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# A Brief Review: Flavonoids as a Pharmacophore

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## ABSTRACT

*Flavonoids or bioflavonoids (Latin word flavus meaning yellow, their colour in nature) are found as a secondary metabolite in plants. Chemically they have 15 carbon skeletons, which consist of three rings including two phenyl A & B and one oxygen containing heterocyclic ring C. They are classified into flavonoids as, Flavonoids or biflavonoids derived from 2-phenylchromen-4-one Isoflavonoids derived from 3-phenylchromen-4-one Neoflavonoids derived from 4-phenyl coumarin. Flavonoids are widely distributed in plants, performing wide range of function. They are associated with diversified biological activities.*

**Keywords:** Flavonoids, Isoflavonoids, Neoflavonoids, Pharmacophore.

## INTRODUCTION

Flavonoids or bioflavonoids (Latin word *flavus* meaning yellow, their colour in nature) are found as a secondary metabolite in plants. Chemically they have 15 carbon skeletons, which consist of three rings including two phenyl A & B and one oxygen containing heterocyclic ring C. This carbon skeleton abbreviated as C-6-C3-C6 [1]. They are classified as under;

- **Flavonoids** or biflavonoids derived from 2-phenylchromen-4-one
- **Isoflavonoids** derived from 3-phenylchromen-4-one
- **Neoflavonoids** derived from 4-phenyl coumarin

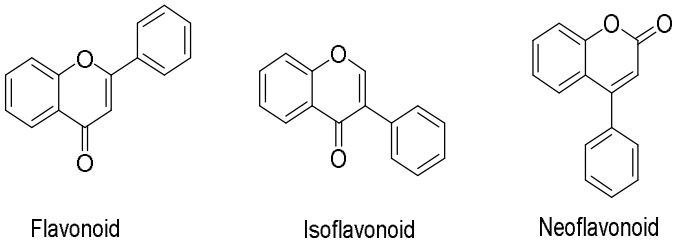



**Figure1.** Classification of flavonoids [2]

The three rings of flavonoids of are called as A, B and C.
Flavonoids are further classified as flavone, flavanone, isoflavone and flavanol as shown below,

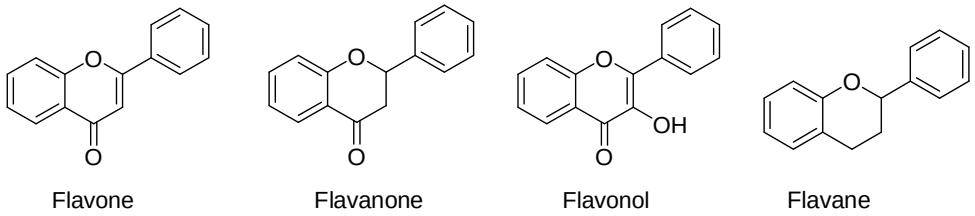



**Figure 2.**Basic flavonoid skeleton

Isoflavonoids are classified as isoflavone, isoflavanone and isoflavane etc. as shown below,

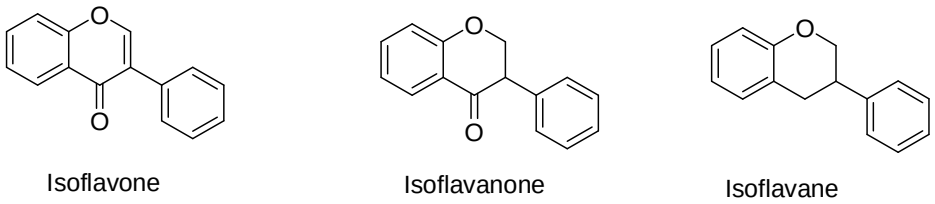



**Figure 3.** Basic Isoflavonoid skeleton

**Functions of flavonoids in plants:** Flavonoids are widely distributed in plants, performing wide range of functions. Flavonoids play an important role in plant by acting as pigments for the coloration of flower, producing yellow, red, blue, green and white pigmentation in petals designed to attract pollinator animals. In higher family of plants, flavonoids needed in UV filtration, nitrogen fixation by symbiotic association and floral pigmentation. Flavonoid plays an important role in to transfer a chemical information, physiological regulators, and cell cycle inhibitors During nitrogen fixation plants secretes flavonoids for defence purpose, due to which Rhizobium makes symbiotic association with legumes like peas, beans, clover and soy. In soil Rhizobium are able to sense the flavonoids and this triggers the secretion of nod factors, plants recognize them and lead to root hair deformation and several cellular responses such as ion fluxes and formation of root noodle.

**Biological activities associated with flavones:** Flavonoids are key skeleton for different target like enzyme, bacteria and viruses. Diversity of skeleton gives large spectrum of activities for flavonoids. Due to which scientist studied SAR of this molecule and synthesized large number of lead molecules and analogues. Comprehensive study of this molecule considering different skeletons and substitution patterns is necessary. Some of the biological activities associated with flavonoids are described as under.

**Antioxidant activity**

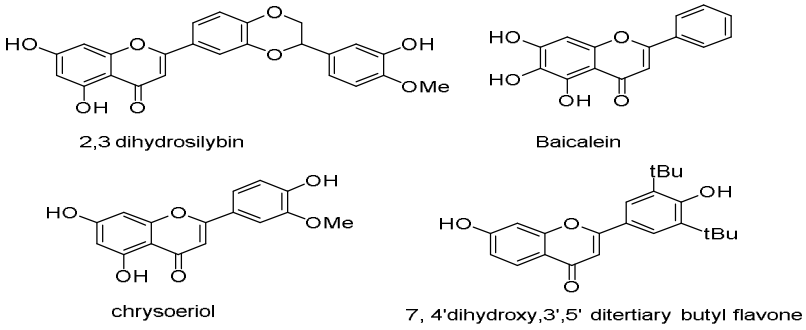



**Figure 4.** Flavone skeleton with an anti-oxidant activity

Free radicals in the human body are responsible for various diseases and breaking of the biomolecules. This leads to cancer, cardiovascular diseases, arteriosclerosis, neural disorders, skin irritations and inflammations. As we know that free radicals are highly reactive species and reacts with plasma membrane to give carbon free radicals which generates peroxy radicals. Due to which peroxidation of lipid takes place. In this way one free radical can damage large number of lipid molecules via chain reaction. Our body generates defense against free radicals by different ways. Many enzymes and proteins generated to act against free radicals [3].Such as superoxide enzyme dismutase, catalase, copper and iron transport proteins also lipid and water soluble antioxidant. If numbers of free radicals are greater than defensive mechanism of body then above mentioned diseases start to grow. Anti-oxidants stops initiation of oxidation or breakdown the chain reaction. Antioxidant stops superoxide ion formation which leads to inhibition of oxidation initiation. Also trace metal ions (copper and iron) forms chelate with antioxidants & stops oxidation process. Another mechanism involved is antioxidants acts as scavenging agents and acts against hydroxyl radicals. In this way avoids damage of proteins, plasma membrane and DNA from free radicals [4, 5]. Some of the flavanol molecule with anti-oxidant activity is mentioned below.

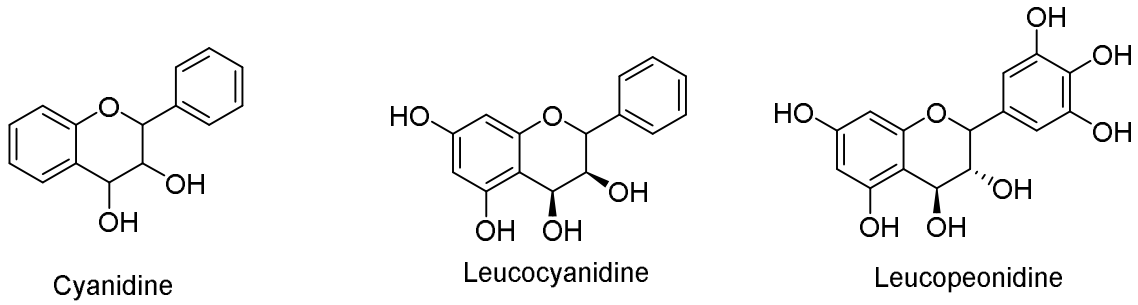


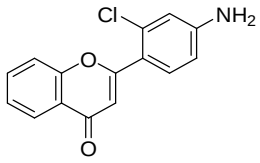

**Figure 5:** Flavanol with anti-oxidant activity.

**Anticancer activity:** Cancer is the most death causing disease in the world. It involves progressive transformation of normal cells towards malignancy. It causes proliferation, angiogenesis, and apoptosis of healthy cells. Various drugs used today called as antitumor, anti-proliferative and anti-neoplastic. Major problem associated with drugs is cytotoxicity caused due to death of normal cells other than abnormal cells. Lack of selectivity of targeted cells is major cause of toxicity. But after 1960 research on flavonoid showed that flavonoids like myricetin, luteolin, apigenin and Kaemferol shows good activity.1970-1990 flavonoids screened for other cancers like lung cancer, malignant neoplasm and ovarian cancer. Research also shows that apigenin reduces cancers like breast, digestive tract, and skin, prostate and haematological malignancy.

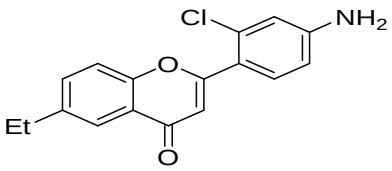
Kinase is enzyme which carries phosphate group from high phosphate donating group to substrate. Various kinases are responsible for cancer. Examples are cyclin dependent kinase (CDKs), glycogen synthase kinase-3 (GSK-3), dual specificity tyrosine phosphorylation regulated kinase 1A are involved in cancer. So inhibition of kinase is important for cancer treatment.

Flavonoids in our diet plays important role for the prevention of cancer. Fruits and vegetables are major source of flavonoids. Mainly quercetin is present in fruits and vegetables. Flavonoids acts against cancer by various mechanisms like cell cycle arrest, tyrosine kinase inhibition, inhibition of heat shock protiens, estrogenic binding, inhibit expression of Ras protein and down regulation of mutant protiens p53.Mutation in protein p53 is common cause of cancer in human beings. This protein expression was inhibited at G2M phase of cell cycle. In human breast cancer cell lines flavones works better by inhibiting expression of this protein. Near the cell membrane a protiens tyrosine are found which involved in transduction of growth factor to nucleus. This expression involved in on cogenesis by override normal regulatory growth control. Various tyrosine kinase inhibitory drugs were available and known as antitumor agents. They don't have any toxicity. Flavonoid quercetin acts as anti-tyrosine kinase in human cells. Heat shock protiens are also

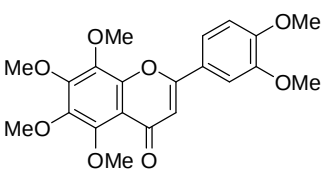
important to treat cancer. Heat shock protiens forms complex with p53 and bypass normal mechanism of cell cycle arrest. Flavonoids inhibit production of heat shock protiens. SAR study also shows that 8-substituited analogues of flavonoids are more active compared to 6-substituted analogues as in case of capitavine. Flavopridol is first anticancer drug in clinical trial and efforts are made to design drug on the basis of flavopridol with heterocyclic ring at 8$^{th}$ position. It is also important to make ring at 8$^{th}$ position of chrysin to get good anticancer lead molecule. QSAR study of flavones also indicates that amino moiety and hydroxyl group at 5$^{th}$ position of flavone increases its anticancer activity by interacting with different kinases related to cancer [6]. Derivative of 1-(3-chloro-4-(4-oxo-4H-chromen-2-yl) phenyl)-3-phenylurea was developed as anticancer agents and works well against cancer. Derivatives of the compound acts inhibitor against Raf1 and JNK1, second compound shown below acts against kinase p38 alpha.



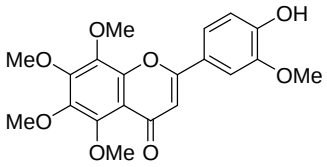

4' amino,2' chloro flavone




4'- amino,2' chloro,
6 ethyl flavone




5,6,7,8,3',4' hexamethoxy flavone




5,6,7,8,3'' pentamethoxy ,4' hydroxy flavone

**Figure 6**. Flavone skeleton with anticancer activity

Breast cancer and tumor cell proliferation is stimulated by estrogen receptors signaling pathway when estrogen binds. In estrogen biosynthesis, aromatase catalyzes conversion of androgen to estrogen. Aromatase develop hormone dependent breast cancer in females. Now it is important to carry research so as to develop aromatase inhibitory drugs. Recently various drugs like latrazole, anastrozole are present in market and works well but cytotoxicity and side effects are major problem associated with these drugs. Now various analogues of chrysin were synthesized by substituting carboxyl, fluoro, nitro, halides, and amino group shows activity against aromatase enzyme. Imidazole ring fused with ring A of flavone shows good anti-breast cancer activity. In the above compounds if nitro group is present at 6th position of ring A increases anticancer activity. Wogonin at a very small dose acts as an anti-tumor and anti-metastatic activity by inhibiting growth factor VEGF-C [7].

Pyrroloazaflavone derivatives are able to exert anti-angiogenic effects by acting on fibroblast growth factor (FGF-2).Anti-angiogenic activity of pyrroloflavone increased by adding phenyl ring at 2-positions.Flavones with an –OH group at C-5 of ring A and 3’ hydroxy-4’-methoxy groups on ring B and methoxy group at C-3 of ring C shows significant anti-tubulin activity. Also all amino flavone shows strong anti-proliferative activity.

Nobiletin a flavone molecule acts against topoisomerase I enzyme. Various pathological states including cataract, rheumatoid arthritis and mitosis caused due to matrix metalloprotien-9 (MMP-9) which plays important role. In human lens epithelial model nobiletin shows good inhibitory effect against MMP-9.

Apigenin is a flavone molecule shows activity against various cancers like hepato-carcinogenesis, neuroblastoma, breast cancer, esophageal squamous cell carcinoma, colon cancer, lung cancer, prostate cancer, cell mitosis impairment and cell apoptosis etc. It is also invented that chloride, nitro, isopropyl, methoxy group on ring A & B decreases hepatocarcinogenesis (HepG2).SAR study shows that substitution of p-hydroxyl,3,5'-dimethoxy,5'-amino,2'-chloro at ring B are important for anticancer activity. If ring A of flavone substituted by aliphatic or aromatic heterocyle at C-6 and C-8 position, OH at C-5 position increase anticancer activity of flavones. It also shows that nitrogen in place of oxygen of ring C and 3-methoxy group leads to anticancer activity of flavones. Quercetin is important flavonol which is known to produce cell cycle arrest in proliferating lymphoid cells. Not only it acts as antineoplastic agent but also exert growth inhibitory effect on malignant tumor cell lines. These cells include P-388 leukaemia cells, gastric cancer cells (HGC-27, NUGC-2, NKN-7 & MKN-28), colon cancer cells, breast cancer cells, human squamous and gliosarcoma cells and ovarian cancer cells. Scientist Barn extensively studied anticancer activity of genestein in vitro as well as vivo.

He also examined daidezin, biochanin-A on mammary carcinogenesis, genestein was found potent to suppress mammary induced cancer without any toxic effects. Hesperidin also important to suppress azoxymethanol induced colon and mammary cancer in rats. So many flavones, flavanones, isoflavone, biochanin-A are reported to show potent anti-mutagenic activity. A carbonyl carbon present at C-4 position in ring C is essential for this activity. Flavone 8-acetic acid is potent anticancer agent. The peoples consuming phytoestrogens are at lower risk of prostate cancer [8a]. Motohashi et. al. isolated some isoflavones are mentioned below[8b].

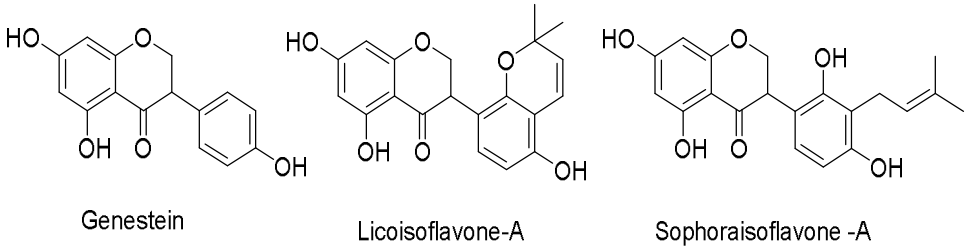
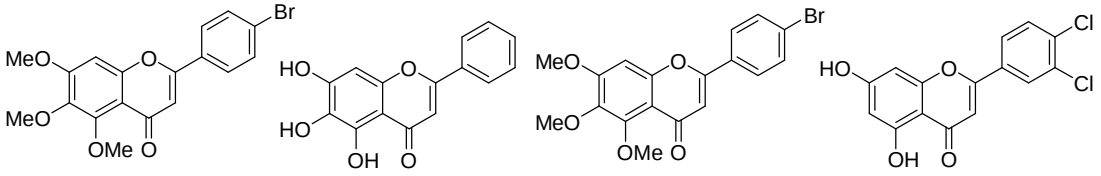



**Figure 7**: Isoflavone skeleton with anticancer activity

**Anti-inflammatory activity:** Inflammation is normal biological process in response to injury, chemical irritation and microbial pathogen infection. Inflammation occurs by migration of immune cells from blood vessels and release of mediators at the side of injury or damage. This mechanism happened when inflammatory cells generated and release of ROS, RNS, and pro-inflammatory cytokinase to remove microbial pathogens. But prolonged and abnormal inflammation causes disorders in the body. Flavonoids inhibits the function of enzymes which are involved in inflammatory action especially tyrosine and serine threonine protien kinases. Due to inflammation various diseases occurs in living organism like Asthma, atherosclerosis, Alzaimer's disease, rheumatoid arthritis, diabetes mellitus, gout, multiple sclerosisosteo-arthritis, psoriasis ,bacterial or viral infections. Different mediators responsible for inflammation are prostaglandins, leukotriene, histamines, serotonin, nitric oxide, interleukins, iNOS production, tumor necrosis factor-a (TNF-a), NFkB and some chemo kinases. Various signalling pathways produce these mediators. Cyclooxygenases, capsases and kinases like cyclin dependent kinases (CDK1 and CDK5), mitogen activated protien kinase38 (MAPK-38), c-Jun N-terminal kinases (JNK), serine threonine kinase (IKK1 and IKK2) interleukin receptor associated kinase (IRAK-4), & Janus kinase (JAK1-JAK3) [9].

Now a days so many steroidal anti-inflammatory drug and NSAID are available to treat inflammation. But the acute and chronic inflammation remains problem and side effects associated with these drugs creates problem. So there is urgent need for development of SAID and NSAID for the treatment of this inflammation. Treatment of traditional way is to use plant extract. So many flavones like apigenin, luteolin and some synthetic flavones invented to bind various protien kinases directly and alter their phosphorylation state. Due to which multiple signaling pathways regulated. Flavonoids from long time used for the treatment of inflammation and immune protective purposes.

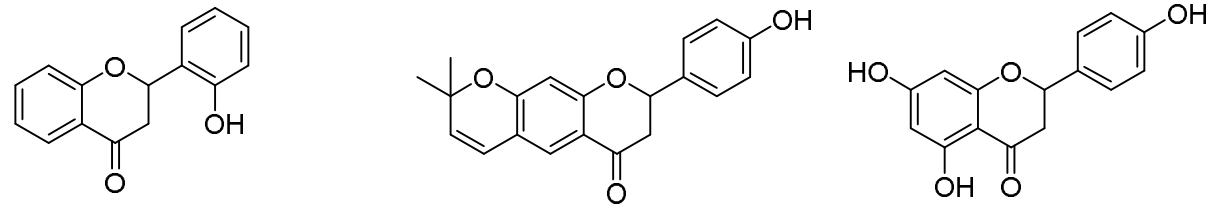
Research on the synthesis of flavones as 5, 6, 7-trimethoxy flavone and 5, 6, 7-trihydroxy flavone shows anti-inflammatory effect.so many derivatives of these type analyzed and find out that 4' bromo, 5, 6, 7-trimethoxy flavone was very potent drug. It is potent against nitric oxide, free radical, PGE2 etc. It also effective to low down LPS induced expression of iNOS and COX-2 at protein and mRNA level and releases TNF-a and IL-6.SAR study also indicates that electronegative group at C-5 position of ring A and bulky substituent at meta position of ring B for NF-kB transcriptional activities. Nobiletin and its analogues show activity against various matrix metalloproteinase MMP-9 productions. It is concluded that 2'-hydroxy nobiletin exerted significant inhibitory effect at very low concentration [10].




4'bromo,5,6,7trimethoxy flavone | 5,6,7 trihydroxy flavone | 5,6,7 trimethoxy,4' bromo flavone | 5,7 dihydroxy,3',4' dichloro flavone

**Figure 8**: Flavone skeleton with anti-inflammatory activity

Biflavonoids also shows effect against phospholipase A2.Biflavones like amentoflavone, morelloflavone and flavone-flavanone derivatives shows significant effect. Enone system present in flavone is necessary for anti-inflammatory activity against cyclooxygenase pathway for PGE2 production. Luteolin, apigenin shows good activity but their content in plant is very low. So synthetic methodology were developed for their synthesis. Chrysin analogues like 3'4' di-chloro chrysin show very good effect against prostaglandin production. In conclusion some structural features are important as flavones having 2', 3', 4' in ring B and methoxy group at 5,6,7 and methylation of C-3 and C-5 OH group shows better reduces toxicity [11].




2' hydroxy flavanone | Lupinofoline | Naringenin

**Fig 9.** Flavanone molecule with anti-inflammatory activity

**Neuroprotective effects:** Central nervous system balanced by various signaling pathways. Neurotransmitter, enzymes, kinases plays important role in these complicated pathways. Neurodegenerative disorders caused due to disturbances in these pathways causing various diseases like alzaimeirs disease, depression, dementia, anxiety, convulsion, Parkinson's disease etc. Dementia caused

due to Alzaimeir's disease and brain control loss. Reason for Alzaimeir's disease is misfolding in protein, aggregation, oxidative stress, mitochondrial abnormalities and neuroinflammatory processes. The enzymes responsible for acetyl choline hydrolysis is acetyl choline esterase (AChE), Butyl cholinesterase (BuChE) and b-secretase-1 (BACE-1).due to which amyloid plaque formed. Inflammation mediators, neurotransmitter, oxidative stress, glutamate neurotoxicity, alpha cynuclein, protein aggregation causes PD. Most important cause of depression is bio transmission of neurotransmitters. Various neurotransmitter monoamines were oxidized by enzyme monoamine A oxidase and monoamine oxidase B. Monoamine A oxidase oxidizes 5-hydroxy tryptamine, norepinephrine, epinephrine whereas monoamine B dominates b-phenyl ethylamine and benzyl amine. So many neuroprotective drugs are available in market but patient suffers side effects.so research must be done in order to avoid the side effect of these drugs. So many analogues of these neurotransmitters are used to overcome side effects. Flavonoids are important for intracellular signals. GABA receptor flavone Oroxylin A is most widely used flavone to improve memory. It is also invented that Oroxyllin A analogues also shows good result [12].

Topoisomerase receptor kinase B is a very important kinase playing important role in neuron disorder causing depression. So many agonists used against this kinase. By phosphorylation process several agonists' acts as a antidepressant. Many receptors like GABA receptor, benzodiazepines, adenosine $A_3$, shows various effects like neuroprotection and neurodegeneration. Among various flavonoid screened 7, 8 dihydroxy flavone shows TrkB agonist activity. Structure activity study demonstrate that 7, 8 dihydroxy group on ring A and middle hetero atom on ring C plays essential role for the Trk B stimulatory effect. SAR study also shows that EWG like F and EDG like OH suppress activity. But dimethyl amino and pyrrolidino group at 4' position gives desired activity. Antidepressant activity of flavone increase when 4' position is substituted by pyrrolidino group. When chromone moiety connected with tacrine it gives better activity against AD. Tacrine and apigenin are potent for AD [13]. But new strategy of synthesizing hybrid molecules of tacrin-flavone shows good activity. Tacrin molecule is potent against cholinesterase and flavone molecule is antioxidant and b-secretase (BACE-1) inhibitory activity. When both molecules were combined they are more potent against BACE-1, ChEs as well as antioxidant and CNS permeable properties. ERK (Extracellular signal regulated pathway) pathway is a chain of protiens in the cell that communicates a signal from receptor on the cell to the DNA in the nucleus of the cell. Flavone increases the expression of neuroprotective and neuromodulators protiens so that number and strength of protein increases. Flavones exhibited interaction with ERK and increases effect. 2'amino, 3' methoxy flavones is good modulator. Synaptic plasticity and memory improved by ERK activation by flavones. Baicalein is another flavone important for Parkinson's diseases. Luteolin-7-O-b-D-gluco-pyranoside shows effect in the cell PC12 and 6-OHDA. Flavonoids plays important role in the delaying process of AD. Flavonoids inhibit beta amyloid aggregation by inhibiting b secretase (BACE-1) and activation of alpha secretase. Flavones with phenyl ring at C-3 & C-8 position shows effect against BACE-1.Prenylated flavones also shows inhibition against b-secretase (BACE-1) [14]. AchE inhibitory activity when pyrrolidin-1-yl methyl or piperidine-1-yl methyl ay at C-4' position. Flavones also reported to show inhibitory effect against monoamine oxidase enzyme MAO-A and MAO-B.

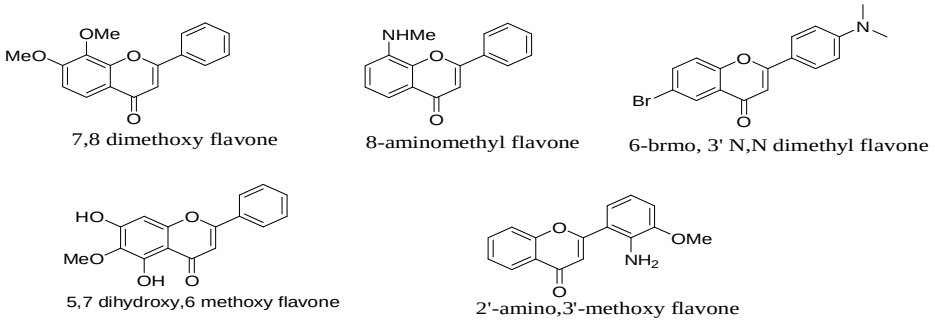



**Figure 10**: Flavone molecule with neuroprotective activity

Flavones having amino methyl moiety at C-8 position show CNS stimulating effect. Bioflavonoids & ginketin inhibit death of neuronal cell induced by amyloid b peptide. Flavones with nitro and halogens at C-6 and C-3' position shows affinity for benzodiazepine receptors. Some compounds like 6, 3' dinitroflavone and 6 bromo-3' nitro flavone shows good affinity for benzodiazepine. Apigenin is important flavone for the inhibition of amyloid fibril. Flavones are important for adenosine A3 antagonist who can be serving as cerebro-protective and anti-asthma agent. Molecule of flavone acts as a adenosine A3 antagonist when hydroxyl group at C-3 and Cl at C-6 and satirically bulky group at C-2' position [15].

**Anti-diabetic activity:** Energy rich diet and fast lifestyle increases obesity and diabetic. Due to increased sugar level metabolism of carbohydrate protein, fat, electrolyte and water affected due to increased sugar level such persons suffer from diabetes. Delayed insulin secretion immediately after meal leads to sudden increase in blood glucose level known as hyperglycemia. Post prandial phase is associated with diabetic complications. So it is important to stop this phase. Some of the unabsorbed oligosaccharides and disaccharides binds with alpha glycoside and absorbed by small intestine when cleave into monosaccharaides. It is metabolic disease in which sugar level increased more than normal because pancreas does not produce enough insulin. Diabetes caused due to various enzymes and kinases. Protein kinase C (PKC), peroxisome proliferator activated receptor-g (PPAR-g), advanced glycation end products, protein tyrosine phosphates, alpha glycoside, aldose reductase (AR) are some examples of protiens and enzymes involved in the diabetic activity. Various anti-diabetic drugs available in market [16]. The most common are glybenclamide, rosiglitazone and metformin etc. Researchers synthesized various drugs based on flavones and their analogues targeting the enzymes and kinases. So the flavonoid hybrids of 6 and 7-hydroxy flavones with amino propanol show potent activity. The screening report also shows that flavones with bulky lipophilic substituent on ring B and small substituent on nitrogen atom shows very good activity [17].

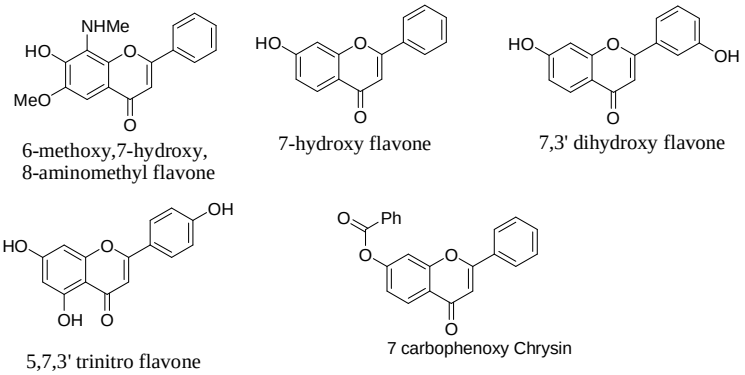



**Figure 11**: Flavone skeleton with anti-diabetic effect

In the hybrid molecule when nitrogen atom substituted with isopropyl group then possess potent activity. The flavone luteolin and baicalin shows potent alpha glucisidase activity. These flavones also inhibit postprandial hyperglycemia in the patient suffering from insulin independent pathway. Mannich reaction is used to attach amino methylated group at 8 position of oroxylin. This derivative shows potent activity against diabetes. 6-amino chrysin is important flavone inhibit α-glucisidase strongly. AR study shows that flavone with 6 amino groups and OH at 7 positions is important for anti-diabetic activity. 7-hydroxyl group was favourable when it is substituted. Amino group at $8^{th}$ position decreases activity. Aldose reductase inhibitors were designed but the most potent flavone is nepthyl group at $2^{nd}$ position [18]. Flavone hybrid with thiazolidine ring in the B ring of flavone and nitrogen of thiazolidine ring substituted by acetic acid increases aldose reductase inhibitory activity. Nitric acid releasing chrysin derivatives are potent AR drugs. Licoflavone is a prenylated flavone who shows PPAR-g ligand binding activity.7-hydroxy flavone also shows good activity against PPAR-g. PPAR-g activity of flavones and isoflavones increased when flavone possess hydroxyl group at 7 position. Protien tyrosine phosphatase (PTB-1B) disturbs metabolic activities of insulin. Therefore drug based on theinhibition of PTB-1B protien is

important for the anti-diabetic drug discovery. 5, 7, 3' trihydroxy flavone and 3, 6, 4' trimethoxy flavone shows hyperglycemic effect. Chrysin molecules with alkyl group show significant hyperglycemic effect. It is also found that baicalin and luteolin shows inhibitory effect against AGE's [19a]. Chongming et. al. isolated different isoflavones with anti-diabetic activity. Some of the anti-diabetic molecules are mentioned below[19b].

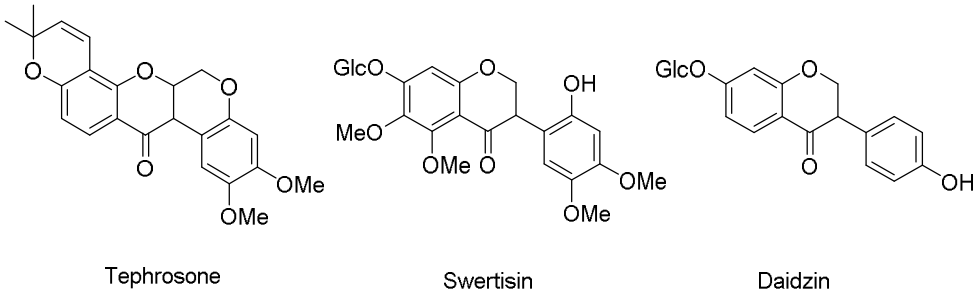



**Figure 12.** Isoflavones with anti-diabetic activity

**Antimicrobial activity:** Recently major problem associated with antimicrobial drug is resistance developed by these drugs. Staphylococcus aurones shows 50% resistant against drugs. So we need new anti-infective drugs for the treatment of bacterial stains. Modification in the skeleton of current drugs like antifungal azoles, antiviral non-nucleoside reverse transcriptase inhibitor and lactams and quinolones is the best way to develop lead molecule. So this strategy will no longer help to protect from bacteria, so the completely new drug must be developed to cure the bacterial infection.

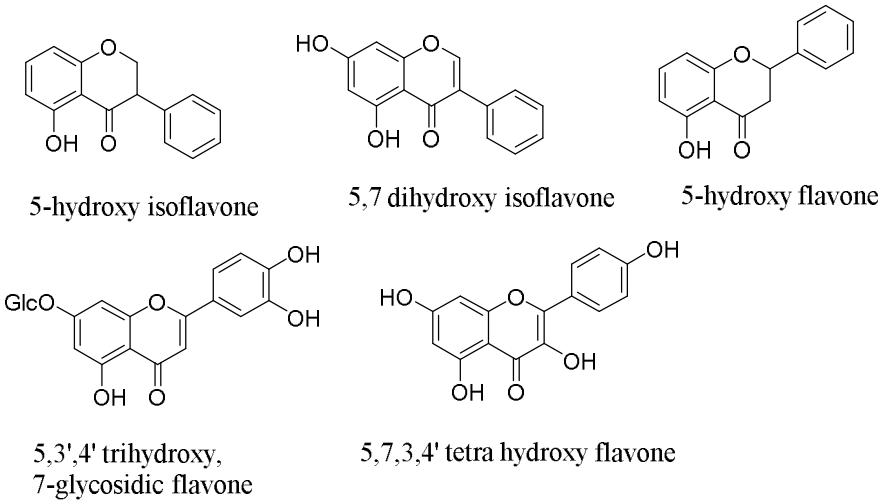



**Figure 13**: Flavone skeleton with anti-microbial activity

Some examples of natural flavones with antibacterial activity are mentioned below, apigenin, galangin pinocembrin, ponciretin, genkwanin, sophoraflavanone G and its derivatives, naringin and naringenin, epigallocatechin gallate and its derivatives, luteolin and luteolin 7-glucoside, quercetin, 3-O-methylquercetin and various quercetin glycosides and Kaemferol and its derivatives. Other flavones, flavone glycosides, isoflavones, flavanones, isoflavanones , isoflavans, flavonols , flavonol glycosides, and chalcone. Some natural occuring flavones also modified and semi-synthesized and screened for antibacterial activity. Compounds like 5, 7, 4' trihydroxy flavone shows better activity. Number of flavone molecule with different substituent was analyzed. SAR study indicates that 2, 4 or 2, 6 dihydroxy in ring B of flavone shows good activity. It was also demonstrated that hydroxyl group at at 5, 7 in ring A position of flavanone shows good activity. If 6 or 8 position of flavone is substituted by a long chain aliphatic group such as lavandulyl (5-methyl-2-isopropenyl-hex-4-enyl) or geranial (trans-3,7-dimethyl-2,6-

octadienyl) also shows enhanced activity in flavone-3-ol. QSAR study also indicates that flavones, flavanones, isoflavones and isoflavanones that 5-hydroxyflavanones and 5-hydroxyisoflavanones with one, two or three additional hydroxyl groups at the 7, 2 and 4 positions inhibited the growth of Streptococcus mutants and Streptococcus sobrinus. Current synthesis of flavonoids indicates presence of hydroxyl group at 5$^{th}$ position is important. Halogenated flavones also screened for antibacterial activity and show that flavone with chloro group at 3 or 4 position and bromo group at 4$^{th}$ position of ring. An increases activity. It was also found that halogenation in ring B lowers the antibacterial activity. Flavones containing nitrogen atom shows considerable activity. The compounds bearing amino-alkenyl, alkyl, amino, cyno-groups shows potent antibacterial activity [20]. Yumuguchi et.al. isolated isoflavones with antimicrobial activity are shown below.

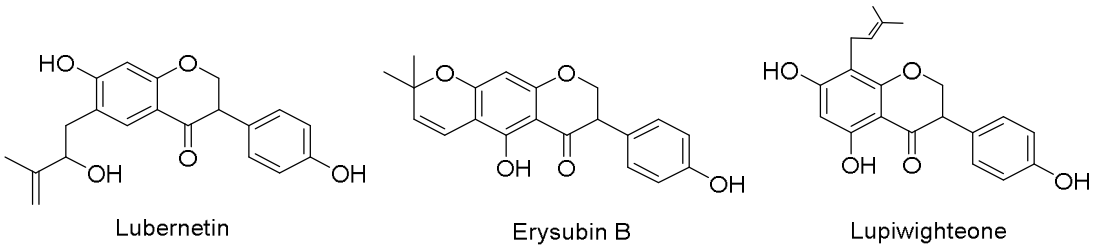



**Figure 14**. Isoflavones with anti-microbial activity

**Anti-Ulcer activity: A**mong all ulcers stomach ulcer is most harmful. Stomach lining damaged due to ulcer. The most of causes for the ulcer is alcohol consumption, tobacco chewing, stress, heredity, consumption of drugs like ibuprofen, aspirin, paracetamol, naproxen regularly damages stomach lining. The most important cause of ulcer is helicobacter pyroli bacteria who damages stomach lining. Consumption of above compounds causes increase in acidity, bile and pepsin in stomach. So combined therapy used to treat bacteria helicobacter pyroli. Now drugs like antacids, sucralfate, histamine-2 receptor, prostaglandins inhibitor etc. are used. But toxicity, side effects and less solubility i.e. bioavaibility is major problem associated with these drugs. Compounds from flavonoid family will acts as promising lead in the treatment of ulcers. Flavonoids are natural product without side effects [21]. Flavonoids are polyphenolic compounds used in the treatment of peptic ulcers. Another important flavone rutin also acts against peptic, gastric and oxidative stress related inflammation. Nobiletin and oroxylin are another flavonoids used as antiulcer. 7-carboxymethoxy-3', 4', 5- trimethoxy flavone acts as a good anti-ulcer agent by targeting NF-kB, kinase ERK. So many flavone molecules screened for their anti-ulcer activity. Glycosidic flavones, 7-methoxy flavones, 7-methoxy chrysin, 5, 4' dimethoxy flavone, 7, 4' dimethoxy flavone, oroxylin, chrysin, baicalein are gastro protective compounds. If we synthesized flavone with replacement of B ring by alkyl group, aromatic heterocyclic rings like thiophene, pyridine, and indole do not disturb the activity [22].

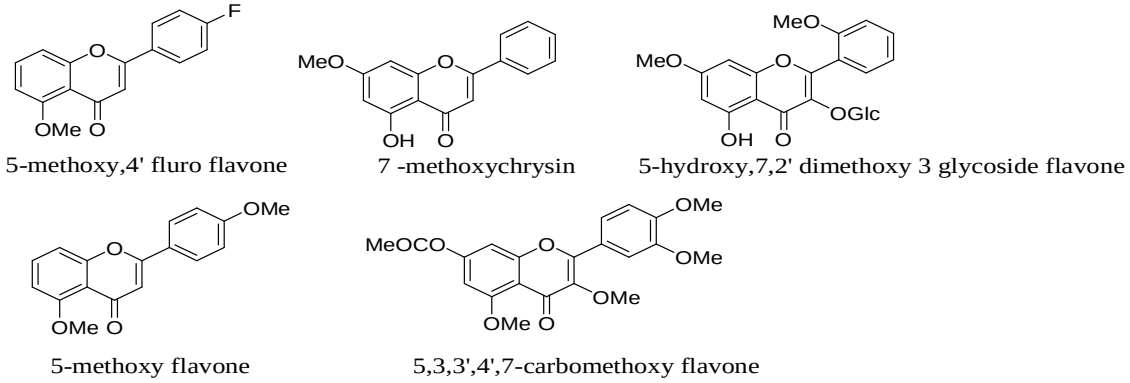



**Figure 15:** Flavone skeleton with anti-ulcer activity

Another important compound is 5-methoxy, 4'-fluroflavone shows a potent gastro protective activity. It is also found out that 5, 7-dihydroxy group at 5 and 7 position of flavone increases activity while its absence decreases activity. It is also found that methylation of 7$^{th}$ hydroxyl group of chrysin increases its activity. Glycosylation of the hydroxyl group 2' in the ring B of the compound enhances gastro protective activity. SAR study also shows that methoxy group at 5 and 7 positions and methyl group at 7 positions retained the activity. But replacement of proton of flavone at 3, 6, 8 position by hydroxyl or methoxy group decreases the activity [23a]. Some of the flavanone molecule with anti-ulcer activity was synthesized and isolated by Batista et. al [23b].

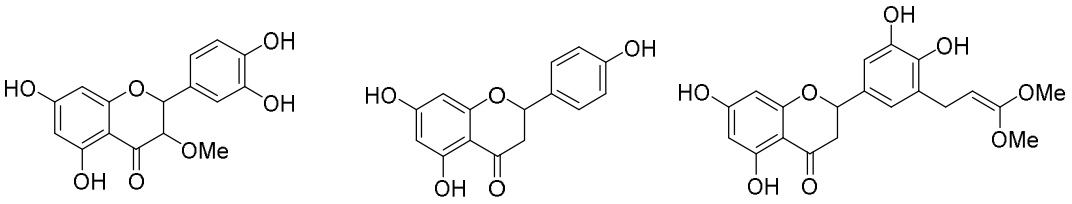



**Figure 16:** Flavanones with anti-ulcer activity

**Antiprotozoal Activity:** Malaria, ameobiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, chagas disease, leishmaniasis, sleeping sickness, dysentery, acanthamoeba, keratitis, primary amoebic meningoencephalitis etc. are some the diseases caused by protozoa. They are the major cause of death in tropical and sub-tropical area of the world. Malaria is the most common disease most in children causing death. Large number of drug screened for malaria but the development of multidrug resistance in the plasmodium falciparum developed. So scientists are in search of new drugs [24].

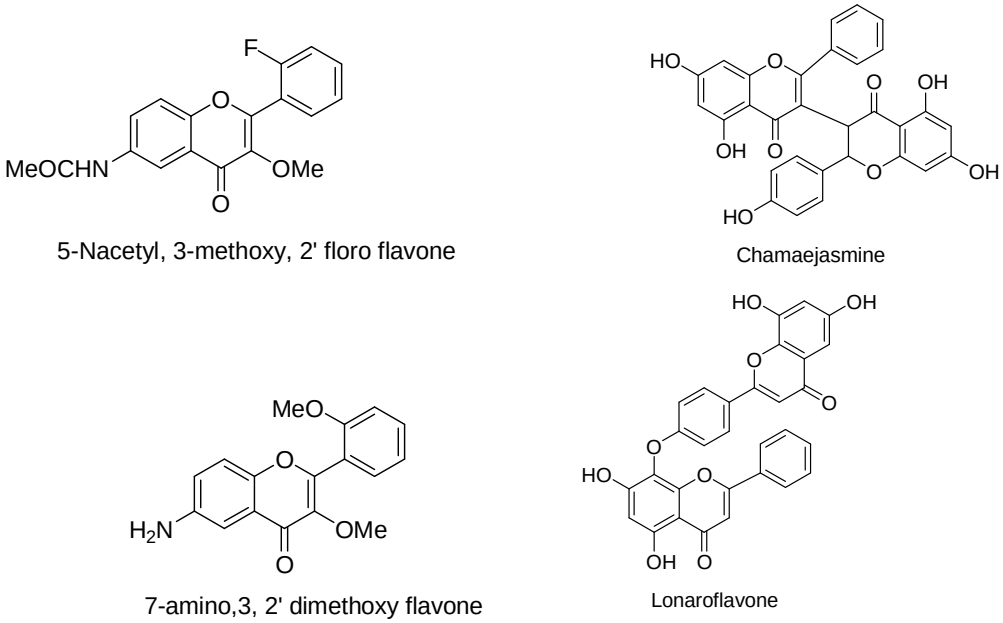



**Figure 17**. Flavone skeleton with anti-protozoal activity

Various natural products were screened for better result flavones shows good result. Various flavones like apigenin & luteolin sops parasite growth by targeting various metabolic pathways [25]. Amino methoxy flavones, fluoro in C-2' position promoted antiplasmodial activity. Bioflavonoids, flavone-flavanone hybrids are some of the potent antiplasmodial agents. Flavonoids with piperazinyl chain show better activity. Flavonoids with 2, 3, 4-tri-methoxy benzylpiperazinyl side chain attached at the 7$^{th}$ position

shows better activity against malaria [26].Some flavanone molecule with anti-protozoal activity are shown below,

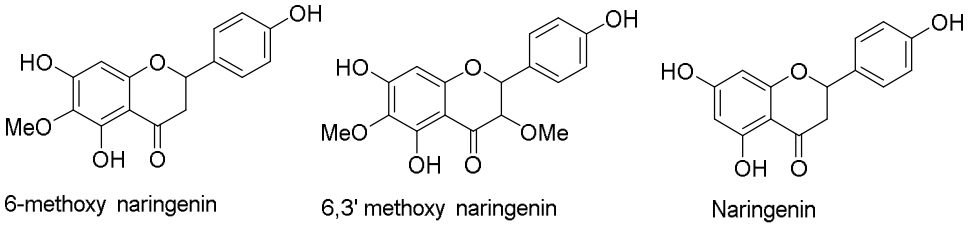



**Figure 18:** Flavanone molecule with anti-protozoal activity

**Anti-HIV activity:** From last three decades HIV (AIDS) is the most dangerous disease in the world causing death. Drugs are designed based on inhibition of reverse transcriptase enzyme. HIV replication caused due to viral protein like HIV-1integrase which catalyzes the integration of viral cDNA into the host genomic DNA. Numerous flavones having anti-HIV activity have been screened. 3, 5, 6, 7, 3', 4' hexahydroxy flavones & Morin shows significant activity [27].

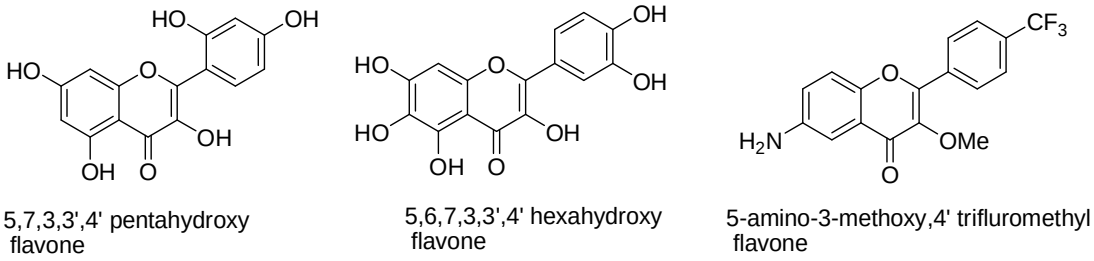



**Figure 19:** Flavanol skeleton with anti-HIV activity

Flavones complexes with enzymes responsible for anti-HIV activity. 3-methoxy flavone and ring B with substitution at para position increases activity. Luteolin molecule with 7-β-D glucopyranosyl-2''-sulphat shows potent activity against HIV virus [28]. QSAR study shows substitution pattern of ring A with amino group at $6^{th}$ position, H, OH, OMe at 3 position of ring C and H, OMe, F, $CF_3$ in various position of ring B shows greater activity. Methoxy or glycoside linkage or saturation of 2, 3 double bond reduces activity [29].

**Cardiovascular activity:** Flavonoids reduce the risk of various diseases like coronary diseases, hypertension, stroke, peripheral arteriopathy, atherosclerosis, cognitive heart failure etc. Flavones also important to inhibit various enzymes like NADPH oxidase, xanthene oxidase, lipoxygenases which are responsible for the formation of free radical in our body. High density lipoprotein (HDL) is one of the five major groups of lipoproteins composed of multiple protiens which transport all fat molecules around the body within the water. The fats carried consist of cholesterol, phospholipids and triglycerides. HDL particles are referred to as good cholesterol because they transport fat molecules out of artery walls, reduce macrophage accumulation, help to prevent atherosclerosis, stroke cardiovascular diseases, stroke etc. Flavonoids increases HDL level, acts as an antioxidant, regulates lipid in the cell, platelet aggregation are inhibited, activates endothelial function etc. A flavone molecule luteolin-7-O-β-D glucopyranoside exhibited cardio protective effects, reduces LDH and creatine kinase (CK) level, decreases intracellular concentration of ROS [30].

SAR study indicates that C2-C3 double bond in ring C and 3´, 4´ hydroxyl group are necessary for vasodilation. 3-methoxy flavone molecule with 1, 4 dihydropyridine ring at $8^{th}$ position shows potent

cardiovascular activity. This compound also acts as a calcium channel modulator [31, 32]. Some of the flavones molecules with anti-cardiovascular activity are shown below

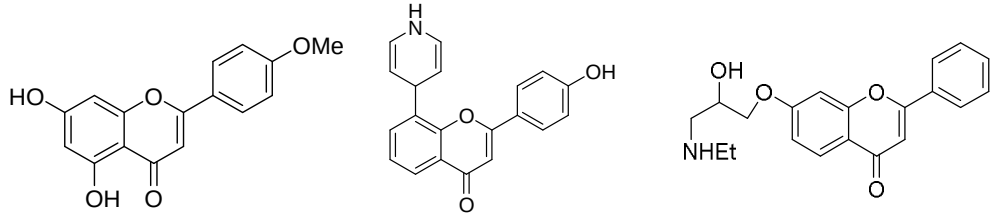



**Figure 20.** Flavone skeleton with cardiovascular activity

**Antiplatelet and antithrombotic activity:** Antithrombotic agents are the molecule that inhibits the formation of blood clots (thrombus means blood clots).Blood clot prevention reduces the risk of stroke, heart attack and pulmonary embolism. Antiplatelet means anti-aggregate drugs which avoids formation of thrombus. Thromboxane B2 is an inactive metabolite/product of thromboxane A2, is important factor for blood aggregation. So the COX-1 enzyme inhibition stops formation of thromboxane A2.CX-1 enzyme is the major source of thromboxane A2 in platelets [33]. Thromboxane A2 (TXA2), produced by activated platelets, has prothrombiotic properties, stimulating activation of new platelets as well as increasing platelet aggregation. Platelet aggregation was mediating expression of the glycoprotein complex GP IIb/IIIa in the cell membrane of platelets [34]. Circulating fibrinogen binds these receptors on adjacent platelets, further strengthening the clots.

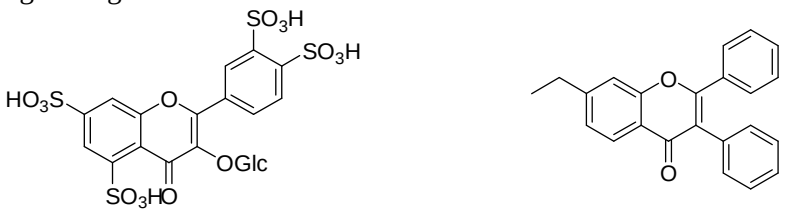



**Figure 21**. Flavone skeleton with anti-platelet activity

Flavonoids have antiplatelet and vasorelaxing properties. Drugs like heparin used to bind the enzyme and prevent platelet formation. O-sulphated analogues of hydroxyl flavone increase activity. Oxime and methyl oxime containing isoflavone-7-yl are the potent flavonoid in the treatment [35].

**Anti-atherogenic activity:** Hardening of the arteries due to formation of hard structures is called atherosclerosis. Cholesterol, fat, lipoprotein and fatty acids causes formation of hard structure. Due to plaque arteries blocked causing problem in the body [36]. Arteries become thick as a result of invasion and accumulation of white blood cells. The accumulation of white blood cells is called as fatty streaks. This accumulation caused due to living WBCs (causing inflammation), remnants of dead cells, cholesterol triglycerides etc [37]. Due to WBCs in the arteries arterial blood vessels affected. This is promoted by low density lipoproteins without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins. It is commonly called as furring of arteries. It is caused by the formation of athermatous plaques within the arteries. Atherosclerosis is initiated by inflammatory processes in the endothelial cells of the vessel wall in response to low density lipoprotein. Flavone molecules have ability to bind and inhibit TNF-alpha through action of NF-kB transcriptional activation [38]. Flavone molecule apigenin and luteolin inhibits up regulation of adhesion molecule. Nitric oxide produced by exited endothelial cells and macrophages helps in the dilation of blood vessel. But sometimes they produce more nitric oxide which reacts with free radicals to give damaging perosynitrite. This peroxynitrite oxidizes low density lipoproteins resulting in irreversible oxidative damage of cell membranes.

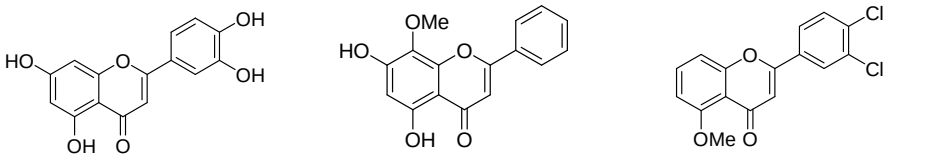



**Figure 22.** Flavone skeleton with anti-atherogenic activity

Flavones play an important role by acting free radical scavenger and antioxidant. Free radical reacts with flavone instead of nitric acid and avoids further reaction. Kaemferol and apigenin also acts as a NOS-2 inhibitor. Inflammation is the main cause for the atherosclerosis in the human being. Arachidonic acid converted to prostaglandins by COX-2. Flavones chrysin and wogonin acts as inhibitor of COX-2 and inducible nitric oxide synthase (iNOS) [39].

Some flavanone molecule with anti-atherogenic activity are shown below,

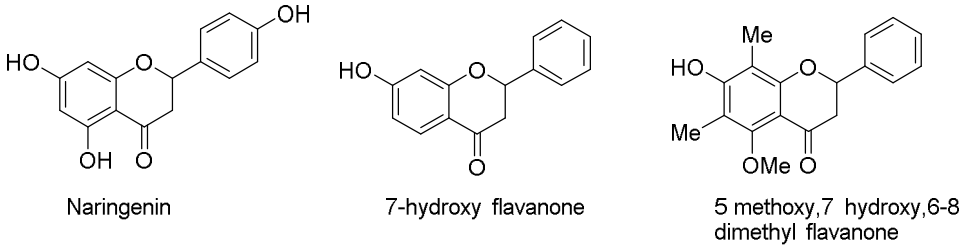



**Figure 23:** Flavanone skeleton with anti-atherogenic activity

**Spasmolytic agents**

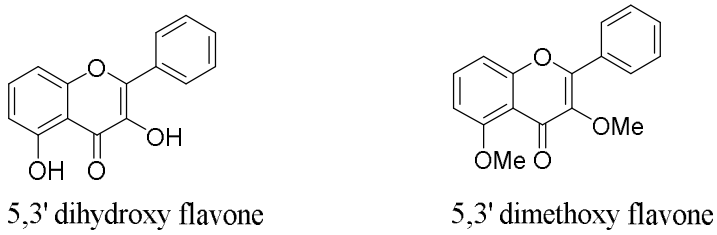



**Figure 24**: Flavone with anti-spasmolytic activity

Antispasmodic agents are the drug that suppresses muscle spasms. They are used for smooth muscle contraction in tubular organs of the gastrointestinal tract. The effect is to prevent spasms of stomach, urinary bladder and intestine. Hyoscyamine and dicyclomine are antispasmodic agents.so many flavone molecules screened for muscle relaxing properties by blocking muscarinic receptors [40]. Hydroxyl and methoxy flavones with selective substitution show potent activity. Flavones with C-3 and C-5 methoxy group with enone system in the ring C shows better activity. Flavoxate shows good anti-choligeneric anti-muscarinic activity [41].

**Antiviral activity**

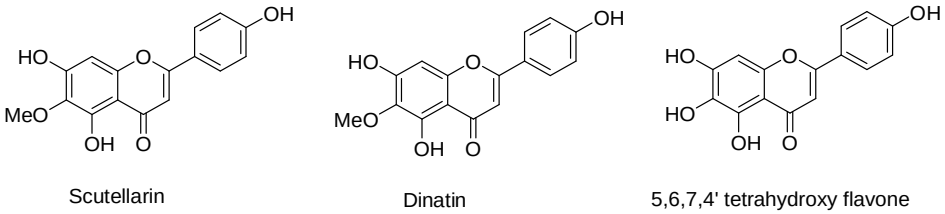



**Figure 25**: Flavone with antiviral activity

Various types of viruses like HIV, Hepatitis B, human herpes simplex virus, measles virus, Epstein-bar virus, human immune deficiency virus, influenza virus, polio virus, rota-virus etc. are harmful to human beings [42]. Flavonoids are compounds acting against them. Influenza is caused due to glycoprotein like hem agglutinin and neuraminidases (NA). NA is important for the life cycle of influenza virus [43]. So targeting this glycoprotein can get better lead for the treatment of influenza. QSAR study indicates that flavones like scutellarin, dinatin are the best drugs for the treatment of influenza. QSAR study also indicates that flavone molecules with hydroxyl groups at different position of ring A and B and different substituent at C-8 position of ring A, C=O and C2, C3 double bond in ring C increases its activity against NA [43-46]. QSAR study also indicates that electron withdrawing groups, hydrophobic groups and electrostatic interaction increases the activity of flavones. Biflavones are effective while alkylated flavones are less effective. Flavones also inhibit polio virus [47].

## CONCLUSIONS

Flavonoids are important pharmacophore for human health. They act medicines as well as food supplements. Different flavonoid skeleton with various substituent patterns show almost all biological activities, moreover they do not have side effects. A researcher on the basis of SAR can synthesize some novel flavonoids.

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