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FLAVONOIDS: THERAPEUTIC POTENTIAL OF NATURAL PHARMACOLOGICAL AGENTS

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ABSTRACT: Flavonoids are the natural compound widely distributed in plant kingdom, it is responsible for the various colors exhibited by bark, leaves, flowers, fruits and seeds of plants. They are the secondary metabolites of plant with significant antioxidant properties. Flavonoids have antioxidant, sedative, antidepressant, anticonvulsant, anti-proliferative, anti-inflammatory, anti-microbial, anticancer, cardioprotective, antihypertensive, antiulcerogenic, antidiabetic and hepatoprotective activity. Many researchers have revealed that the above mentioned pharmacological actions are mainly due to its antioxidant property. Flavonoids have effect on mammalian enzymes like protein kinases, alpha-glucosidase and aldose reductase, thereby regulate multiple cellular signaling pathway that were altered during disease conditions. Various researches on flavonoids are in progress due to its versatile health benefits. En number of flavonoids are available in the market as pharmaceutical products because of its cost effective bulk production and health benefits. The present review is focused on the classification, metabolism, pharmacological and biological actions and flavonoid supplement available in market.

INTRODUCTION: Flavonoids belong to a group of natural substances with low molecular weight phenolic compound, derived from secondary metabolites found in fruit, vegetables, nuts, seeds, grains, bark, roots, stems, flowers, tea and wine.[1] Flavonoids have been identified, many of which are responsible for the attractive colors of flowers, fruit, and leaves. More than 4000 flavonoids are found in nature.

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Classification and chemical structure:

Flavonoids occur both in freestate and as glycosides. The aglycone part of Flavonoids consists of a benzene ring (A) condensed with a six membered ring (C), which in the 2-position carries a phenyl ring (B) as a substituent. Flavonoids are characterized by C6-C3-C6.[2] Structurally flavonoids can be classified according to the benzopyrone saturation and different substitution on the ring. The Flavonoids are categorized into flavonols, flavones, catechins, flavanones, anthocyanidins and isoflavonoids. The structures of the major classes are shown in **Fig. 1**. Flavonoids can be classified into various classes.[3]

Flavonols - Quercetin, Kaempferol, Myricetin, Fisetin

Flavones - Luteolin, Apigenin

Flavanones - Hesperetin, Naringenin

Flavonoid Glycosides - Astragalin, Rutin

Flavonolignans - Silibinin

Isoflavones - Genistein, Daidzein

Anthocyanidins - Cyanidin, Delphinidin

Aurones - Leptosidin, Aureusidin

Leucoanthocyanidins - Teracacidin

Neoflavonoids - Coutareagenin, Dalbergin

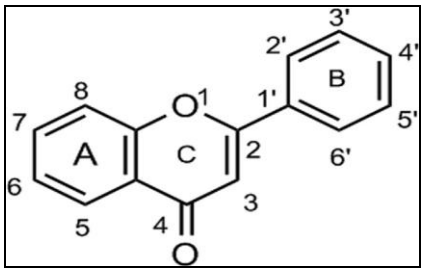

FIG. 1: BASIC STRUCTURE OF FLAVONOID

The biological activity of Flavonoids was first evidenced by Hungarian Physiologist Albert Szent – Gyorgyii in 1938. He reported the citrus peel flavonoid having preventive action against capillary bleeding and fragility.[4] Flavonoids have broad spectrum of biological activity.

They have been shown to exert antimicrobial, antiviral, antiatherosclerosis, cardioprotective, antiulcerogenic, antineoplastic, mutagenic, antidiabetic, anti-inflammatory, antioxidant, anti-aging, antihepatotoxic, antihypertensive, hypolipidaemic and antiplatelet activities.

Functions of Flavonoids in plant:

TABLE 1: FUNCTIONS OF FLAVONOIDS IN PLANT

Part of the plant	Function
Flower (Anthocyanins)	Help in pollination
Leaves	Protect plant from - Fungal infection - UV radiations
Fruits , seeds, bark, root	Photosensitisation Energy transfer Morphogenesis

Metabolism of Flavonoids: [5]

Many dietary flavonoids occurs in O- glycosides, the common glycosides are glucose, galactose, arabinose and rhamnose. The presence of sugar moieties resists the Beta hydrolysis by pancreatic enzyme. 2β-endoglycosidase in small intestine is capable of flavonoid glycoside hydrolysis. Lactase phlorizin hydrolase and nonspecific cytosolic enzyme are reported to deglycosylate flavonoid and allow for conjugation reaction. The bioavilability of flavonoid vary with the location and structure of sugar moiety in the flavonoid. Absorption depend upon the dosage, diet, sex difference and the microbial population in the colon. Liver plays major role in the absorption of flavonoid that is absorbed in small intestine than in colon. Metabolism of Flavonoid depend upon the gut flora. The pyrone ring in the Flavonoid is cleaved by microflora, result in the formation of phenyl acetic acid, phenyl propionic acid and inert by products.

During pyrone ring breakage the sugar moiety in Flavonoid will be removed by microflora, and result in aglycone moiety of Flavonoid that can easily penetrate through intestinal wall. HPLC technique in analysis of Flavonoid in urine and feaces provide evidence of methylation, hydroxylation, O-methylation, sulfation, glucuronisation which occurs as a byproduct primarily of Liver and intestine microbial transformation.

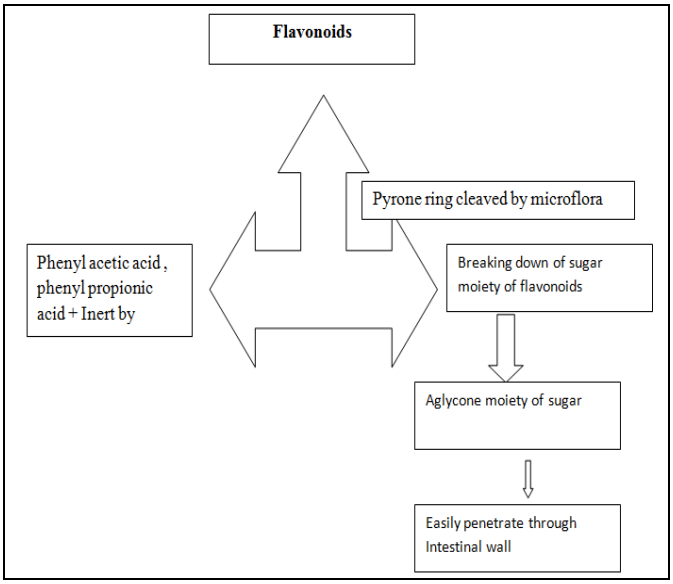

FIG. 2: METABOLISM DEPENDS ON GUT FLORA: DIAGRAMMATIC REPRESENTATION

Pharmacological action of Flavonoid:

Flavonoids have been reported to have wide range of biological activities, it includes antioxidant, anti-inflammatory, anticancer, cardioprotective, hepatoprotective, antimicrobial, antiviral, antiallergic, vasodilatory and also in treatment of neurodegenerative diseases. They were reported to inhibit various enzymes like hydrolases, hyalouronidase, lipase, alkaline phosphatase, cAMP phosphodiesterase, α-glucosidase and kinase.

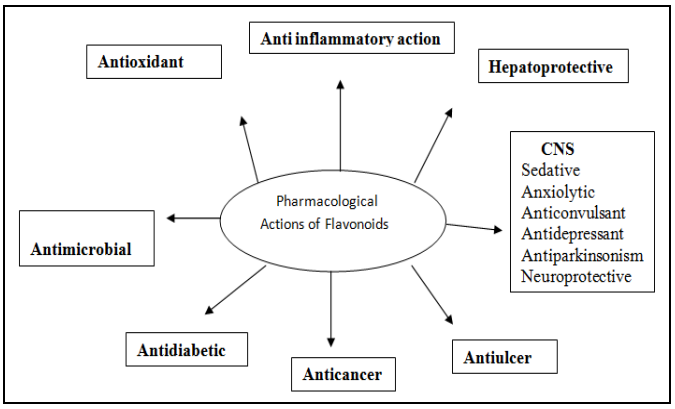

FIG. 3: BROAD SPECTRUM OF ACTIVITIES OF FLAVONOIDS

Flavonoids as antioxidants:

Mechanism of flavonoids as antioxidants [6, 7]:

Flavonoids are also called as free-radical scavengers. The antioxidant activity was mainly due to their ability to donate hydrogen. Free radical scavenging capacity is primarily attributed to high reactivities of hydroxyl substituents that participate in the reaction.

The increased levels of free radicals leading to produce an imbalance in antioxidant defense mechanism and leads to oxidative stress. This causes death of cells, leading to tissue damages. Various researches have been done to investigate the antioxidant potential of different Flavonoids.

Flavonoids have been demonstrated to have antiallergic, anti-inflammatory, anti cancer and anti diabetic activity. The broad range of therapeutic effects of flavonoids can be attributed to their antioxidant properties.

Central nervous system:

Flavonoids are reported to produce CNS activity by various mechanisms.

- They bind to the benzodiazepine site on the GABA (A) receptor. GABA is an inhibitory neurotransmitter, so binding of flavonoid to GABA receptor results in sedation, anxiolytic and anticonvulsant action [8]. Flavonoid reported to have antidepressant and antiparkinsonism action by inhibiting monoamine oxidase A or B [9].

- Flavonoids exert neuroprotective effect in *in vitro* cells and animal models by attenuation of oxidative stress, regulation of kinase signal cascade and apoptotic neuronal dealth[10].

- The flavonoids derived from *Peltiphyllum pelatum* were shown to have anticholinesterase activity, this results in therapy against Alzemiers disease [11].

-

- Flavonoids from *cudrania tricuspidata* produce anti inflammatory action by decreasing NF- κB signaling and phosphorylation of MAPKs [12].

-

- Baicalein is a flavonoid isolated from *scutellaria baicalensis* protect neuronal tissue damage and facilitate cognitive behavioural performance. Several researches reported baicalein reduces brain infarction from focal brain ischemia, mainly due it inhibitory action on MMP-9 [13].

Cardiovascular system:

Flavonoids are good source of antioxidant, it has been reported that it increases the endothelial nitric oxide release and result in relaxation of blood vessels in conditions like hypertension and stroke[14]. Studies on hespiridine and naringin revealed they are effective in age related increases in blood pressure [15]. Epicatechin, quercetin, avicularin are reported to have effect in cardioprotective activity[16].

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[17].

Quercetin [18], Isoquercitrin, biochanin- A and formononetin are reported to have effective action against controlling cholesterol in experimental models. The total flavonoids from leaves of Nelumbo nucifera [19] evidenced to have hypolipidemic activity in Wistar rats with high-fat diet-induced hyperlipidemia

Diabetes

Many flavonoids are reported to have antidiabetic action by acting on the biological targets that involved in diabetes mellitus type –2 such as aldose reducatse and α- glucosidase [21, 22].

TABLE 2: MECHANISM OF ACTION ENZYMES INVOLVED IN DIABETES.

Enzymes	Mechansim
Aldose reductase	Involves in polyol pathway - glucose break into sorbitol and its accumulation linked to diabetic complications. involves in the formation of advanced glycation products
Alpha - glucosidase	Involved in breaking down complex carbohydrates, helps in the absorption of ingested carbohydrates, increases postprandial glycemia and insulin peaks.
PPAR-g	Regulates fatty acid storage and glucose metabolism.

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. Flavonoids are shown to reduce the deleterious effect of hyperglyemia due to their antioxidant property.

- In Insulin dependent diabetes mellitus, flavonoid Quercetin reported to increase the insulin release by improving the regeneration of pancreatic islets cell.[23]

- In non Insulin dependent diabetes mellitus, Fiestin was shown to increase calcium uptake from islets cells.[24, 25]

Anti inflammatory action: [26, 27]

Flavonoids are reported to have anti-inflammatory action, these accounts for many pharmacological actions of it. Many mechanism have proposed to explain the anti-inflammatory action of Flavonoids, it includes antioxidant action, inhibitory action on eicosanoid generating enzymes and in the production of pro inflammatory mediators. They also modulate the cells involved in inflammation such as lymphocyte, monocytes, natural killer cells, mast cells, neutrophils, and macrophages.

Analgesic action: [28]

A number of flavonoids are reported to possess anti-inflammatory activity. Hesperidin, apigenin, luteolin, silymarin and quercetin have been reported to exhibit anti- inflammatory activity [27, 28]. But the mechanism behind this has yet to be studied.

Anticancer:

Various epidemiological studies showed that flavonoid are having beneficial effect against various type of cancer such as colon, breast, lung, prostate and pancreas [29, 30]. Flavonoids are reported to have anticancer activity by various mechanism such as carcinogen inactivation, cell cycle arrest, antiproliferation, induction of apoptosis and inhibition of angiogenesis [32, 33]. Various research studies revealed that kinases such as dual specificity tyrosine phosphorylation- regulated kinase 1A (DYRK-1A), glycogen synthase kinase-3 (GSK3), cyclin-dependent kinases (CDKs) are involved in cancer [34, 35].

TABLE 3: FLAVONOIDS AND THEIR MODE OF ACTION AGAINST CANCER

Flavonoid	Mechanism	Reference
Quercetin , rutin, hespiridin, silymarin	Antiproliferative action in different cell line	31
curcumin	Inhibit angiogenesis	36
Naringenin, quercetin	Inhibit CYP3A4	37
Apigenin, luteolin	Cell cycle arrest	38

Various research work were carried out to prove the anticancer properties of flavonoids.[39, 40]

Respiratory tract:

The antioxidant, anti-inflammatory, anti allergic and antispasmodic action of Flavonoids accounts for it beneficial effect in respiratory tract diseases[41]. Many Flavonoids are reported to have modulate

airway mucus secretion, it includes apigenin, silibinin and wogonin [20].

Digestive tract:
Flavonoids are reported to have beneficial effect in treating digestive tract problem. Many research reveals that flavnoids are having anti ulcer, Hepatoprotective, antidiarhoeal action.[42- 44]

- Naringenin and apigenin are reported have antiulcer action in ethanol induced animal model [41].

Flavonoids exhibit antiulcer activity by the following mechanism

- Inhibits c AMP
- Inhibits Protein Kinase
- Inhibits COX
- Inhibits Protein phosphorylation

Genitourinary tract:
Many Flavonoids containing herbal products are prescribed for genitourinary tract ailment involving prostatitis and urinary tract infections [45, 46].

Flavonoids are reported to have antispasmodic actions in the bladder and uterus preparations [47].

Skin ailments: [48]
Various research studies revealed that the flavonoids have beneficial effects in skin ailments primary due to its antioxidant, anti inflammatory and soothing action.

Antimicrobial actions: [49-53]
Most of the flavonoids are proven to have antimicrobial effects and used in various preparations as a therapeutic agent.

TABLE 4: FLAVONOIDS AND THEIR SPECTRUM OF ACTION

Flavonoid	Action against
Quercetin and kaempferol	Antimicrobial
Chrysin	Streptococcus species
Quercetin	Candida albicans
Rutin , apigenin	Anti fungal
Galangin, kaempferl, quercetin	HIV
Quercetin 3- rhamnoside	Influenza antiviral

Flavonoids as natural antioxidant supplement:
Many flavonoids are available in market as natural supplement. It is available in India and throughout the world.

FIG.4: SOME OF THE FLAVONOID SUPPLEMENTS AVAILABLE IN MARKET

CONCLUSION: This review confirms that flavonoids are having beneficial effects in neurodegenerative disease, cancer, diabetes, respiratory, cardiovascular, digestive ailments. It is also proven to have antibacterial, antifungal and antiviral effects. Most of the pharmacological activities of flavonoids are mainly due to its antioxidant activity. Many of the flavonoids are used as the nutritional supplements worldwide.

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