids as cardioprotective agents Cancer Chemotherapy Pharmacol 1995; 37:55-62.
73. Bast A, Kaiserov H, den Hartog GJM, Haenen GRMM, van der Vijgh WJF. Protectors against doxorubicin-induced cardiotoxicity: Flavonoids.Cell Biol Toxicol 2007; 23:39-47.
74. Jager W, Zembsch B, Wolschann P, Pittenauer E, Senderavicz AM, *et al*. Metabolism of the anticancer drug flavopiridol, a new inhibitor of cyclin-dependent kinases in rat liver. *Life Sci* 1998;62:1861-73.
75. Koch HP, Jager W, Groh U, Plank G. *In vitro* inhibition of adenosine deaminase by flavonoids and related compounds. New insight into the mechanism of action of plant phenolics. *Methods Find Exp Clin Pharmacol* 1992;14:413- 17.
76. Alcaraz MJ, Ferrandiz ML. Modification of arachidonic metabolism by flavonoids. *J Ethnopharmacol* 1987;21:209-29.

77. Scerola D, Barbarini G, Grosso A, Bona S, Perissoud D. Flavonoids and hepatic cyclic monophosphates in liver injury. *Boll 1st seiroter Milan* 1984;63:77-82.
78. Baumann J, Von Brucchau Sen F, Wurm G. Flavonoids and related compounds as inhibition of arachidonic acid peroxidation. *Prostaglandins* 1980;20:627-39.
79. Varma SD, Kinoshita JH. Inhibitory effects of plant polyphenols on rat liver glutathione-S-transferase. *Biochem Pharmacol* 1976;25:2505-10.
80. Nagai T, Miyaichi Y, Tomimori T, Suzuki Y, Yamaha H. Antiviral activity of two flavonoids from Tanacetum microphyllum. *Antiviral Res* 1992;19:207-16.
81.Musci I, Pragathi M. The nutritional significance of flavonoids, some physiological consideration. *Experientia* 1985;41:930.
82.Noro T, Oda Y, Miyasa, Ueno A, Fukushim S. Inhibition of adenosine deaminase activity of aortic endothelial cells by selected flavonoids. *Chem Pharm Bull* 1983;31:3984-91.
83. Petkov E, Nickdor N, Uzunov P. Inhibitory effects of flavonoids on xanthine oxidase. *Planta Med* 1981;43:183-87.
84 G. Griffiths, L. Trueman, T. Crowther, B. Thomas and B. Smith, "Onions-A global benefit to health," Phytother. Res. Vol.16: pp 603-615 2002.
85. K. Herrmann, " On the occurrence of flavonol and flavone glycosides in vegetables," Z. Lebensm. Unters. F. A. 1988; 186; 1-5.
86. Fimognari C., Berti F., Nusse M., Cantelli Forti G., Hrelia P. (2005): *In vitro* antitumor activity of cyanidin-3-O-glucopyranoside. Chemotherapy 51: 332-335
87. Mouly P., Gaydou E.M., Auff ray A. (1998). Simultaneous separation of flavanone glycosides and polymethoxylated flavones in citrus juices using liquid chromatography. J. Chromatogr. 800:171-179
88.Oufedjikh H., Mahrouz M., Lacroix M., Amiot M.J., Taccini M.(1998). The influence of gamma irradiation on fl avonoidscontent during storage of irradiated Clementine. Radiat. Phys.Chem. 52: 107-112Pellegrini N., Serafi ni M., Colombia B., Del Rio D., Salvatore S.,
89.Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. Transplantation 1998; 66:147–52.
90.De Groot H. Reactive oxygen species in tissue injury. Hepatogastroenterol 1994; 41: 328–32.
91. Kerry NL, Abbey M. Red wine and fractionated phenolic compounds prepared from red wine inhibits low density lipoprotein oxidation in vitro. Atherosclerosis 1997; 135: 93–102.
92. Arts I, D. J, Harnack L, Gross M, Folsom A. Dietary catechins in relation to coronary heart disease among postmenopausal women. Epidemiology. 2001;12:668–675