Beyond Pigments: The Diverse Biological Activities of Flavonoids

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Abstract-

Flavonoids are a diverse class of plant-derived secondary metabolites widely recognized for their vibrant colors and diverse biological activities. This review delves into the fascinating world of flavonoids, exploring their chemical structures, various types, and their potential health benefits. We comprehensively analyze the existing scientific literature on the antioxidant, anti-inflammatory, anticancer, and other promising biological activities exhibited by these potent compounds. Additionally, the review discusses the potential role of flavonoids in the prevention and treatment of various chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and metabolic syndrome. The article also sheds light on the challenges associated with the bioavailability and biotransformation of flavonoids and explores potential strategies to overcome these limitations. With their multifaceted health-promoting effects and readily available sources, flavonoids represent a promising avenue for developing novel therapeutic interventions and promoting overall well-being. This review aims to provide a comprehensive overview of the current understanding of flavonoids and their potential as potent allies in our quest for a healthier future.

Keywords- Flavonoids, antioxidant, anti-inflammatory, anticancer, therapeutic interventions

Introduction-

Flavonoids are a group of polyphenolic natural substances, which are present in fruits, vegetables, grains, barks, roots, stems, flowers, tea, chocolate and red wine etc. These are relevant to essential component in variety of nutraceutical, pharmaceutical, medicinal and cosmetic products. These properties are attributed to their anti-oxidative, anti-inflammatory, anti-mutagenic, anti-thrombogenic, anti-diabetic, anti-hepatotoxic, anti-tumor, anti-microbial, anti-viral, anti-carcinogenic and modulate key cellular enzyme function. These help our body to ward off every day from toxins; they normalize cellular activity and fight off free radicals that cause oxidative stress on our body. Flavonoids play numerous types of biological activities in plants, animals and bacteria. These are responsible for the color and aroma of flowers and in fruits to attract pollinators and dispersion to help in seed and spore germination and growth of seedling. Flavonoids protect plants from biotic and abiotic stresses and act as unique UV filtration, Nitrogen fixation, and floral pigmentation. Flavonoid demonstrates cytotoxicity on cancer cell, having free radical scavenging capacity on variety of human cancer cell. Some flavonoids prevent cell replication of H1N1flu, HIV, SARS, RSV viruses, Hepatitis, AIDS, Flu, different DNA and RNA viruses.

Structures of Flavanoids:- Flavonoids are 2-phenyl benzo-γ-pyrone derivatives compounds. Chemical structure of flavonoids has 15 carbon atoms constituted by two phenyl rings (A & B) linked by a heterocyclic pyrane or pyrone ring-C. Their structure is referred as C_6-C_3-C_6.[i,ii] The B ring is attached at position-2, 3 and 4 of ring-C. Hydroxylated positions of flavonoids are 3, 5, 7, and 3, 4, 5. These hydroxyl groups are also methylated, acetylated, phenylated and sulfated etc.[iii] the A ring is synthetized in the polyacetate pathway, the B ring is synthetized in the shikimate pathway and the C ring comes from both of these pathways, as a condensation product of secondary metabolites.[iv]

1.3: Classification:- Flavonoids are classified into various types depending on their chemical structure, degree of un saturation, and oxidation of carbon ring.[v] Their basic structures consist of C_6-C_3-C_6 rings.[vi] The term flavonoid is used in a restricted sense as comprising only those compounds with a C_6-C_3-C_6 carbon framework exhibiting the structure of a chromane or that of a 1-benzopyran (chromene), in which the fused benzene ring is designated as ring-A and the 3,4-dihydro-2*H*-pyran or the pyran as ring-C, along with a phenyl group (ring-B) on ring-C. Depending on the position of the linkage of ring-B to the chromane /1-benzopyran (chromene) moiety, three different classes can be assigned. In flavonoids (1), when ring-B is attached at position-2 of the ring-C, then flavonoids are divided into several subgroups on the basis of structural features like, Flavanols (2), Flavanones (3), Flavones (4) Flavonols (5), anthocyanins (6), isoflavonoids (7). If ring-B is attached at position-3 and 4of the ring-C is called Isoflavonoids and neoflavonoids (8) respectively. The other flavonoids categories having a structure with a C_6-C_3-C_6 carbon framework are the chalcones (9), xanthones (10), pterocarpans and their 3,4-didehydro derivatives.[vii, viii, ix].

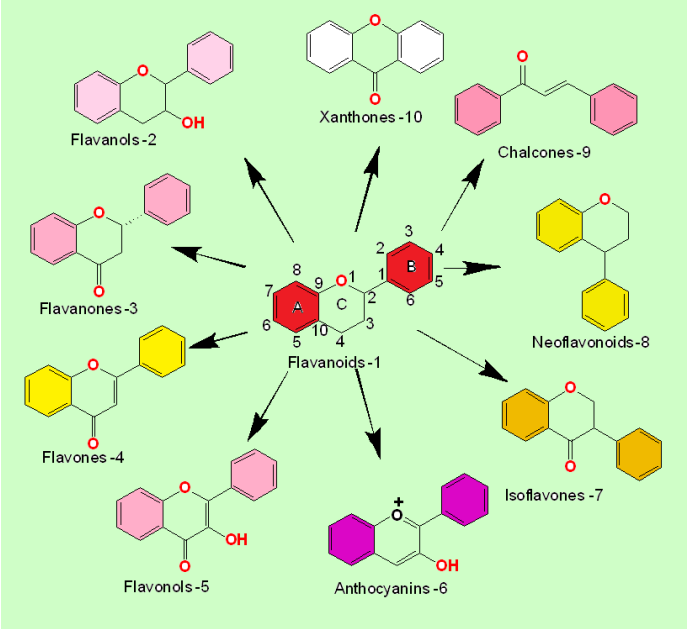


Fig-1: Classification of Flavanoids

(a) Flavanols:- In flavanol (2), ring-C has no double bond between position C_2 & C_3 and it has no Carbonyl group at position C_4, but a hydroxyl group at C_3 position, Due to hydroxyl group at C_3 and phenyl group at C_2, flavanols have two chiral centre (R-S). It presents in foods and beverages as monomers (epicatechin- (11) or catechin- (12) and oligomers (procyanidins) present at dimer in peanut skins (12) and in cocoa beans (13).[x]

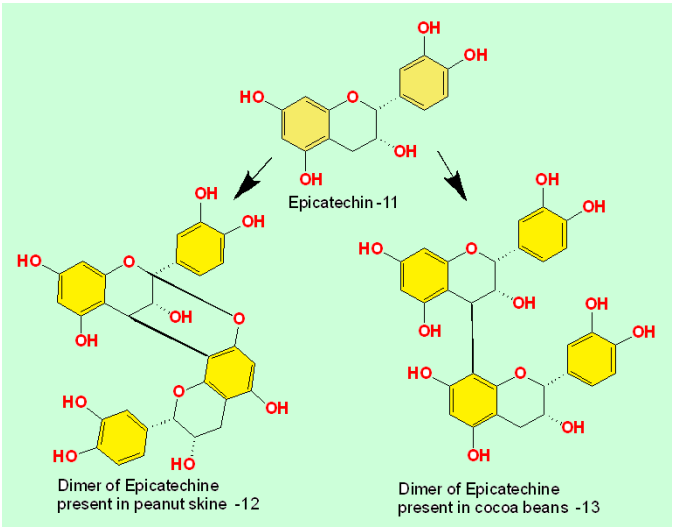


Fig-2: Different types of Flavnols

(b): Flavanones:- Flavanones (3) have no double bound in ring-C between position C_2 & C_3. but it has a carbonyl group at C_4 position, due to basic structure of flavonoid ring-C has phenyl group at C_2 position, the position C_2 show one chiral centre. They are mainly present in Hesperitin, (14) Naringenin, (15) Eriodictyol, (16) and Isosakuranetin, (17) Flavanones in sweet oranges, tangerines, and tango's were midway between sour and sweet.[xi] Flavanones (3) within the organism including absorption, metabolism, distribution, and excretion moreover as possible kinetic interactions with clinically used drugs. They are rapidly metabolized specifically into conjugates, sulfates and glucuronides, which foremost forms circulating in plasma.[xii]

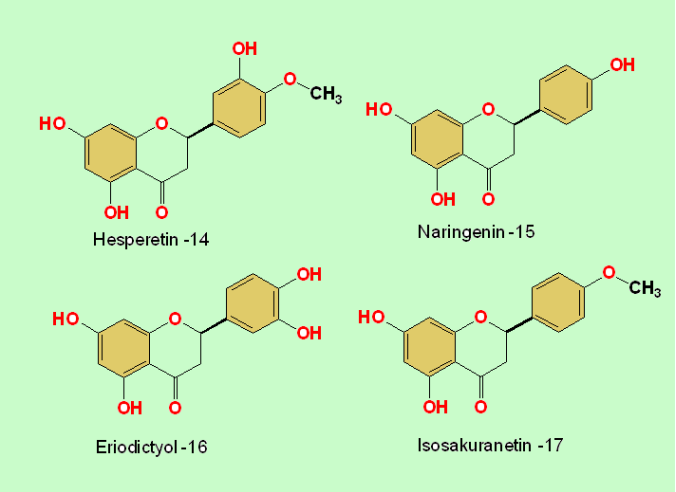


Fig-3: Different types of Flavanones

(c): Flavones:- Flavones (4) are important groups of flavonoids. In flavones ring-C have double bond in position C_2 & C_3 and it have carbonyl (ketone) group in position C_4. Due to double bond at C_2 and C_3 it has not show chiral centre or optical isomerism but it can show gometrical isomerism. They are widely present in Chrysin (18), Apigenin (19), Luteolin (20), Wogonin (21), and Tangeritin (22).

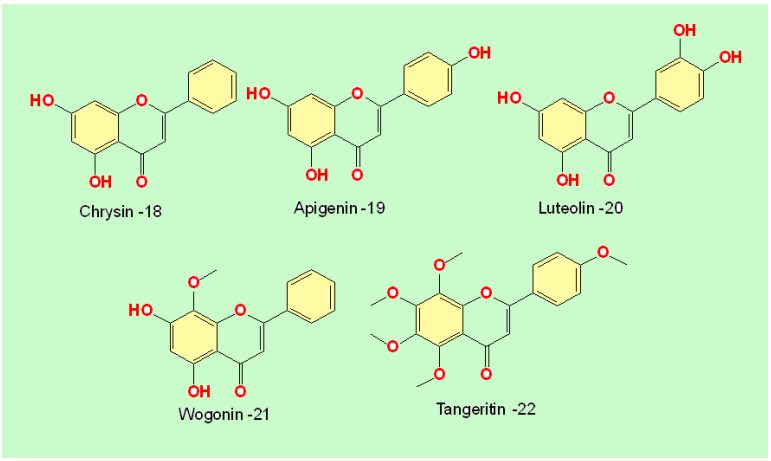


Fig-4: Different types of Flavones

(d): c

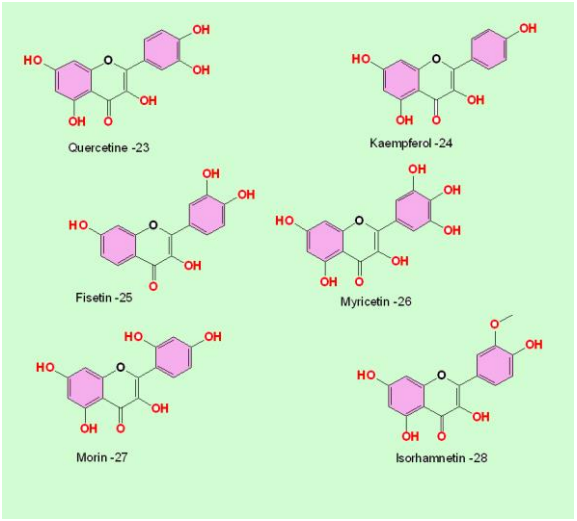


Fig-5: Different types of Flavonols

(e): Isoflavonoids:-Isoflavones (6) are ecophysiologically active secondary metabolites They were mostly found in leguminous plants.[xiii] In isoflavonoid ring-C has no double bond between position C_2 & C_3. It has no Carbonyl group at position C_4 and It has phenyl group at position C_3 instead of position C_2. Moreover, small amounts of isoflavonoids are also contained in other plant products (cereals, potatoes, vegetables, fruits), as well as in milk, meat, and beer.[xiv] Daidzein (29), Genistein (30), Glycitein (31), Biochanin (32), and Formononetin (33) belong to isoflavone phytoestrogens.[xv] These are structurally same as estrogens, exerting both estrogenic and antiestrogenic properties in various tissues. Daidzein puts forth shielding effects against a large number of diseases, especially those associated with the control of estrogen.[xvi] Some protective effect of their consumption in immunomodulation, cognition, risk reduction of certain cancers, cardiovascular and skin diseases, osteoporosis and obesity, as well as relief of menopausal symptoms.[xvii,] Daidzein (29) is a phytoestrogen isoflavone found in soybeans and other legumes. Daidzein puts forth shielding effects against a great number of diseases, especially those associated with the control of estrogen, such as breast cancer, diabetes, osteoporosis, and cardiovascular disease, its best known effects alleviating postmenopausal symptoms to its potential anticancer and antiaging properties.[xviii]

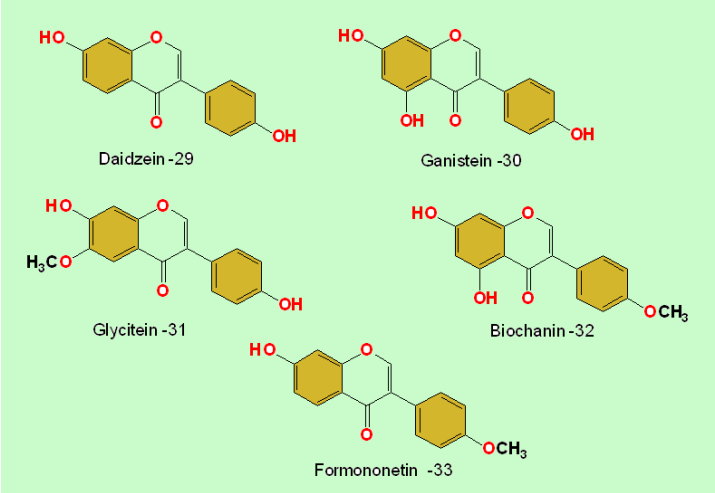


Fig-6: Different types of Isoflavonoids

(f): Neoflavonoids:- Neoflavonoids are (8) not found in food and edible plants, but widely isolatedfrom different plant. They are commonly being identified in various plants, belonging to Dalbergia genus.[xix] In Neoflavonoid, ring-C has no double bond between C_2 & C_3 and instead of carbonyl group at position C_4 having phenyl group at C_4. Neoflavonoid have 4-phenylchromen backbone without hydroxyl group at C_2. *Dalbergia* species have been found to display several health beneficial effects.[xx]

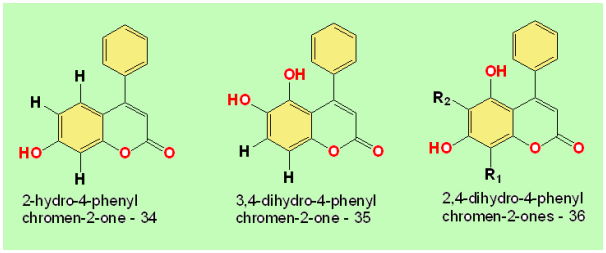


Fig-7: Different types of Neoflavonoids

(g): Anthocyanin: -In Anthocyanin (6) phenyl group is at C_2 position in ring-C and two double bond between C_1 & C_2 and C_3 & C_4. Its basic structure is derived from flavylium ion, that is a lack of a ketone oxygen at the 4-position. The empirical formula for flavylium ion is $C_{15}H_{11}O^+$ with a molecular weight of 207.24724 g/mol.[xxi] These compounds are formed by a flavylium cation backbone hydroxylated in different positions (generally on carbons C_3, C_5, C_6, C_7 and C_3', C_4´, C_5´) to give rise to different anthocyanidins. these molecules contain an oxonium group in their structure, the flavonoid skeleton maintains its ring nomenclature with the charged oxygen atom on the ring-C.[xxii] Anthocyanins (6) are the glycosylated form of Anthocyanidins. Anthocyanidins are grouped into 3-hydroxyanthocyanidins, 3-deoxyanthocyanidins, and *O*-methylated anthocyanidins, The most common types of anthocyanidins are pelargonidin (37), cyaniding (38), delphinidin (39), peonidin, (40), pelunidin (41), and malvidin (42). Acylated anthocyanins are also detected in plants besides the typical anthocyanins. Acylated anthocyanin is further divided into acrylated anthocyanin, coumaroylated anthocyanin, caffeoylated anthocyanin, and malonylated anthocyanin.[xxiii]

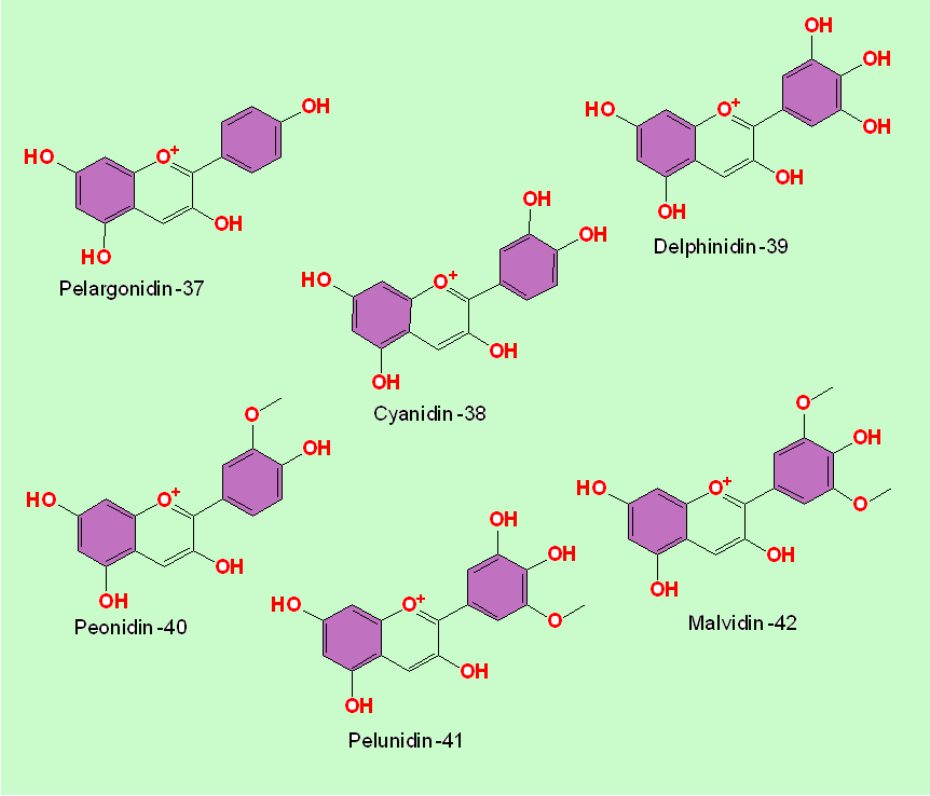


Fig-8: Different types of Anthocyanins

(h):Chalcones:- Chalcones (9), belong to the phenolic compounds of flavonoid group, ring-C of flavonoid is open in chalcones and compounds have a common chemical scaffold of 1,3-diaryl-2-propen-1-one, They are generally α, β-unsaturated ketone consisting of two aromatic rings (rings A and B) linked through a three-carbon alkenone unit.[xxiv]

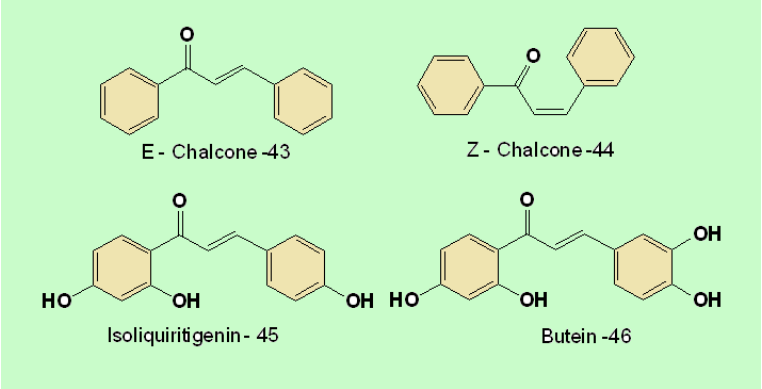


Fig-9: Different types of Chalcones

(i): Xanthones:- Xanthones (10), are related to that of flavonoids and their chromatographic behaviours are similar.[xxv] Xanthone is a tricyclic scaffold, containing oxygen as the heteroatom, namely, dibenzo -γ- pyrone ring,[xxvi] designated by the rings -A and B, the central pyranoid ring-C with partial aromatic character. It is essentially planar due to the conjugated ring systems, which deviates 0.13 Å from the plane, xanthone is present in solid state. The rigidity of this scaffold contributes to the stability of the compound. Xanthones come from the biosynthetic pathways for the compounds from higher plants,

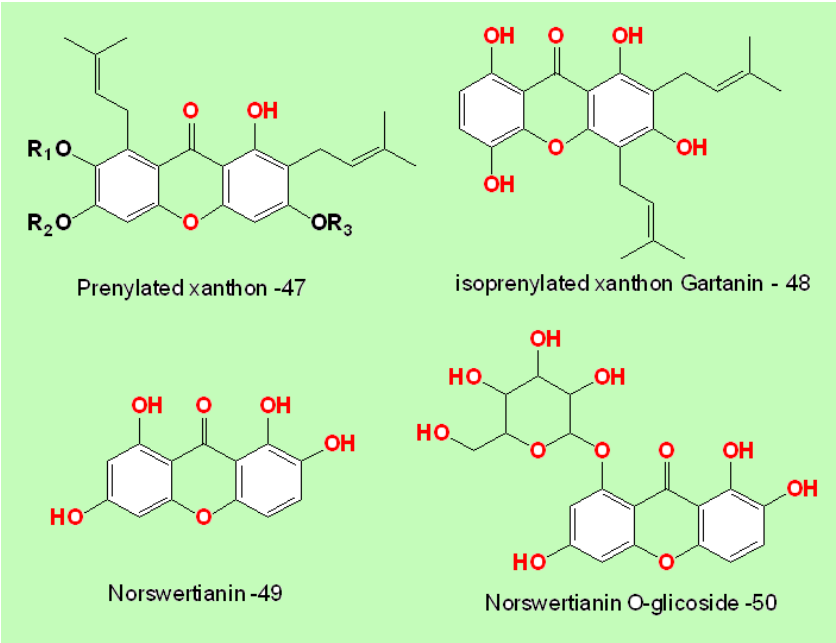


Fig-10: Different types of Xanthones

1.4: Biological Activities:

1.4.1: Anticancer agents: Many flavanols and their derivatives having potential anticancer activities. Catechins (51), epicatechin (52), epigallocatechin (53), and epigallocatechin gallate (54) are extracted from green tea could synergistically enhance cancer treatment efficacy and reduce the adverse side effects of anticancer drugs in cancer patients.[xxvii] catechins, especially epigallocatechin galate, inhibited NF-κB, leading to cyclooxygenase-2(COX) overexpression. Moreover, it increased Bax/Bcl-2 ratio, upregulated p53, p21, caspases-3, and -9, and down-regulated PI3K, Akt, and Bcl-2 in T47D and HFF cells.[xxviii]

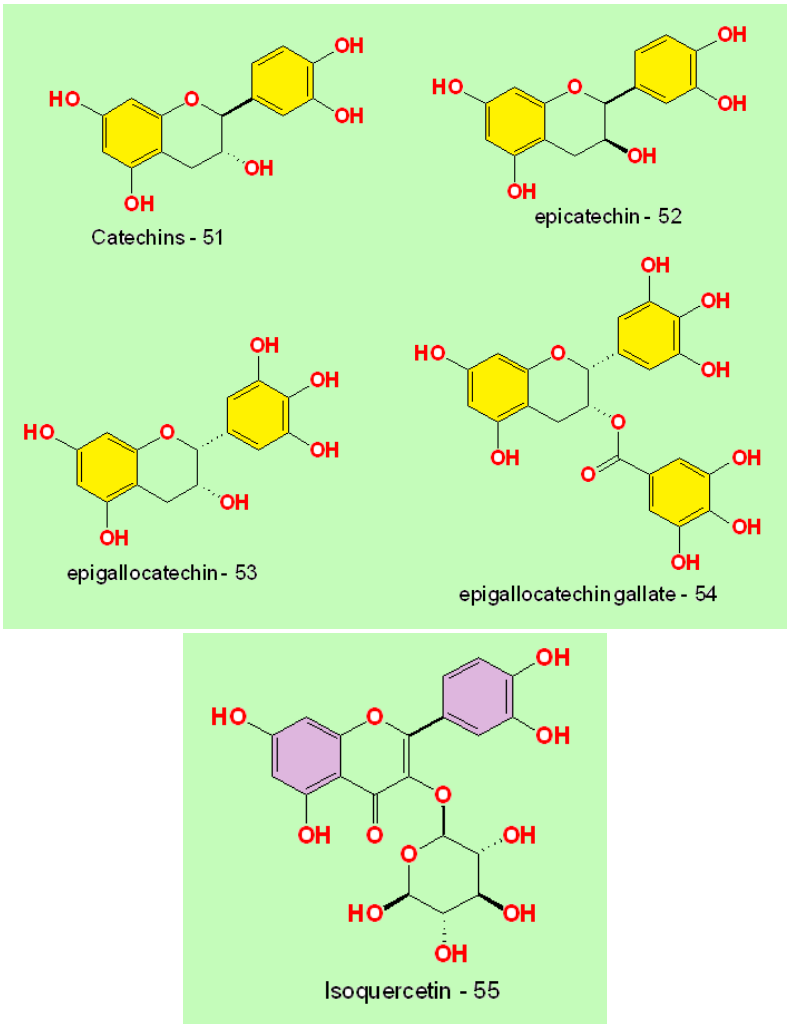


Fig-11: Different type of Anticancer Agent

Quercetin (23) are natural, non-toxic chemo preventers, regulates numerous tumor-related activities, such as oxidative stress, angiogenesis, cell-cycle, with limited toxic effects on normal cells.[xxix] These are affects on several cell lines of the tongue cancer: SAS, OSC20, SCC25, SCC-9, HSC-3, Tca8113, SCC-15, TW206; throat cancer: FaDu line; oral cavity cancer HN22 and TW206 cell lines. IC_{50} value of Quercetin (23) is relation to tongue cancer cell lines was variable and equaled from 20 μM in case of HSC-3 cell line up to 160 μM in relation to SAS and OSC20 cell lines.[xxx] Isoquercetin (55) effectively inhibited the proliferation of SK-MEL-2 skin cancer cell line. Morphological analysis and clonogenic assay also showed that IQ can alter the growth and long-term survival of SK-MEL-2 cells.[xxxi] Kaempferol (24) is able to inhibit HIF-1α ERK1/ERK2- nuclear translocation. In addition to HIF-1α, 40 μM, HepG2 and Hep3B cell lines pre-treated with Kaempferol. In combination of oxaliplatin, HCT116 and RKO cell lines treated with low concentrations of Kaempferol. Myricetin (26) acts against HepG2 cell line, and able to induce Caco-2 and HT-29 cell lines. It is tested alone or in combination with the docetaxel, on MDA-MB-231 cells and enhanced the anti-cancer activity of docetaxel.[xxxii] Fisetin (25) inhibits cancer by modulating important enzymes and receptors in signal transduction pathways related to proliferation, differentiation, apoptosis, inflammation, angiogenesis, metastasis and reversal of multidrug resistance.[xxxiii] It affects Ca9-22 cell line of gingival squamous cell carcinoma, CAL-27 & HSC3 cell line of the tongue

carcinoma and decreases viability of SCC-4 cells depending on the dose and time.[xxxiv] It induces apoptotic cell death in oral squamous cell carcinoma cell lines (Ca9-22 and CAL-27) and (HSC-3, Ca9-22, and CAL-27) via the mitochondrial pathway, human laryngeal cancer cell lines (TU212, M2e, and Hep-2) via inhibiting tumor cell proliferation. It enhances the activity of pro-apoptotic proteins (e.g., BAD, BAX, NOXA, BOK) and caspase-3, caspase-8, and caspase-9 in head and neck cancer cells but alleviates the activity of anti-apoptotic BCL-2, MCL-1, XIAP, and BCL-X.[xxxv] Morin (27) hydrate and Isorhamnetin also exhibit potential anticancer activities.[xxxvi,xxxvii] Flavan-3-ol derivatives compound….(2*R*,3*S*)-3,3′,5′,7-tetrahydroxy-4′-methoxyflavane,(56) compound….*(2R,3S)*-3′,5′,7-trihydroxy-4′methoxy flavane-3-*O*-β-D-glucopyranoside (57) and compound….*(2R,3S,4S)*-3,3′,4,5′,7 pentahydroxy-4′-methoxyflavane (58).active against both recalcitrant leukemia cell lines with IC_{50} values of 21.90 μM towards CCRF-CEM and 50.80 towards CEM/ADR5000.[xxxviii]

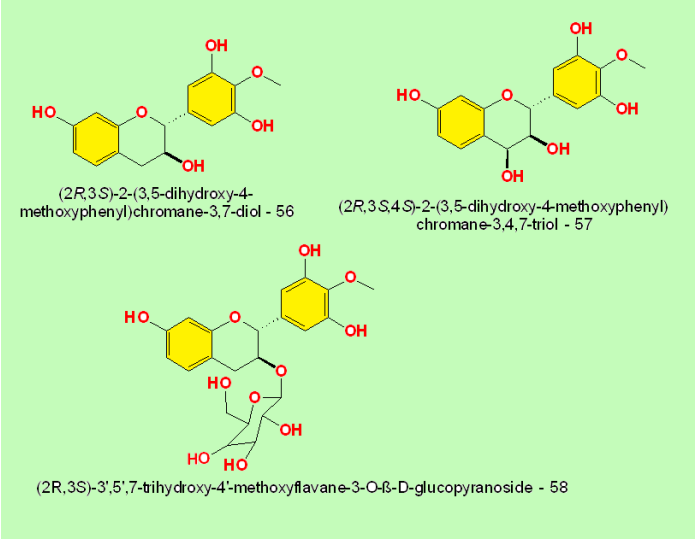


Fig-12 Different Chemical Structure of drugs active in Leukemia

Most common flavanones (3) a glycones and their corresponding glycosilated are Hesperetin (14), naringenin (15), eriodictyol (16), isosakuranetin (17) and taxifolin and their glycosylated derivatives. These compounds support and enhance the body's defenses against oxidative stress andcancer.[xxxix] Anthocyanins acid demonstrated anti-invasive potential in breast cancer cell lines, MDA-MB-231 and MCF7 and human HT-29 colon cancer cells.[xl] Neoflavonoid (8) increased cell death on T47D and MDA-MB-231 cells with and without radiotherapy.[xli] The compound 4′-Hydroxy-6,7-methylenedioxy-3-methoxyflavone showed enzyme inhibition and used for cancer therapy.[xlii] Isoliquiritigenin (45) (2′,4′,4-trihydroxychalcone, ISL) is potential therapeutic against various cancers, including breast cancer, colon cancer, gastrointestinal cancer, lung cancer, ovarian cancer, and leukemia. Butein (46) shows anticarcinogenic action in non-small cell lung cancer (NSCLC) through endoplasmic reticulum stress-dependent Reactive Oxygen Species (ROS) generation and an apoptosis pathway both in vivo and in vitro.[xliii] Norswertianin (49) and Norswertianin *O*-glicoside (50) were investigated for antiglioma activity. The results of the crystal violet assay indicated that NOR and NOR-1-O-P inhibit U25 glioblastoma cells growth in a dose-dependent manner (IC50 =31.2 μM for NOR and 48.3 μM for NOR-1-O-P, respectively). derivatives are cytotoxic in the human leukemia cell line HL 60 and may therefore mediate the mitochondrial pathway during apoptosis, which include swelling, loss of membrane potential (DYm), a decrease in intracellular ATP.

(b): Antioxidative:- Flavanols (2) are good antioxidants.[xliv], Citrus species have potential antioxidant activity for cancer treatment.[xlv]Alpinia galanga has a large number of flavonoids, that can be applied to cosmeceutical product development because of their antioxidant, anti-aging and many other potential biological activities.[xlvi]Acai fruit has luteolin and dihydroKaempferol (24) havinghigh anti-oxidant capacity. Anti-oxidant capacities of these flavonoids were evaluated by oxygen radical absorbance capacity (ORAC) assay, cell-based anti-oxidant protection (CAP-e) assay and reactive oxygen species (ROS) hydroxyl groups and other substitute groups.[xlvii] Quercetin (23) inhibits significantly AChE & BChE and having radical scavenging abilities with Fe^{2+}-chelating ability. The inhibition of cholinesterases and antioxidative properties are possible mechanisms by which the flavonoids can be used in the management of oxidative stress–induced neurodegeneration.[xlviii] They clearly exert to neuroprotective benefits, improve normal cognitive function and exert a protective role on cardiovascular function impaired sleep loss.[xlix] Metal-flavonoid complexes improve biological and physicochemical properties, with increase in antioxidant properties. In the structure-activity relationship on the antioxidant properties of three series of metal-flavonoid complexes: Metal-(quercetin) (59), Metal-(morin) (60), and Metal-(rutin) (61), it is observed that the coordination sites, the metal ion type used, and the molar ratio metal:flavonoid present in the complexes, are important factors to increase the antioxidant activity. The development of metal-flavonoid compounds is a potentially viable approach for combating neurodegenerative diseases.[l]

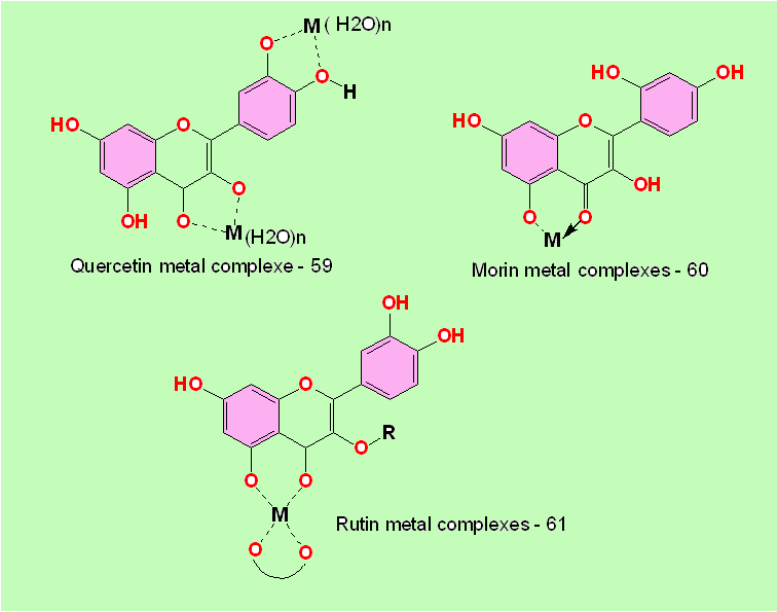


Fig-13 Different Structure of Antioxidative Agents

(c): Anti-inflammatory:-Inflammation plays key role in diseases like diabetes, asthma, cardiovascular diseases and cancer. Polyphenolic compounds, like flavonoids (1) have anti-inflammatory properties by inhibiting regulatory enzymes or transcription factors important for controlling mediators involved in inflammation.[li] A natural geranylated Flavanones have anti-inflammatory activity with possible mechanism of action. Two new compounds were characterized paulownione C (62), and tomentodiplacone O (63), inhibit cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX). However, only the compound tomentodiplacone O showed more selectivity against COX-2 versus COX-1 when compared

with ibuprofen.[lii] Flavonoids have been studied in order to establish and characterize their potential utility as therapeutic agents in the treatment of inflammatory diseases.[liii, liv] Luteolin (20) is an anti-inflammatory flavonoid commonly found in many edible plants. luteolin that showed both dose-dependent anti-inflammatory activity and cytotoxicity when tested in lipopolysaccharide-stimulated macrophages, the polyluteolin nanoparticles possess dose-dependent anti-inflammatory activity without causing cell death even at high concentrations.[lv]

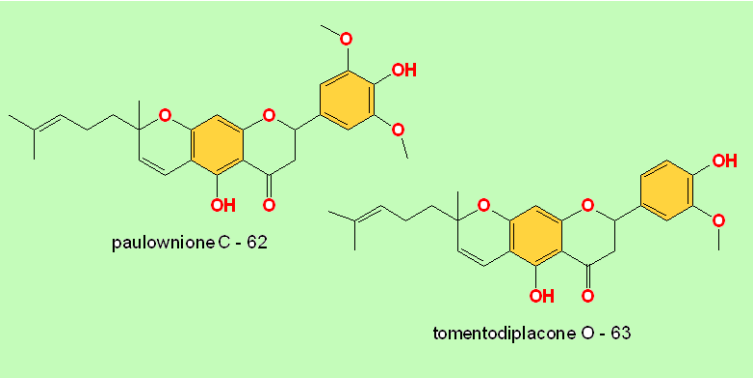


Fig-14 Different Structure of Anti-inflammatory Agents

(d): Anti-thrombogenic: Flavonoids exert innumerable beneficial effects on cardiovascular health including the reduction of platelet activation, and thereby, thrombosis. Synthesis flavones containing a sulfur molecule (66) at the 4th carbon position of the C-ring. This structure-activity relationship of flavonoids with the modulation of platelet function and development of flavonoid scaffolds as antiplatelet agents. Hydroxy flavone with free hydroxyls and carbonyl moiety significantly inhibited CRP-XL-stimulated platelet aggregation at lower concentrations such as 3.125, 6.25 and 12.5 μM. The hydroxy 4-thioflavone showed significant inhibitory effects at all the concentrations. However, the methoxy flavone inhibited the aggregation significantly only at 100 μM. Furan B-ring and hydroxyl 4-thioflavone (67) inhibited the CRP-XL-induced platelet activation at all the concentrations. Pyridine ring-B (68) displayed inhibitory effects on CRP-XL-stimulated platelet aggregation at concentrations up to 100 μM.[lvi]

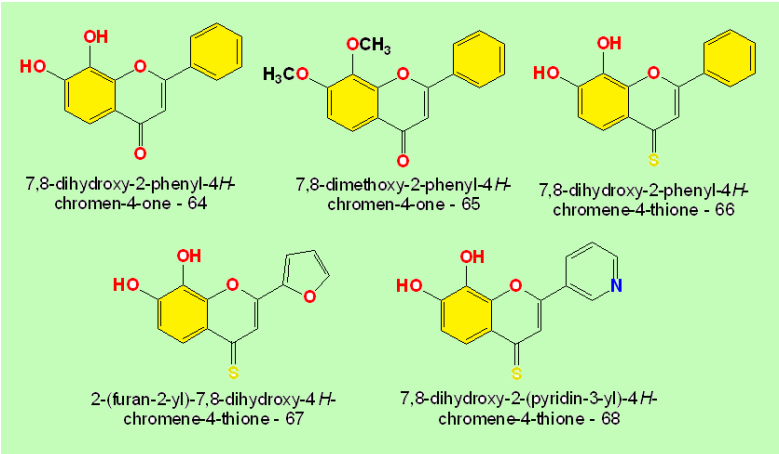


Fig-15 Different Structure of **Anti-thrombogenic** Agents

Anthocyanin (6) has been exhibit anti-dyslipidemic and anti-thrombotic properties. They have been associated with high bleeding risk and increased response variability. Natural dietary anthocyanins is targeting simultaneous mechanistic pathways in alleviating platelet activation,

dyslipidemia, and oxidative stress-associated thrombus acceleration in obese pro-thrombotic populations[lvii, lviii]. Flavanol (2) act in part through signaling pathways that affect vascular function, nitric oxide availability, and the release of endothelial-derived relaxing and constricting factors. They induce reductions in blood pressure during exercise may decrease the work of the heart.[lix] Flavonoids may reduce the risk of hyper-activation of platelets, cardiovascular diseases (CVD), pain, and thrombosis; they reduce the risk of atherosclerosis and atherothrombotic disease by inhibiting excessive tissue factor (TF) availability in the endothelium[lx, lxi]

(f): Anti-diabetic*:* Diabetes mellitus (DM) is a complex chronic illness associated with a state of high blood glucose level, or hyperglycemia, occurring from deficiencies in insulin secretion, and action. The chronic metabolic imbalance associated with this disease puts patients at high risk for long-term macro- and microvascular complications,[lxii] Flavonoids possess anti-diabetic effects several molecular mechanisms on selected pathways Glucose transporter, hepatic enzymes, tyrosine kinase inhibitor, AMPK, PPAR, and NF-κB.[lxiii] Flavonoids have antidiabetic features respectively. Apigenin (19), baicalein (20), and catechin (51) mainly reduces blood glucose via anti-oxidation; hesperidin (71) is good for diabetic neuropathy; glycyrrhiza flavonoids have a significant effect on gestational DM; Quercetin (23) takes advantage of crossing the blood–brain barrier and improving renal function. Some compounds have protective and preventive effects on diabetic complications, such as Kaempferol (24), Myricetin (26), has therapeutic potential in the treatment of DN; dihydromyricetin might improve CI.[lxiv] The total number and the configuration of hydroxyl groups played an important role in regulating antioxidant and antidiabetic properties in scavenging DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical, $ABTS^{+}$ radical, and FRAP assays and improved both α-glucosidase and DPP-4 activities. Presence of C_2-C_3 double bond and C-$_4$ ketonic group are especially for antidiabetic property. Methylation and acetylation of hydroxyl groups were found to diminish the antioxidant and antidiabetic properties of the flavonoids.[lxv]

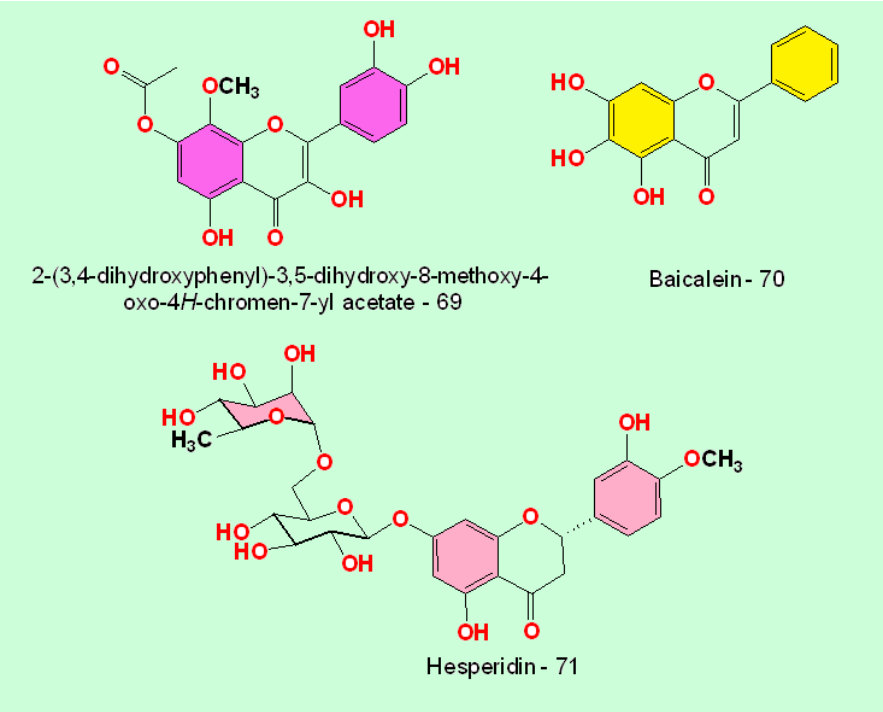


Fig-16 Different Structure of **Anti-diabetic** Agents

Four main flavonoids present in Sophora davidi plant namely Apigenin (19), Maackiain (72), leachianone A (73) and leachianone B (74) have antidiabetic activities. SD-FRE promoted GLUT4 expression and activated AMPK phosphorylation in insulin target tissues (muscle, adipose tissue and liver) of KK-Ay mice, thus facilitating glucose utilization to ameliorate insulin resistance. With these findings it is proved that SD-FRE has the potential to alleviate type-2 diabetes.[lxvi]

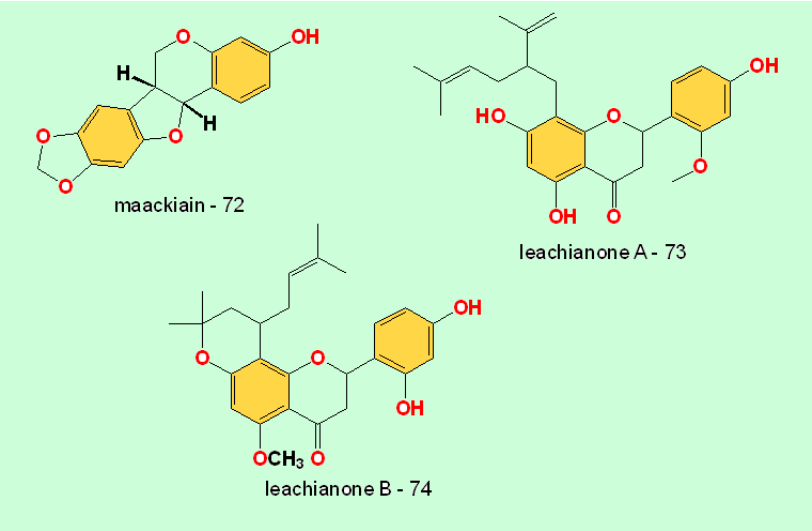


Fig-17 Different Structure of **Anti-diabetic** Agents (Flavanoids)

Brown Sorghum grains are unique in that they contain diverse phytochemicals, particularly polyphenols, which are known to significantly impact human health. These phytochemicals are reported to be beneficial in the prevention of metabolic syndromes such as type 2 diabetes.[lxvii] Chalcone based PPAR-alpha agonists were synthesized and evaluated for their antidyslipidemic activity in high fructose high fat fed dyslipidemic Syrian golden hamsters. Most of the compounds exhibited antidyslipidemic activity.[lxviii]

(g)**: Anti-hepatotoxic***:* Flavonoids prevented the biochemical measurable changes induced by CCl_4 in the liver. The flavonoids Morin (60), Quercetin (23), Primuletin, their Cu (II) and Fe (III) complexes were selected to explore their radical scavenging potential. Metal complexes of flavonoids (M-Fls) showed better radical scavenging activity (RSA) corresponding flavonoids. The RSA is improved in the presence of HP-βCD. The compounds displayed hepatoprotection against alloxan induced liver damage as flavonoid injected group displayed lower levels of enzymes and intermediates aspartate/alanine transaminase (AST), alanine aminotransferase (ALT), Lipid peroxidation (MDA), Hydroxyproline (HYP), Sailic acid (SA) and higher Albumin and total proteins level compared with alloxan treated group.[lxix] Flavonoid is used to protect the liver.[lxx] Methanol extracts of Satureja macrostema showed, kidney protective, and hepatoprotective activities in-depth chromatographic investigation resulted in the identification of six new flavonoid glycosides (1) 5-hydroxy-3,6,4′-trimethoxyflavonol-7-C-α-L-rhamnopyranosyl(1 → 3)-β-Dglucopyranoside (76). (**2**),4′-methoxy-5,7,3′,5′-tetra-hydroxy flavanone-3-O-β-D-rhamnopyranosyl-(1 → 2)-β-D-rhamnopyranoside (77) (**3**),5,4′-dimethoxy-7,3′,5′-trihydroxyflavanone-3-O-β-D-rhamnopyranoside (78), (**4**),5,3′,4′,5′-tetrahydroxy flavanone-7-O-β-D-rhamnopyranoside (79), (5), 5,3′,4′,5′-tetramethoxyflavanone-7-O-β-D-rhamnopyranoside (80) and (**6**), 5,4′-dimethoxy-3′-

hydroxyflavone-7-β-D-rhamnopyranoside (75). The present study revealed that *S*.macrostema leaves have a significant radical scavenging and hepatoprotective activity.[lxxi]

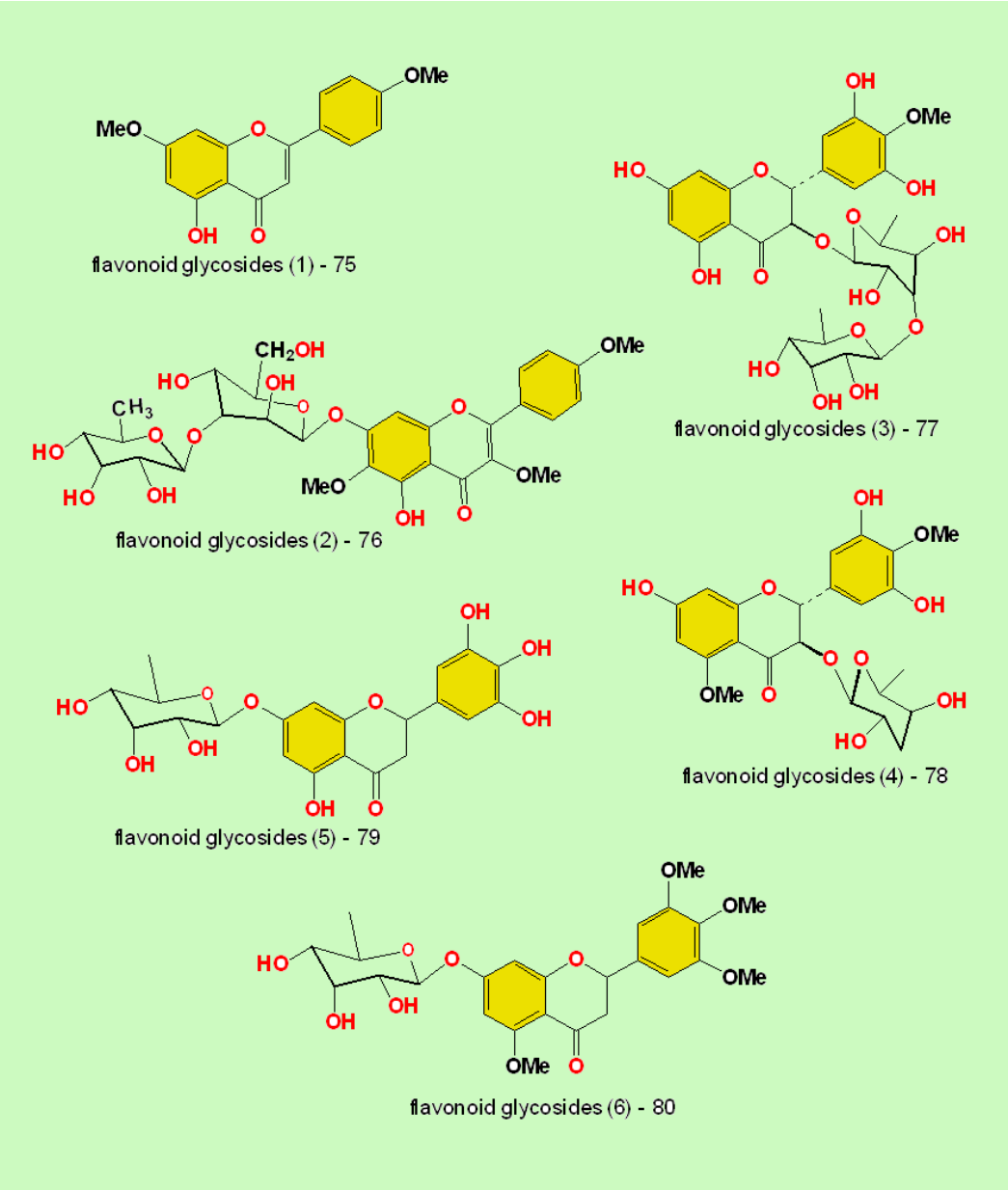


Fig-18 Different Structure of **Anti-hepatotoxic** Agents

The liver is participate in innate immune function and thus exposed to frequent target thus, they are the frequent target of physical injury. Interestingly, liver has the unique ability to regenerate and completely recoup from most acute, non-iterative situation. Flavonoid, have potential medicinal activity with its mode of action mitigating liver associated complications.[lxxiilxxiii]

1.4.8: Anti-microbial: Flavonoids (1) display a wide range of pharmacological and beneficial health effects for humans. These are response to potent antimicrobial agent against a wide range of pathogenic microorganisms. Flavonoids manifest ability to reverse the antibiotic resistance and enhance action of the current antibiotic drugs.[lxxiv] The hydroxylation of C_5, C_7, C_3', and C_4', (Fig-81) and geranylation or prenylation at C_6 have been extensively studied to increase bacterial inhibition of flavonoids.

The structure activity relationship of flavonoids (1) to discover safe and potent antibacterial agents as natural products.[lxxv] Most flavonoids against gram-positive bacteria could be roughly calculated from their ACD/LogP and the minimum MIC was predicted as approximately 10.2 or 4.8 μM, more likely falls into the range from 2.6 to 10.2 μM. Both tendentiously concave indicated that the lipophilicity is a key factor of flavonoids against gram-positive bacteria. These results suggested that the cell membrane is the main site of flavonoids acting on gram-positive bacteria, and which likely involves the damage of phospholipid bilayers, the inhibition of the respiratory chain or the ATP synthesis, or some others.[lxxvi]

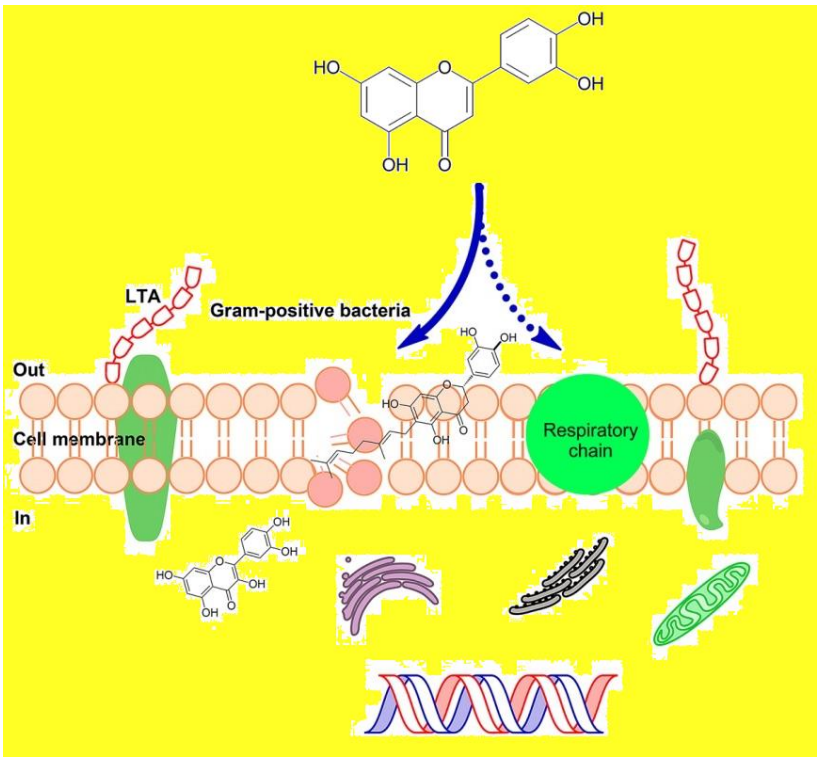


Fig-19 Different Structure of **Anti-microbial** Agents

Flavonoid metal complexes possess more effective functional properties than flavonoids. However, Iso zinc complex (Iso−Zn, [Zn3(C21H14O11)2]·4H2O)(83) had been synthesized and characterized. The radical scavenger and antibacterial potencies of Iso−Zn were significantly stronger than those of Iso. The Iso−Zn exhibited better water solubility, and antibacterial activities, and lower cytotoxicity and provided a theoretical basis for expanding the utilization scope of Iso through enhancing its hydrophilicity.[lxxvii]

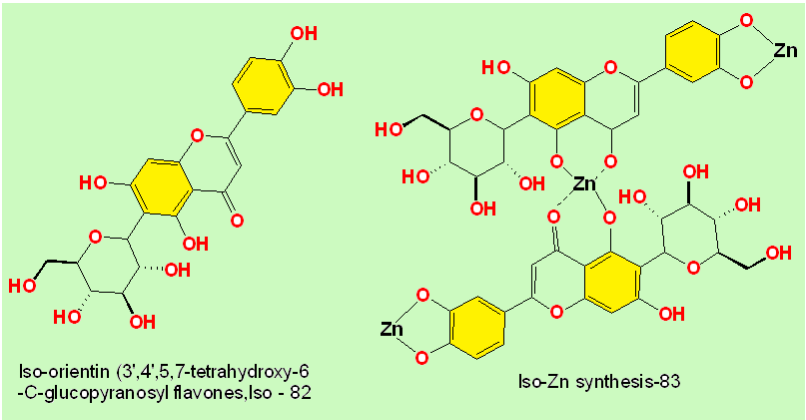


Fig-20 Different Structure of **Anti-microbial** Agents (Flavanoid)

The activity of Quercetin (23), has been partially attributed to inhibition of DNA gyrase. It has been proposed that sophoraflavone G and (−)-epigallocatechin gallate (54) inhibit cytoplasmic membrane function. These compounds represent the development of a pharmacologically acceptable antimicrobial agent.[lxxviii,lxxix] A novel synthetic sulfur containing tricyclic flavonoid with chlorine as halogen substituent at the benzopyran core (84) could be a reliable solution due to their important antimicrobial activity. The antimicrobial effects were tested using the minimum inhibitory concentration, more active than other synthetic flavonoids. These compounds showed significantly enhanced antibacterial activities, at Gram positive bacteria compared to the Gram negative ones.[lxxx] Most of the synthetic flavonoids were found to be effective against pathogenic microorganisms.[lxxxi]

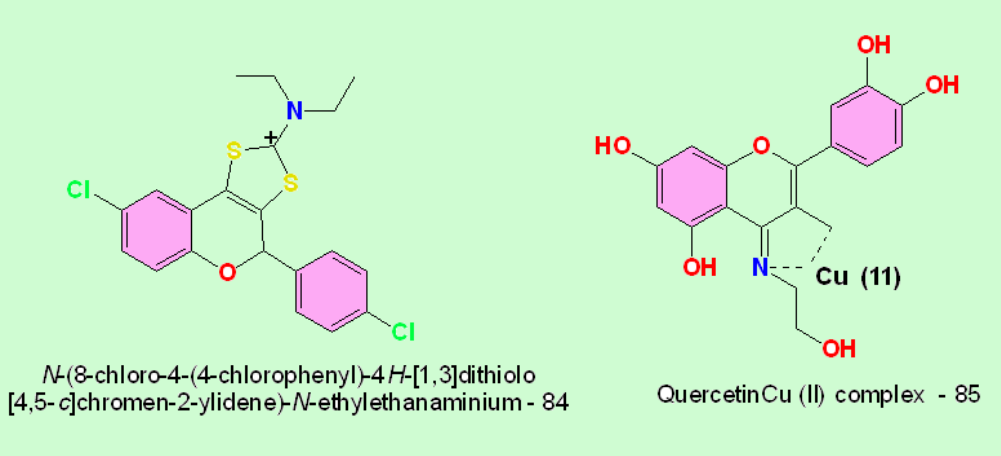


Fig-20 Different Structure of Anti-inflammatory Agents

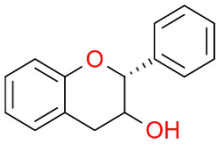
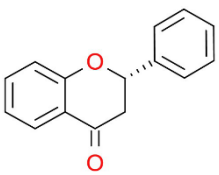
Quercetin has the ability to bind with several metal ions to increase its biological activities. Quercetin and ethanolamine were used for the synthesis Schiff base complex, The Schiff base has been employed as a ligand for the synthesis of novel nanoscale Cu (II) complex. These nanoscale Cu(II) complex (85) exhibited a strong antibacterial activity against both Gram-positive and Gram-negative bacteria.[lxxxii]

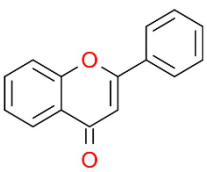
1.4.9: Antiviral: several natural flavonoids exhibited significant anti-viral properties both in vitro and in vivo.[lxxxiii] Neoflavonoids (8) have been evaluated against HIV-1. Antiviral activity was assessed on MT-2 cells infected with viral clones carrying the luciferase reporter gene.4-phenylchromen-2-one (86) derivatives showed HIV transcriptional inhibitory activity.[lxxxiv] Phosphorylation of protein by cytokines is inhibited by flavonoids which help in the cell arrestation of HIV at integration traction phage of virus.[lxxxv, lxxxvi]

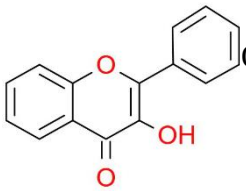
Flavonoids act on five RNA viruses with similar clinical manifestation streatments, including influenza, human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Ebola. Flavonoids have shown antiviral activity via inhibition of viral protease, RNA polymerase, and mRNA, virus replication, factor-κB and N-terminal kinases. Baicalin (70), Quercetin (23), and its derivatives, hesperidin (71), and Catechins (51), are promising treatment options against COVID-19 infection.[lxxxvii,lxxxviii] Viral infections caused by the human immunodeficiency, virus types (HIV-1 and HIV-2), hepatitis virus B and C, influenza, A virus and the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) present a significant global burden.

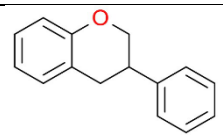
Jamaican medicinal plants, to show their antiviral activity.[lxxxix] Quercetin with highest binding energy against NS2B-NS3 protease which is evident by the formation of six hydrogen bonds with the amino acid residues at the binding site of the receptor. Flavonoids from *Carica papaya* have significant anti-dengue activities.[xc, xci] Quercetin can interfere with various stages of the coronavirus entry and replication cycle such as PLpro, 3CLpro, and NTPhelicase. Due to its pleiotropic activities and lack of systemic toxicity, quercetin and its derivatives may represent target compounds to be tested in future clinical trials to enrich the drug arsenal against coronavirus infections.[xcii]

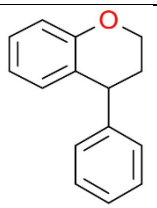
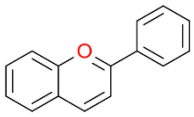
Table-1- Different types of flavonoids, their structure and biological Activity-

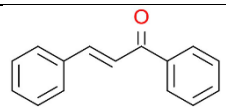
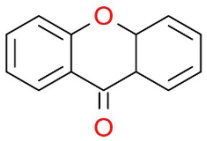
Flavonoids	**Structure**	**Compounds name**	**Biological activities**	**Compounds Number**	**Natural Sources**	**Reference**
Favanols		Catechin	antioxidant, antiviral, anti-inflammatory anti-allergenic, and anti-cancer	51	Camellia sinensis, tea, apples, persimmons, cacaos, grapes, and berries	xciii, xciv
		epicatechin	Antioxidant,	11	dark chocolate, rich cocoa,	xcv, xcvi
		procyanidins	Alzheimer's disease, diabetes, rheumatoid arthritis, tumors, and obesity.	12,13	Pea nut skins, cocoa beans. fruits, vegetables, nuts, legumes, and grains	xcvii
Flavanones		Hesperidin,	anti-inflammatory, Anti-cardiovascular, antiviral, antibacterial, ant carcinogenic, antioxidants.	14	lemons, limes, oranges, citrus grapefruits,	xcviii, xcix
		Naringin,	antioxidant, anti-inflammatory, anti-cardiovascular, and, antiviral, blood lipid-lowering	15	lemons, oranges, grapefruits, citrus	c, ci

		Narirutin,	Neurobehavioral,		Grape fruit juice, citrus fruit jabara.	[cii]
		Eriocitrin,	weight loss in the gastrocnemius muscle, cancer, cardiovascular disease.	16	lemon peel	[ciii], [civ]
		Eeohesperidin,	anti-inflammatory and antioxidant, osteoporosis and osteoarthritis.		seeds, grains, tea, coffee, wine, cocoa, chocolate, vegetables and, citrus fruits.	[cv]
		Didymin,	anticancer, antioxidant, antinociceptive, neuroprotective, hepatoprotective, inflammatory, cardiovascular, anti-diabetic		citrus fruits, lemons, mandarin, bergamot, grapefruit, chachi fruit, and citrus juices.	[cvi]
		Neoeriocitrin,	Antioxidant, diabetes, Alzheimer's and bone resorption		grapefruit. Apples,	[cvii]
		Poncirin	inflammation, colitis, human gastric cancer, liver injury and Alzheimer's disease. antioxidation,		Medicinal plants.	[cviii], [cix]
Flavone		Chrysin,	Alzheimer's Parkinson's. Nevertheless. Cancers	18	honey, fruits.	[cx]. [cxi]
		Apigenin,	antibacterial, antifungal, antiviral, diabetes, amnesia,Alzhei	19	Apium graveolens, fruits, vegetables and Chinese	[cxii], [cxiii]

			mer's disease, depression, insomnia, cancer,		medicinal herbs	
		Luteolin,	anti-inflammatory, anti-cardiovascular, and antiviral,	20	Dracocephalum integrifolium, Lonicera japonica, Capsicum annuum.	[cxiv],
		Wogonin,	anti-inflammatory, antiviral, anticancer, and antioxidant.	21	naturally in seeds, fruits, stems, nuts, spices, pigments, vegetables, herbs, and flowers .	[cxv], [cxvi]
		Tangeritin	anticancer potential, antioxidant activities and anti-inflammatory.	22	citrus peel, Fruits, vegetables, grains.	[cxvii]
Flavonols		Quercetin,	antioxidant, anti-inflammatory, anti-cardiovascular, antibacterial, and antifungal	23	vegetables, fruit, seeds, nuts, tea, and red wine.	[cxviii]
		Kaempferol,	antioxidant, anti-inflammatory, antibacterial, antiviral, and anticancer	24	fruits, vegetables, herbs, and other natural plants.	[cxix]
		Myricetin,	antioxidant, anti-inflammatory, and anti-cardiovascular	26	Myrica rubra	[cxx]
		Fisetin,	Antioxidant.	25	strawberry, apple,	[cxxi]

					onion, cucumber, and other fruits and vegetables	
		Morin	antioxidant and anti-inflammatory	27	Cudrania cochinchinensis, Maclura pomifera.	cxxii
		Isorhamnetin	antiviral and anticancer. type 2 diabetes mellitus, age-related, cardiovascular.	28	Ginkgo biloba, Hippophae,rhamnoides, pears, grapes, apples, berries, almonds, cherries	cxxiii
Isoflavonoids		Daidzein,	cognition, cancers, cardiovascular, skin diseases, osteoporosis, and menopausal,	29	miso, natto, soy milk, tofu.	cxxiv
		Genistein,	antioxidant, antifungal, antiviral, and anticancer.	30	soybeans.soy products, tofu, legumes.	cxxv
		Glycitein,	osteoporosis, cardiovascular, obesity, diabetes, anxiety, depression, and breast cancer.	31	soybeans.	cxxvi
		Biochanin,	menopausal symptoms, anti-inflammatory, anti-oxidant, anti-cancer and neuroprotective.	32	chickpea, red clover and soybean.	cxxvii
		Formononetin	inflammation and metabolism,		soybeans and legumes, breast milk, amniotic fluid,	cxxviii

Neoflavonoids		2-hydro-4-phenylch0men-2-0ne	osteoporosis, inflammatory, microbial, allergic, antioxidant, antifungal, antidiabetic, and anticancer	34	Fabaceae, Clusiaceae, Leguminosae, Rubiaceae, Passifloraceae, Thelypteridaceae, and Polypodiaceae	cxxix
Anthocyanins		pelargonidin,	antioxidant, anticancer, antidiabetic, anti-obesity, antimicrobial, and anti-inflammatory	37	strawberries and food products with red pigmentation. blue colored berry fruits.	cxxx
		cyanidin	Antioxidant anti-inflammatory. Anti-Apoptosis	38	Bifidobacterium and Akkermansia,	cxxxi
		delphinidin,	anticancer medicines, antioxidants, enzyme inhibitors, immunomodulators, antibiotics. antioxidant and anti-inflammatory,	39	berries, eggplant, purple-colored plant pigment, roselle, and wine.	cxxxii, cxxxiii
		peonidin,	cardiovascular disease, hypertension, obesity, diabetes, and cancer.	40	Purple corn,	cxxxiv
		pelunidin,		41		
		Malvidin	antioxidant and anti-inflammatory, anti-carcinogenic, cardioprotective,	42	red, purple, and blue pigments observed in a variety of fruits, vegetables,	cxxxv

			antidiabetic, and neuroprotective.			
Chalcones		Isoliquiritigenin	antimicrobial, anticancer, antitubercular, antioxidant, anti-inflammatory.	45	licorice root. Licorice, Glycyrrhiza, Glycyrrhiza uralensis, Glycyrrhiza radix, and Glycyrrhiza glabra	cxxxvi
		Butein	anti-cancer, Lung and breast cancer.	(46)	cucumber, Cucumaria frondosa, stem bark of cashews (Semecarpus anacardium), Rhus verniciflua, Caragana jubata, and the heartwood of Dalbergia odorifera .	cxxxvii
Xanthones		Norswertiann	glioblastoma cells Hepatoprotective, anticarcinogenic, antileprosy, cardioprotective, skin cancers,	49	higher plants, Guttiferae and Gentianaceae	cxxxviii

Conclusion:- Flavonoids are a vibrant tapestry of plant-derived compounds with remarkable versatility and an array of potential health benefits. Their impressive antioxidant, anti-inflammatory, and anti-cancer properties, coupled with their potential to combat chronic diseases like cardiovascular disorders and neurodegenerative conditions, paint a promising picture for their future in healthcare.

While challenges remain regarding bioavailability and biotransformation, ongoing research is actively exploring strategies to overcome these hurdles and unlock the full therapeutic potential of flavonoids. Dietary diversification, focusing on fruits, vegetables, and other rich sources of these compounds, represents a readily available strategy to harness their health benefits.

Moreover, advancements in extraction and processing methods hold the potential to enhance the bioavailability and efficacy of flavonoids, making them even more accessible for promoting human health.

As we continue to unravel the complex tapestry of flavonoid activity, one thing is certain: these colourful compounds hold immense promise for revolutionizing the way we approach health and disease. By embracing the power of nature's pharmacy, we can unlock a rainbow of possibilities for a healthier and brighter future.

Looking ahead, future research should focus on:

- Identifying novel flavonoids with specific bioactivities
- Developing strategies to enhance their bioavailability and biotransformation
- Conducting clinical trials to evaluate their efficacy in treating various diseases
- Exploring synergistic interactions between different flavonoids and other bioactive compounds
- Investigating the potential side effects and interactions of flavonoids
- Developing food-based approaches to increase dietary intake of flavonoids

Unlocking the full potential of flavonoids requires a multifaceted approach that combines scientific research, technological innovation, and public awareness. By working together, we can harness the power of these natural wonders to create a healthier and more vibrant world for all.

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