SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF FLAVONES: A REVIEW

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ABSTRACT
Flavones are a class of flavonoids based on backbone of 2-phenylchromen-4-one. Flavones are synthesized by various methods of synthesis such as solvent free, micro assisted, photocyclization, alkene hydrogen replacement, wacker oxidation, photo-wittig and many more. It contains pharmacological activities- Antifungal, Antibacterial, Antioxidant, Antidiabetic, DNA Gyrase inhibitory activity, Anti-inflammatory, Oestrogenic. The toxicity is likely said to be minimal.

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INTRODUCTION

Flavones (flavus = yellow), are a class of flavonoids based on the backbone of 2-phenylchromen-4-one. Apart from flavones, other flavonoids are isoflavonoids, derived from 3-phenylchromen-4-one structure, and neoflavonoids derived from 4-phenylcoumarine structure. The three flavonoid classes are all ketone-containing compounds, and as such, are anthoxanthins (flavones and flavonols). Flavones (2-phenylchromone) derivatives are naturally occurring heterocyclic compounds belonging to the flavonoid group. The biological activity of flavone has been enhanced by introducing heteroaryl moiety in C-2 position of chromone derivatives. Flavonoids represent a highly diverse class of secondary plant metabolites with about 9000 structures. These compounds are found in all vascular plants as well as in some mosses. Even in the same species a number of different flavonoids may occur. It is already well established that flavonoids have a significant impact on various aspects of plant biology. Flavones have the absorption maximum in the UV region of the spectrum. They are generally stored in the cells as 7-O-glycosides and can be found in almost all tissues of most plants, except for the Brassicaceae, which do not produce flavones. Flavones function to protect plant cells from UV radiation and may also act as allelochemicals, i.e., compounds that inhibit growth of competing photosynthetic organisms. They may also serve to attract and guide pollinators. Colorless flavones fluoresce under UV light, and the patterns can be detected by bees and some other potential pollinators. The flavones serve as a nectar guide but also ensure that pollen is transferred onto the insect.

New Flavone and Flavonol O-Glycosides

Some 228 new flavone O-glycosides and over 500 new flavonol O-glycosides have been reported in the period 1992 to 2003. The sugars are assumed to be in the pyranose form and to have the appropriate linkage, i.e., β for glucose, α for rhamnose, etc., except where otherwise stated. Reports of new monosaccharides, disaccharides, trisaccharides, tetrasaccharides, acylating agents, and sulfate conjugates will be considered first.

Monosaccharides

The monosaccharides have been found in O-combination with flavones or flavonols. These include five sugars, fructose, allulose, lyxose, fucose, and glucosamine, which have been recorded since 1992. α-D-Fructofuranoside has been reported from leaves of Crataegus pinnatifida (Rosaceae) linked to both the C-8 position and the 7-hydroxyl of apigenin. Here, the C- and O-glycosidic linkages to the sugar form a unique ring structure (Pinnatifinoside A). There has been one previous report of fructose, as a tricin fructosylglucoside in Hyacinthus orientalis (Liliaceae), but the structure of this glycoside was never confirmed. An acetylated derivative, Pinnatifinoside B, and two related acylated glycosides, Pinnatifinosides C and D, in which the fructose has been replaced by the sugars β-D-allulofuranose and α-D-allulofuranose, respectively, co-occurred with Pinnatifinoside A. A second pentose sugar, α-D-lyxose, was found attached to the 8-hydroxy of gossypetin (8-hydroxy-6H-1-benzopyran-6-one) in the aerial parts of Orostachys japonicus, a member of the Crassulaceae. This is an unexpected discovery as the 2-epimer of xylose is very rare in nature. Fucose, a characteristic constituent of algal and plant polysaccharides, has been found in combination with 5,6-dihydroxy-7-methoxyflavone (negletein) as the 6-rhamnosyl fucoside in Origanum vulgare.

2-amino-2-deoxyglucose.

Glucosamine (2-amino-2-deoxyglucose) is the only amino sugar to have been found in combination with flavones or flavonols. This sugar is important in animal physiology as a component of chitin, mucoproteins and mucopolysaccharides. The presence of α-D-glucosamine in the aerial parts of Halocnemum strobilaceum (Chenopodiaceae) at the 7-hydroxyl of isorhamnetin is totally unexpected and should be further investigated to establish its exact location in the plant and to screen related plants for similar structures.
Disaccharides

Twenty-one new disaccharides have been found in combination with flavones or flavonols since 1992. Four of the new structures are novel sugar combinations: xylose–xylose, rhamnose–fucose, apiosyl–rhamnose, and glucose–arabinose. Both xylosyl xylose and xylosyl xylose have been found, the former at the 7-hydroxy of scutellarein 6-methyl ether (patuletin) from roots of Chirita fimbrisepala (Gesneriaceae) and its isomer from Mosla chinensis (Labiateae) at the 7-hydroxy of 5,7-,dihydroxy-6-C-methyl flavone.

Rhamnosyl fucose has already been dealt with under monosaccharides above. Apiofuranosyl rhamnose has been recorded from Chenopodium murale in combination with kaempferol at the 3-position and with rhamnose at the 7-hydroxy. Arabinose can occur in either the pyranose or furanose form, with a or b linkage and with five possible linkage positions, which can all now be easily distinguished by modern NMR techniques. Glucosyl α-L-rabinopyranose was found at the 7-position of the flavone luteolin in seed of Cassia glauca and its linked furanose isomer in annuals of the legume, Retama sphaerocarpa, at the 3-hydroxyl of quercetin 7,3'-dimethyl ether (rhamnazin).

Glucosyl α-L-rabinopyranose occurs at the 7-hydroxyl of 8-prenylchysoriel in seeds of Erythrina indica. The other two isomers were present only in acetylated form. Thus, glucosyl β-arabinopyranose was recorded at the 3-hydroxyl of quercetin with glucose at the 7-hydroxyl and a furuloyl group at the 6-position of the glucose in a whole plant extract of Carrichtera annua (Cruciferae), while the remaining isomer, glucosyl α-L-arabinofuranose, from Euphorbia pachyrrhiza was found attached to the 3-hydroxyl of quercetin with a galloyl group at the 2-hydroxyl of the glucose.

All the other new disaccharides are new isomers of known sugar combinations. Among the pentose–pentose disaccharides are three new isomers: xylose, xylosyl xylose, and xylosyl rhamnose. The only previously known trisaccharide containing xylose is the branched tetrasaccharide [rhamnosyl glucosyl] sophorose, which was present of isorhamnetin in leaves of Peganum harmala (Zygophyllaceae) and its isomer from Mosla chinensis (Labiateae) at the 7-hydroxy of 5,7-,dihydroxy-6-C-methyl flavone.

Trisaccharides

The linear trisaccharide, xylosyl rhamnosyl glucose was found attached to the 3-hydroxyl of quercetin in leaves of Camellia saluensis (Theaceae), while its isomer, xylosyl rhamharmnosyl glucose, was found at the 3-position of isorhamnetin in Hamada scoparia (Chenopodiaceae). The other two structures were both found in combination with kaempferol at the 3-position, xylosyl glucosyl rhamnose from Helicia nilagirica (Proteaeeae) and xylosyl rhamnosyl galactose from the legume Astragalus caprinus. The former was also present in similar combination with quercetin. The first linear trirhamnose, rhamnosyl rhamnosyl rhamnose, has been recorded from Planchonia grandis (Lecythidaceae). This sugar occurred at the 7-hydroxyl of kaempferol acylated with p-coumaric acid at the 4-position of the first rhamnose and with a known acetylated branched trisaccharide at the 3-hydroxyl.

Tetrasaccharides

Only one branched tetrasaccharide [rhamnosyl glucosyl] sophorose, which was present at the 7-hydroxyl of acacetin andacetylated at the 6''-position of the sophorose in leaves of Peganum harmala (Zygophyllaceae). Since then some eight new branched tetrasaccharides have been reported, all attached to flavonoids and all with unique sugar combinations. No linear tetrasaccharide has yet been recorded. Apiosyl apiosyl [rhamnosyl glucose], which was found at the 7-hydroxyl of kaempferol 7-methyl ether in the mistletoe, Viscum angulatum, is the first report of any sugar to contain two linked apiose moieties. These are three new structures with xylose as the terminal sugar. Two were found in combination with quercetin at the 3-position. Three of the remaining structures were found attached to the 3-hydroxyl of kaempferol, which was isolated from leaves of Maytenus aquifolium.

Sulfate Conjugate

Only a comparatively small number of new flavonoid sulfate conjugates have been recorded mostly from plants that grow in water-stress conditions. Amongst the flavones the most notable are six sulfate conjugates discovered in some Australian species of the monocot family, the Restionaceae. These plants are unusual in having no true leaves so that the compounds were isolated from culm tissue. Four are hypolaetin (8-hydroxyateolin) derivatives: the 7-sulfatoglucoside and 7-sulfatoglucuronide from Leptocarpus elegans, the 7-sulfatoglucuronide from Meeboldina thysanthes, and the 7-sulfate–8-glucoside from Hypolaena fastigiata. The other two flavone sulfates are hypolaetin 7-methyl ether 3''-sulfatogalactoside from Leptocarpus tenax and the corresponding 3''-sulfatogalacturonide from L. elegans. Flavonoid sulfates were found to be characteristic constituents of the Restionaceae being detected in 27% of the 115 taxa surveyed. The first report of a sulfate 2''-linked to glucose is from the water plant, Thalassia testudinum, another monocot, where it is found in association with luteolin at the 7-position.

The other flavone sulfates are 8-hydroxyapigenin (isoscultellarein) 8-(2''-sulfatoglucuronide) and 8-(2''4''-disulfatoglucuronide) and the corresponding isoscultellarein 4''-methyl ether conjugates from fruits of Helicteres isora (Sterculiaceae).
Acylated derivatives

Some 77 new acylated flavone and 224 new acylated flavonol derivatives are included. Only one new acylating acid has been found in combination with flavones and three new aliphatic acids, a new aliphatic alcohol, a lignan, and a new aromatic acid have been discovered in association with flavonols. Thus, the lignan, p,p-dihydroxytruxillic acid has been found linked to two molecules of apigenin 7-dihydroxytruxillic acid has been identified more recently in the biflavonol flavonolides from Monochaetum multiflorum (Melastomataceae)35.

The aliphatic acid, vinylpropionic, has been found in seeds of Psidium guajava (Myrtaceae) directly attached to the 4'-hydroxyl of quercetin 3-(3''-galloylglucoside) and n-butanoic acid as quercetin 3-(6''-n-butyldihydroxylglucuronide) in leaves of the vine, Parthenocissus tricuspidata36.

New Flavone Glycosides

Some 228 new flavone glycosides are included in 26 new apigenin, 25 new luteolin, 8 new chrysoeriol, and 2 new tricin glycosides bringing their totals to, 99, 111, 44, and 44, respectively. There are a small number of new monoglycosides still discovered37. Among the most interesting finds are three 5-glycosides of simple flavones, i.e. baicalein 6-methyl ether 5-rhamnoside from seeds of Trichosanthes anguina (Cucurbitaceae), and the 5-glucosides of 5,7,8-trihydroxyflavone (norwogonin) and 5,2'-dihydroxy-7-methoxyflavone from Pyracantha coccinea (Rosaceae) and Andrographis alata (Acanthaceae), respectively38. The new structures also include 32 flavone aglycones that have been found in glycosidic combination for the first time. For example, scutellaren 5,4'-dimethyl ether as the 7-glucoside and 7-(4Rha-acetylglucoside) from Striga passargei (Scrophulariaceae) and four new luteolin methyl ethers, the 5,3'-dimethyl ether as the 7-glucoside and 4'-glucoside from Pyrus serotina, the 5,4'-di- and 5,3',4'-trimethyl ether as their 7-xylosyl glucosides from Dirca palustris (Thymelaeaceae), and the 7,3',4'-trimethyl ether as the 5-glucoside and 5-xylosyl glucoside in Lethedon tannaensis, another member of the Thymelaeaceae39. Among the 8-hydroxyluteolin (hypolaetin) derivatives are three glycosides from the Restionaceae: hypolaetin 7-methyl ether 3'-sulfatoglucuronide and 3'-sulfatoglactoside and hypolaetin 7,3'-dimethyl ether 4'-glucoside from three Leptocarpus species38. Four glycosides, the 5- and 7-glucosides, the 5-gentiobioside, and the 7-rutinoside, of the trimethylated flavone, nevadensin (5,7-dihydroxy-6,8,4'-trimethoxyflavone), have been reported from Lysionotus pauciflorus (Gesneriaceae). 2'-Methylation and 2'-glycosylation are characteristic features of Scutellaria and other Labiate species41. Therefore, it is not surprising to find reports of further 2',6'-dihydroxylated flavones in glycosidic combination in Scutellaria baicalensis and S. rivularis. Glycosides of several new methyl ethers of tricetin and 6-hydroxytricetin have also been discovered42. These include further glycosides from Lethedon tannaensis namely, tricetin 7,3',4'-trimethyl ether 5-glucoside and tricetin 7,3',4',5'-tetramethyl ether 5-glucoside and 5-xylosyl glucoside43. Two C-methylated flavones have been found in glycosidic combination for the first time bringing the total number of known structures to five. One of the novel glycosides, 5,7-dihydroxy-6,8-dimethylflavone 7-[6''-(3-methylglutareryl)glucoside], was isolated from the rhizomes of the fern, Matteuccia orientalis and the other, 5,7-dihydroxy-6-C-methylflavone 7-xylosyl xyloside, from the Labiate, Mosla chinensis44.

METHODS OF SYNTHESIS

Traditionally, flavones have been prepared by BakerVenkatramann rearrangement and Claisen Schmidt condensation, which involves the conversion of 2-hydroxyacetophenone into benzoyl esters, followed by rearrangement in base to 1,3-diphenylpropane1,3diones which upon cyclization under acidic conditions furnishes flavones. On the other hand hydroxychalcones synthesized from 2-hydroxyacetophenone anbenzaldehyde under Claisen Schmidt conditions can undergo oxidative cyclization to furnish flavones rings.

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Basic reactions for the synthesis of flavones
Basic schemes related to the synthesis of flavones:

Scheme 1: Palladium catalyzed synthesis is carried out in sense of basic environment\(^45\).

\[
\begin{align*}
R_1^+ & \quad \overset{\text{I}}{\text{OAc}} + R_2 & \xrightarrow{\text{Pd(O), CO}} & \text{Base} & \xrightarrow{\text{Claisen Schmidt}} & \text{R1}^+ \quad \overset{\text{O}}{\text{OH}} \\
& & & & & \text{R2}
\end{align*}
\]

Scheme 2: Solvent free synthesis of flavones is carried out\(^46\).

\[
\begin{align*}
\text{OH} & \quad \overset{\text{OH}}{\text{OH}} + R_2 \overset{\text{R1}^+ \quad \overset{\text{Et}}{\text{OEt}} \quad \text{microwave}}{\text{EtO}} & \xrightarrow{\text{microwave}} & \text{R1}^+ \quad \overset{\text{OH}}{\text{OH}} \\
& & & & & \text{R2}
\end{align*}
\]

Scheme 3: Flavones via a Micro-Assisted, One-Pot Sonogashira "Carbonylation" Annulation Reactions\(^47\).

\[
\begin{align*}
R_1^+ & \quad \overset{\text{X}}{\text{H}} \xrightarrow{TMS} & \xrightarrow{\text{Pd}_2 \text{dba}_3 \text{PA-Ph}} & \text{microwave, 30 min.} & \xrightarrow{\text{Pd}_2 \text{dba}_3 \text{PA-Ph}} & \text{1 atm., CO} \\
& & & & & \text{TBA, DbU, DMF} \\
& & & & & \text{mw, 30 min.}
\end{align*}
\]
Scheme 4: Photo cyclization of 2-Chloro-Substituted 1,3-Diarylpropan-1,3-diones to Flavones is invented\(^48\).

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 & \quad \text{R}_3 & \quad \text{R}_4 \\
| & | & | & | \\
\text{Cl} & & & \\
\text{CH}_3\text{CN} & \rightarrow & & \text{R}_1 & \quad \text{R}_2 & \quad \text{R}_3 & \quad \text{R}_4 \\
& & & \\
& \text{Light} & & \\
\end{align*}
\]

Scheme 5: Conversion of intermediate 1,3 dione is carried out\(^49\).

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad \text{Si supported} & \quad \text{heteropoly acid} & \quad \text{10 min.} \\
\text{OH} & \quad \text{O} & \quad \text{R} & \quad \text{R} \\
\text{OH} & \quad \text{O} & \quad \text{R} & \quad \text{R} \\
\end{align*}
\]

Scheme 6: Alkene hydrogen is replaced\(^50\).

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad 1. \ \text{TMP2Zn,2MgCl,2LiCl} \\
\text{O} & \quad \text{O} & \quad \text{THF, -30 C} \\
\text{E} & \quad \text{E} \\
\end{align*}
\]

\(E=\text{allyl, acyl, aryl}\)

Scheme 7: A Novel Synthesis of 4H-Chromen-4-ones via Intramolecular Wittig Reaction is used for the synthesis of flavones\(^51\).

\[
\begin{align*}
\text{R}_1 & \quad \text{R} & \quad \text{PPh}_3 & \quad \text{SiMe}_3 \\
\text{OCOR}_1 & \quad + & \quad & \\
\text{OCOR}_1 & \quad \rightarrow & \quad \text{R}_1 \\
\end{align*}
\]

Scheme 8: This invention converts 1,3-dione into flavones. Only base is used for this purpose\(^52\).

\[
\begin{align*}
\text{R}_1 & \quad \text{R} & \quad 20 \text{ moles, K}_2\text{CO}_3 \\
\text{O} & \quad \text{O} & \quad \text{DMF, N}_2 \\
\text{A}=\text{Et,Me,Ph} \\
\end{align*}
\]
Scheme 9: Oxygen of flavone come from water molecule.$^{33}$

Scheme 10: A two step synthesis of flavones via Wacker oxidation is carried out in this process.$^{34}$

Scheme 11: Microwave assisted synthesis of flavones. Copper chloride is used as a catalyst for this process.$^{35}$

Scheme 12: Photo-Wittig reaction is applied for the synthesis of flavones.$^{36}$

Scheme 13: Oxidative cyclization of chalcone to flavone is carried out for the synthesis of flavones. Here n-tetrabutylammonium tribromide is used as a catalyst.$^{37}$
Scheme 14: 2’allyoxy chalcone undergoes oxidative coupling when treated with iodine & DMSO\textsuperscript{58}.

\[
\begin{align*}
\text{Scheme 15: Palladium acetate is used catalyst for the synthesis of flavones}^\text{59}. \\
\text{Scheme 16: Construction of flavones through regioselective carboxylative annihilation of 2 bromo phenols & terminal alkynes is carried out}^\text{60}.
\end{align*}
\]

Scheme 17: Synthesis includes synthesis of flavones using O-hydroxy acetophenone & acetyl chloride as a precursor\textsuperscript{61}.

\[
\begin{align*}
\text{Scheme 18: One pot synthesis of flavones using ferric chloride is efficient method carried out}^\text{62}.
\end{align*}
\]

Scheme 19: Silica supported lewis acids indium chloride & indium bromide undergoes oxidative coupling to give flavones\textsuperscript{63}.
Scheme 20: Wet acetone is efficient catalyst for the one pot synthesis of flavones from 2-hydroxy acetophenone & acetyl chloride.

\[
\begin{align*}
\text{R}_1 & \quad \text{C} \quad \text{R}_2 \\
\text{R}_3 & \quad \text{O} \\
\text{R}_4 & \quad \text{O}
\end{align*}
\]

\[
\text{pR}_3\text{C}_6\text{H}_4\text{COCl} \quad \text{K}_2\text{CO}_3,\text{wet acetone} \quad \text{Reflux}
\]

Scheme 21: Formation of 1,3 dione using LiHDMs followed by cyclization using acid catalyst is achieved.

\[
\begin{align*}
\text{R}_2 & \quad \text{R}_1 \\
\text{R}_3 & \quad \text{Cl} \\
\text{R}_4 & \quad \text{O}
\end{align*}
\]

\[
\text{LiHDMs} \quad \text{THF}
\]

Scheme 22: Carbonylative coupling using Pd catalyst is invention of this method.

\[
\begin{align*}
\text{I} \quad \text{OH} \\
\text{R}_1 & \quad \text{CO} \\
\text{R}_2 & \quad \text{Pd Catalyst} \\
\text{O} & \quad \text{20 atm.}
\end{align*}
\]

Scheme 23: Oxidative cyclization followed by bromination is carried out by this process.

\[
\begin{align*}
\text{R}_1 & \quad \text{OH} \\
\text{R}_2 & \quad \text{Cl} \\
\text{R}_3 & \quad \text{Br}
\end{align*}
\]

\[
\text{V}_2\text{O}_5,\text{H}_2\text{O}_2/\text{NH}_4\text{Br} \quad \text{CH}_2\text{Cl}_2,0-5^\circ\text{C} \\
\text{0.2M KOH,EtOH.H}_2\text{O}(4:1)
\]

Scheme 24:
Scheme 25: Hydrogen peroxide is used as catalyst for this one pot method³⁸.

\[
\begin{align*}
\text{OMe} & \quad \text{OH} & \quad 1. \text{ArCHO} & \quad \text{OMe} & \quad \text{O} \\
\end{align*}
\]

Scheme 26: New catalyst at present is use of hetero poly acid is used for the synthesis of flavones. This solvent free synthesis avoids excess loss of solvents³⁹.

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad \text{HPA, Reflux} & \quad \text{Solvent or solvent free} \\
\end{align*}
\]

Scheme 27: CuI is another important catalyst invented. This method gives new catalyst for oxidative coupling of flavones⁷⁰.

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad 1. \text{CuI, 10 mole %} & \quad 2. \text{solvent, heat, air} \\
\end{align*}
\]

**REVIEW LITERATURE**

Mellou F *et al.*, carried out enzymatic synthesis of acylated derivatives of a monosaccharidic flavonoid chrysoeriol-7-O-β-d-(3"-E-p-coumaroyl)-glucopyranoside as well as of a disaccharidic flavonoid chrysoeriol-7-[6"-O-acetyl-β-d-allosyl-(1→2)-β-d-glucopyranoside], was performed using an immobilized *Candida antarctica* lipase in non-toxic organic solvents. The acylated derivative of disaccharidic flavonoid increased its antimicrobial activity against two Gram-positive bacteria⁷¹.

Hakan Goker *et al.*, synthesized series of flavones and methyl-4H-1-benzopyran-4-ones carrying mono or diamidinobenzimidazoles at different positions and evaluated for their evaluated for antibacterial and antifungal activities against *E. coli*, *S. aureus*, MRSA, MRSE, *S. faecalis* and *C. albicans*, *C. krusei*. The compounds having monoamidinobenzimidazoles at the C-6 position of the 2-phenyl-4H-1-benzopyran-4-one have potent antibacterial activities, particularly, against Gram-positive bacteria. Some compounds exhibited the best inhibitory activity with MIC values of 1.56 l g/mL against *S. aureus*, MRSA, MRSE and 3.12 l g/mL against *C. albicans*⁷².
Ehsan UM et al., synthesized 4-thioflavones (i) and 4-iminoflavones (ii) with the substitution of variable halogens, methyl, methoxy and nitro groups in the A, B and AB rings and also reported their antibacterial activity. Compounds were found to be active against *Escherichia coli*, *Bacillus subtilis*, *Shigella flexnari*, *Salmonella aureus*, *Salmonella typhi* and *Pseudomonas aeruginosa*. Activity of 4-thioflavones and 4-iminoflavones was found to be higher than that of their corresponding flavone analogues. Investigated compounds having substituents like F, OMe and NO$_2$ at 4'-position in ring-B exhibited enhanced activity.
Cushnie Tim TP and Lamb AJ, studied the antimicrobial activity of flavonoids including its occurrence, functions, medicinal properties. The further studies also include the toxicity studies, their mechanism of action and various inhibition synthesis.

Vidyasagar NC and Nanda RK, synthesized some flavonoids derivatives and carried out their studies on its Antioxidant activity and In vivo Antidiabetic activity. Two compounds from the synthesized flavonoids were found to be effective in oral glucose tolerance test, hypoglycemic study and two week STZ-induced antidiabetic activity. Compounds showing good antidiabetic and lipid lowering properties are also having good antioxidant properties.

Sato M et al., prepared the methanolic extracts, obtained from 13 plants were studied for their antibacterial activity against cariogenic bacteria. Among them, the extract from Artocarpus heterophyllus showed the most intensive activity. Two active compounds were identified as 6-(3-methyl-1-butenyl)-5,2',4'-trihydroxy-3-isoprenyl-7-methoxyflavone(i) and 5,7,2',4'-tetrahydroxy-6-isoprenylflavone(ii). Both isolates completely inhibited the growth of primary cariogenic bacteria at 3.13-12.5 pg/ml. They also exhibited the growth inhibitory effects on plaque-forming streptococci.
Ohemeng KA et al., studied a series of flavones for their DNA-gyrase inhibitory and antibacterial activities which led to the identification of compounds with potent Escherichia coli DNA-gyrase inhibitory activity and modest antimicrobial activity. The most active compound, ellagic acid has an IC$_{50}$ = 3.3 µg/ml, which is comparable to some of the currently marketed 4-quinolone antibacterials$^{77}$.

Mandalari G et al, tested Bergamot peel extract against Gram negative bacteria (Escherichia coli, Pseudomonas putida, Salmonella enteric), Gram positive bacteria (Listeria innocua, Bacillus subtilis, Staphylococcus aureus, Lactococcus lactis) and the yeast Saccharomyces cerevisiae. Bergamot fractions were found to be active against all the Gram-negative bacteria tested, and their antimicrobial potency increased after enzymatic deglycosylation. The minimum inhibitory concentrations of the fractions and the pure flavonoids, neohesperidin, hesperetin (aglycone), neoeriocitrin, eriodictyol (aglycone), naringin and naringenin (aglycone), were found to be in the range 200 to 800 µg ml$^{-1}$. Deglycosylation increased the antimicrobial potency of Citrus flavonoids. Combinations of eriodictyol, naringenin and hesperetin showed both synergistic and indifferent interactions$^{78}$.

Rauha JP et al., studied antimicrobial activity of Finnish plant containing flavonoids and other phenolic compounds. The tests were carried out using diffusion methods with four to nine microbial species (Aspergillus niger, Bacillus subtilis, Candida albicans, Escherichia coli, Micrococcus luteus, Pseudomonas aeruginosa, Saccharomyces cerevisiae, Staphylococcus aureus and Staphylococcus epidermidis). Flavone, quercetin and naringenin were effective in inhibiting the growth of the organisms. The most active plant extracts were purple loosestrife (Lythrum salicaria L.) against Candida albicans, meadowsweet (Filipendula ulmaria (L.) Maxim.), willow herb (Epilobium angustifolium L.), cloudberry (Rubus chamaemorus L.) and raspberry (Rubus idaeus L.) against bacteria, and white birch (Betula pubescens Ehrh.), pine (Pinus sylvestris L.) and potato (Solanum tuberosum L.) against gram-positive Staphylococcus aureus$^{79}$.

Harborne JF and Williams CA, reviewed some of the recent advances in the flavonoid research. The role of anthocyanins and flavones in providing stable blue colours in angiosperms is outlined. Advances discussed regarding the understanding the part played by flavonoids in warding off microbial infection and protecting plants from herbivory. The biological properties of flavonoids are considered in medicinal and nutritional values of these compounds$^{80}$.

Guz NR et al., reported the discovery of potent naturally occurring flavonolignan inhibitor of the NorA MDR pump of Staphylococcus aureus provided a structural foundation upon which SARs could be assessed via synthetic analogues. Several flavonolignans were prepared which proved to have greater potency than the natural isolate, 5′-methoxyhydnocarpin-D, while others showed decreased potency. Some simple alkylated flavones also were quite active MDR pump inhibitors$^{81}$.

Venkatesan P and Maruthavanam T, carried out the synthesis of some flavones derivatives as potent antimicrobial agents. The biological activity of flavone has been enhanced by introducing heteroaryl moiety in C-2 position of chromone derivatives. Thus, 2-(1H-Indol-3-yl)-4H-chromen-4-one derivatives and 2-(2-chloroquinolin-3-yl)-4H-chromen-4-one derivatives were synthesized from corresponding chalcone. The compound, 2-(2-chloroquinolin-3-yl)-6-methoxy-4H-chromen-4-one showed excellent antifungal activity against all the test fungi. The antibacterial activity of the quinolyl flavones increased when compared to that of indolyl chalcone$^{82}$.

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Martins S and Methofer A, carried out studies on flavones and flavone synthases. The biosynthesis of flavones in plants was found to be catalyzed by two completely different flavone synthase proteins (FNS), a unique feature within the flavonoids. FNS I, a soluble dioxygenase, was only described for members of the Apiaceae family. FNS II, a membrane bound cytochrome P450 enzyme, has been found in all other flavone accumulating tissues. FNS I and FNS II genes have been cloned from a number of plant species. This now enables modifications of flavone synthesis in plants to improve their nutritional and/or biopharmaceutical value.

Flavone formation catalyzed by flavone synthase I or II.

Basile A et al., isolated and identified seven pure flavonoids from five moss species namely- flavones apigenin, apigenin-7-O-triglycoside, luteolin-7-O-hesperidoside, saponarine and vitexin; and the biflavonoid bartramiaflavone. Apigenin is shown to have pronounced antibacterial effects against E. cloaceae, E. aerogenes and P. aeruginosa.

Fawe A et al., studied the silicon-mediated accumulation of flavonoids Phytoalexins in cucumber. Silicon is involved in the increased resistance of cucumber to powdery mildew by enhancing the antifungal activity of infected leaves. One of these metabolites, described here as a phytoalexin, was identified as a flavonol aglycone rhamnetin (3,5,3′,4′-tetrahydroxy-7-O-methoxyflavone). The antifungal activity of leaf extracts was expressed after acid hydrolysis.

PHARMACOLOGICAL ACTIVITIES

Antifungal activity-

Antifungal activity was assessed by the poisoned food technique, in a modified condition. Fluconazole (200 µg/disc) was used as standard fungicide. Potato dextrose agar (PDA) was used as basal medium for test fungi. Dimethyl sulphoxide (DMSO) was used as solvent to prepare desired solutions (10 mg/ ml) of the compounds initially and also to maintain proper control. Five plant pathogenic and mould fungi were studied, Colletotrichum gloeosporioides (plant pathogen), Candida albicans (human pathogen), Aspergillus niger (mould), Aspergillus flavus (mould) and Penicillium sp. (blue mould).

Antibacterial activity-

Antibacterial activities were studied against four human pathogenic bacteria, Shigella dysenteriae (G−), Pseudomonas aeruginosa (G−), Sarcina lutea (G+) and Bacillus subtilis (G+). Kanamycin was used as standard antibiotic for antibacterial activities. Nutrient agar (NA) was used as basal medium for test bacteria. Discs with only DMSO were used as control. MIC values were determined against Pseudomonas aeruginosa (G−) and Bacillus subtilis (G+).
Antioxidant activity-
(Lipid peroxidase antioxidant assay) Tissue homogenates: Chicken liver tissue homogenate was prepared in a ratio of 25 gm of wet tissue to 25 ml of 40 mM tris buffer by homogenizing the tissue for 30 minutes at 3000 rpm. This procedure yielded 25% w/v tissue liver homogenate. The test compounds were dissolved in suitable water miscible solvent and 100 µg/ml standard solutions were prepared. In one test tube 1 ml of test solution, 0.1 ml of 40 mM tris buffer (pH-7), 0.1 ml of KCl (30 mM), 0.1 ml of ascorbic acid (0.6 mM), 0.1 ml of ferrous sulphate (0.16 mM) were added and incubated at 37oC for 1 hour. After 1 h, 0.4 ml of reaction mixture was treated with 0.2 ml of sodium dodecyl sulphate (8.1%), 1.5 ml of thiobarburic acid (0.8%) and 1.5 ml of acetic acid (20%). The total volume was made up to 4 ml with distilled water and kept in an oil bath at 95°C for 1 h. After cooling the mixture, 1 ml of distilled water and 5 ml of butanol: pyridine (15:1 v/v) was added to the reaction mixture and shaken vigorously. The test tubes were then centrifuged at 1500 rpm for 15 minutes and the absorbance of upper colored layer was measured at 532 nm using UV-Visible spectrophotometer. Percentage inhibition was calculated by using the formula;

\[
% \text{ Inhibition} = \frac{(AT-AC)}{(AC)} \times 100
\]

where, AT-absorbance of test; AC-absorbance of control\(^75\).

Antidiabetic activity-(In vivo)
Oral glucose tolerance test: The rats were given the test compounds and standard drug orally and two hours later, glucose (2 g/kg, p.o.) was administered to all rats. For serum glucose determination, blood samples were collected at 0, ½, 1 and 2 h after glucose administration. The antidiabetic properties were quantified, in vivo, by their ability to improve glucose tolerance during an OGTT performed on normal (non-diabetic) rats\(^75\).

In vitro-
The in vitro antibacterial activity were evaluated against pathogenic bacteria including Staphylococcus aureus (G+), Bacillus subtilis (G+), Escherichia coli (G-) and Salmonella typhi (G-). Penicillin was used as standard for comparing the antibacterial activities and the diameter of observed inhibition zone were measured (in mM)\(^82\).

DNA Gyrase inhibitory activity-
The compounds were tested in the DNA-gyrase supercoiling inhibition and the DNA-gyrase “cleavable complex” assay. The MIC’s of the compounds against the six test organisms was determined in either Mueller Hinton Broth for gram-negatives, or Luria Broth for gram-positives in a microtiter well dilution series. Two-fold serial dilutions (range 0.015-500 µg/mL) of compound in broth were inoculated with adjusted suspensions of test organisms to approximately 5 x 10\(^5\) CPU/mL. Microtiter plates were incubated overnight at 35°C. MIC was defined as the well concentration with no visible growth. PMBN was used in conjunction with test compounds being screened at doses (at levels of PMBN exhibiting no antibacterial activity itself) lower than the MIC, and compared to PMBN-free controls\(^37\).

Anti-inflammatory-
Flavonoids may inhibit the cyclo-oxygenase and the 5-lipoxygenase pathways arachidonate metabolism. From the recent reports it was found that the major surface of flavonoid of feverfew (Tanacetum parthenium) inhibited both enzymes with similar potency when using rat leukocytes activated by the calcium ionophore A23187. This active compound was first identified as 6-hydroxykaempferol 3,7,4’-trimethyl ether and named tanetin. Santin may contribute to the well known anti-inflammatory activity of this plant. In the later study the leaf surface flavones of feverfew were compared with the leaf surface flavones of the related plant, tansy. The two further flavonols were tested from feverfew: 6-hydroxykaempferol 3,6-dimethyl ether, which gave a similar enzyme profile to santin and quercetagetin 3,6,3’-trimethyl ether which showed preferential activity against cyclo-oxygenase\(^87\).

Oestrogenic activity-
The main group of flavonoids that are well known to possess oestrogenic activity are the isoflavones, such as genistein. In recent research for new phyto-oestrogens have isolated 8-isopentenylnaringenin from thai crude drug derived from the heartwood of Anaxagorea luzonensis. In In vitro test they found that this flavanone had an oestrogen agonist activity greater than that of genistein and that the presence of the 8-isopentenyl group is an important factor for bining to the oestrogen receptor. Other flavonones, flavanones and flavonols with an isopentenyl group at C-8 also showed considerable affinity for the oestrogen receptor but 8-isopentenylisoflavones were not active\(^68\).

TOXICITY
It has been suggested that because flavonoids are widely distributed in edible plants and beverages and have previously been used in traditional medicine, they are likely to have minimal toxicity\(^89\). However, this family of compounds has diverse range of activities in mammalian cells and In vivo confirmation of their side effects would be necessary for a full evaluation of their practical usefulness in the field of modern medicine. Given that the selectivity of flavonoids for eukaryotic enzymes appears to vary from compound to compound, such a study would need to assess the toxicity of these phytochemicals on an individual basis\(^30\).
CONCLUSION

From the above article, we can conclude that the flavones persist biological activities such as- Antifungal, Antibacterial, Antioxidant, Antidiabetic, Anti-inflammatory, Oestrogenic activities. The several methods of synthesis of flavones using different reactions are also described here, along with the toxicities caused by flavonoids.

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ABBREVIATIONS

UV- Ultra-violet
NMR- Nuclear magnetic resonance
DMSO- Dimethyl sulphoxide
MIC- Minimum inhibitory concentration
MRSA- Methicillin resistant Staphylococcus aureus
KCl- Potassium Chloride

REFERENCES


