A REVIEW ON FLAVONES AS A POTENTIAL THERAPEUTIC AGENT

Dr.K.Dhunmati, Assistant professor, Department of Pharmaceutical Chemistry ,C.L Baid Metha College of Pharmacy.

Manimegalai.V, Department of Pharmaceutical Chemistry,C.L Baid Metha College of Pharmacy.

Mrs.Sankari .E,Assistant Professor, Department of Pharmaceutical Chemistry ,C.L Baid Metha College of Pharmacy.

Dr.N.Ramalakshmi,Vice Principal, Professor and Head , Department of Pharmaceutical Chemistry ,C.L Baid Metha College of Pharmacy.

Abstract

Flavonoids from the Latin word flavus, meaning yellow, their color in nature are a class of polyphenolic molecules containing 15 carbon atoms and are soluble in water. These molecules are found in a variety of fruits and vegetables. Flavonoids can be found in plants in glycoside-bound and free aglycone forms. They consist of two benzene rings connected by a short three carbon chain. One of the carbons in this chain is connected to a carbon in one of the benzine rings, either through an oxygen bridge or directly, which gives a third middle ring. The flavonoids can be divided into six major subtypes, which include chalcones, flavones, isoflavonoids, flavanones, anthoxanthins and anthocyanins. In this review we focused on the flavonoids derivatives possessing various biological activities such as antibacterial, anticancer, antifungal, anticonvulsant, anti-inflammatory, antimalarial, antioxidant, antiproliferative, anti tumour etc.

Keywords: Flavonoids, Pharmacological activity,Chalcones,Fruits and vegetables,

Definition

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Variations in the heterocyclic ring C give rise to flavonols, flavones, catechins, flavanones, anthocyanidins and isoflavonoids. In addition, the basic structure of flavonoids allows a multitude of substitution patterns in the benzene rings A and B within each class of flavonoids: phenolic hydroxyls, O-sugars, methoxy groups, sulfates and glucuronides [1]. Overall, about 10,000 flavonoids have been recorded which represent the third largest group of natural products following the alkaloids (12,000) and terpenoids (30,000) [2,3]. Many studies have shown that flavonoids exhibit biological and pharmacological activities, including antioxidant [4, 5], cytotoxic [6, 7], anticancer [8], antifungal [9], estrogenic [10] pre-oxidant , TG inhibitor , anti-tubulin antibacterial , anti-inflammatory , anti-HIV, antitumour , glucosidase inhibitor , anti-nociceptive, antimalarial, Topoisomerase IV . Their anticancer activity observed at the initiation, promotion, and progression stages of cancer is considered to be a most promising biological phenomenon

The anticancer activity of flavonoids, as polyphenolic compounds, is due to their antioxidant properties. These antioxidant features are mediated by different mechanisms including scavenging radical species (e.g., nitric oxide synthase) and suppressing some enzymes or chelating trace metals involved in free radical production (e.g., protein kinase C,

cyclooxygenase, lipoxygenase, microsomal succinoxidase, and NADH oxidase). Flavones were the core of several synthetic and structure-activity relationship studies in order to improve their biological activities . Based in flavone structure-activity relationship studies, it has been reported that the double bond between C2 and C3, the carbonyl group at position 4, hydroxy, methoxy, or amino groups appended at the 5 and 7 positions frequently improve the biological activity. Such flavone derivatives showed high potency as antineoplastic agents and/or inhibitors for some selective kinase enzymes, such as cyclin-dependent kinase, several protein-tyrosine kinases, aromatase, topoisomerase, or protein kinase C .[11-14]

Chemical structure of flavonoids

The chemical nature of flavonoids varies according to the hydroxylation pattern, conjugation between the aromatic rings, glycosidic moieties, methoxy groups and other substituents [15-17]. Flavonoids contain conjugated double bonds and groups (hydroxyl or other substituents) that can donate electrons through resonance to stabilize the free radicals, which originate in the electronic spectra of flavonoids [18].

Studies on flavonoids by UV spectroscopy have shown that most the most flavonoids consist of two major absorption maxima: band II (240-285 nm) which corresponds to the benzoyl system of the A ring, while band I (300-400 nm) represents the cinnamoyl system of the B ring (Figure 1) [19,20].

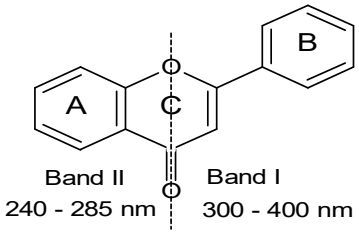


Figure 1

Functional groups attached to the flavonoid skeleton may cause a shift in absorption. The application of standardized UV or UV-Vis spectroscopy has for years been used in analyses pf flavonoids [21].

Flavonoids have the ability to sequester free radicals, are natural antioxidants derived from plants and are commonly found in foods and beverages [44]. The main structural features of flavonoids required for antioxidant activity can be determined by three fundamental factors: (1) a 3′, 4′- dihydroxyl (catechol) structure in the B ring favors the electron delocalization (A), (2) an unsaturated 2-3 bond in conjugation with a 4-keto group provides electron delocalization from the B ring (B) and (3) hydroxyl groups at positions 3 and 5 form intramolecular hydrogen bonding to the keto group (C) (Figure 2). These effects lead to the increases of the radical scavenging by delocalization of electrons or by donation of hydrogen .

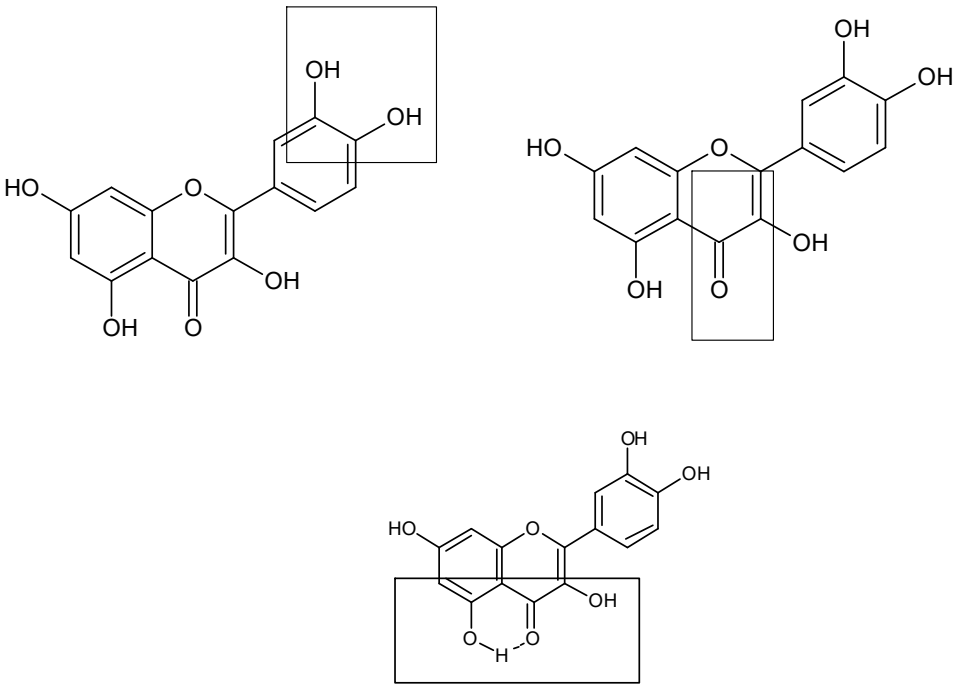


Figure 2

Flavonoids have different activity mechanisms such as free radical scavenging, inactivation of peroxides and other reactive oxygen species, chelation of metals and quenching of secondary lipid oxidation products. The radical scavenging properties associated with the structure of flavonoids defend against oxidative stress and in doing so reduce heart disease, prevent cancer and slow down the aging processes in cells responsible for degenerative diseases [22].

PHARMACOLOGICAL ACTIVITIES

Antibacterial activity

Zhu-ping Xiao et al 2014 designed and synthesized novel twenty-one fluroquinolone-flavonoid hybrids derived from naringenin. *Invitro* antibacterial was evaluated for the synthesized compounds using ciprofloxacin as a standard drug, in which the compound (Figure 3) Naringenin-ethylidene-ciprofloxacin have showed excellent activity with MIC value of 0.71, 0.062, 0.29 and 0.14 µg/ml against *E. coli, B. subtilis, S. aureus* and *C. albicans* respectively. [23]

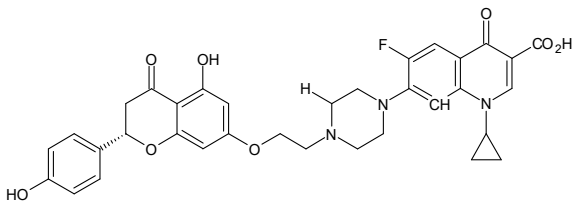


Figure 3

Angel Amesty et al 2018 synthesized twenty-eight 4-substitued 1,2,3-Triazole-coumarin derivatives by using a copper (I)-catalysed Huisgen 1,3, dipolar cycloaddition reaction. In antimicrobial activity of compound (Figure 4) 4-((1-(2-Methoxyphenyl)-1H-1,2,3-triazole-4-yl)methoxy)-2H-chromen-2-one have showed most active agent with Enterococcus faecalis at MICs range with 12.5% having a 2-oMe-ph group are attached with the triazole nucleus and an -ocH2-linker respectively. [24]

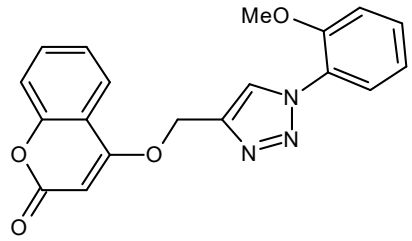
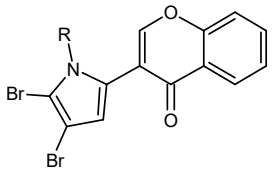


Figure 4

Anticancer activity

Rajesh A. Rane et al 2013 synthesized and evaluated twenty-three hybrids of bromo pyrrole alkaloids (Figure 5) for anticancer activity of compound **(24a)** with hydro and **(24b)** with methyl have showed most promising activity against cancer cell lines PA1 and KB403 with MIC value of 0.41 and 1.28 μM. Almost thirteen had showed promising anticancer activity of IC50 < 1.00 μM. [25]



Compound	R
24a	H
24b	CH_3

Figure 5

Designed a novel of 3-arylcoumarins was synthesized by Yong Zou et al 2010. Cytotoxicity of compound are evaluated for four human cancer cell lines are KB, MCF-7, MCF-7/ADR by MIT assay. In anticancer activity of compound (Figure 6) was characterized by a 7,8-dihydroxy group or 7, 8-diacetyloxy group showed most promising activity with IC50 value of 5.18 mmol/L against KB cell lines. [26]

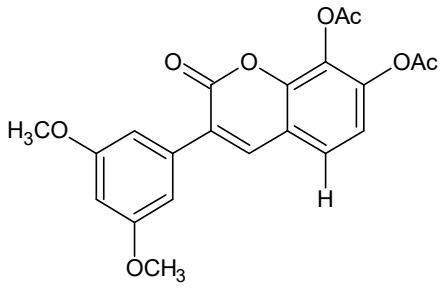


Figure 6

Yong Sup Lee et al 2019 synthesized and evaluated thirty-one- flavone based arylamide **(26)** (Figure 7). Compounds **(26a)** with X-Y = CONH, R_1 = MeO, R_2 = 4-CH_3 and **(26b)** with X-Y = CONH, R_1 = MeO, R_2 = 4-Cl with the amides carbon is joined with TMF-3 position possess 4-methyl or 4-chloro substituents with broad spectrum are highly effective against all the nine tested cancer disease showed most promising anticancer activity. In docking studies, compound of **(20a)** was docked into the ATP- binding pocket and mechanism of action involves the induction of cell cycle arrest of HT29 cells in G1 Phase. [27]

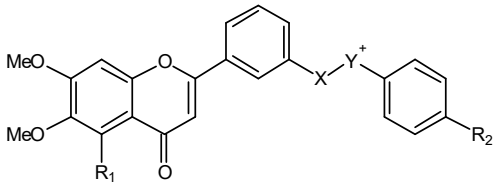


Figure 7

Compound	X-Y	R_1	R_2
26a	CONH	MeO	4-CH_3
26b	CONH	MeO	4-Cl

Anti-Tumour activity

Jiefu Wang et al 2020 designed and synthesized structure of flavone and isoflavones of twenty-eight potential HDCAs inhibitors. *Invivo* and *invitro* compound (Figure 8) 6-((2-(4-(2-(Dimethylamino)ethoxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-7-yl)oxy)-N-hydroxy hexanamide showed more potent anti-proliferative activity could suppress the breast cancer cells. *Invitro* dose-dependent manner the compound of 15a and SAHA reduced the growth of two triple-negative breast cancer cells, MDA-MB-231 and 4TI. *Invivo* compound (Figure 8) have reduced hERG potency with IC50 = 120nM and could inhibit both HDACs and p-STAT3 suppress the growth of tumor cells. [28]

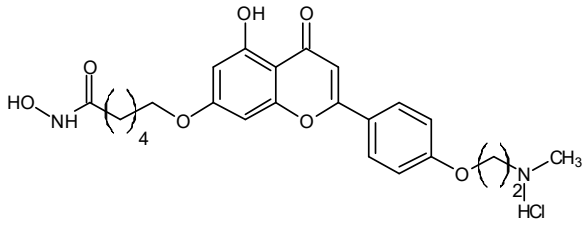


Figure 8

Alameqdad Y. Habashneh et al 2014 an antitumor activity of 6-flavone-subsituted amidrazones is a newly synthesized compounds were characterized by MS and NMR spectral. Compound (Figure 9) 6-[2-(1-Morpholino-2-oxopropylident)hydrazinyl]-2-phenyl-4H-chromen-4-one showed most active against leukemic (K562) and breast cancer (MCF-7) cancer cell lines with IC50 values of 5.18 and 2.89 μM. [29]

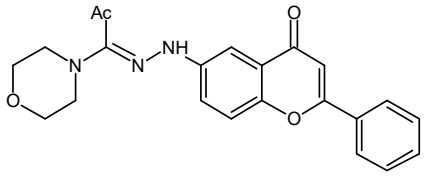


Figure 9

Thomas H. Corbett et al Flavone acetic acid (Figure 10) is a 2-phenyl-8-(carboxymethyl)-benzopyran-4-one with substitution was detected by DTP is screened and active against P388 leukaemia's and the agent not need to activate outside the tumor cell by *invitro* antitumor agent. Then the administration of route is modified by Harvard pump. [30]

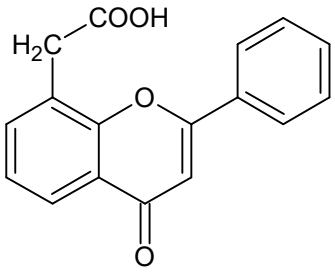


Figure 10

Neuroprotective activity

Designed and synthesized a scutellarein and tertramethylpyrazines active metabolites **(38)** (Figure 11). Compounds **(38a)** with R = CH_3, **(38b)** with R = $CH_2CH(CH_3)_2$ and **(38C)** with R = $CH(CH_3)C_2H_5$ have showed good neuroprotective activity in PC12 cells against H2O2 induced cell death. In this studies optimization of ischemic stroke agents and significantly developed. [31]

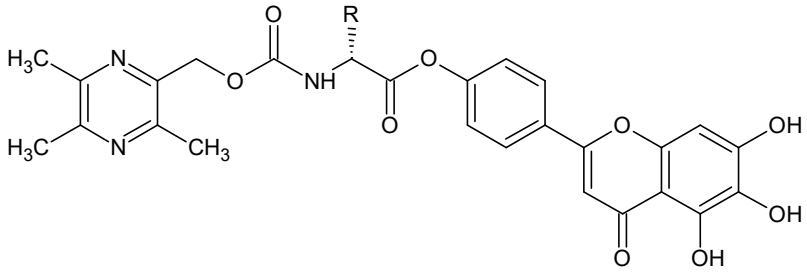


Figure 11

Compound	R
38a	CH_3
38b	$CH_2CH(CH_3)_2$
38c	$CH(CH_3)C_2H_5$

Zhipei sang et al 2019 a series of apigenin rivastigmine hybrids are designed and based on MTDLs. In neuroprotective effect of compound (Figure 12) 2-(4-((Ethyl(methyl)carbamoyl)oxy)phenyl)-5-hydroxy-4-oxo-4H-chromen-7-ylethyl(methyl)carbamate have showed promising activity against H2O2 induced PC12 cell

injury. Furthermore, the compound against Ab1-42 have induced SH-SY5Y was carried by MIT assay. [32]

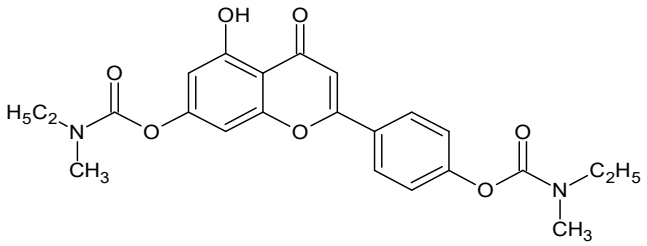


Figure 12

Antiproliferative activity

Y. Jayaprakash Raw et al 2017 synthesized an isomer of 1,4-disubstutued 1,2,3-riazole flavone hybrid heterocycles from 7a-7n via Sharpless Cu(I) catalysed. Synthesized compounds were evaluated against four human cancer cell lines are HeLa, MIA, PaCa, MDA-MB-231, and IMR 32 for *invitro* antiproliferative activity of compound (Figure 13) 6-[(1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methylamino]-2-phenyl-4H-chromen-4-one showed promising activity against (MBA-MB-231) breast cancer cell line with G150 ≤ 0.01 μM. [33]

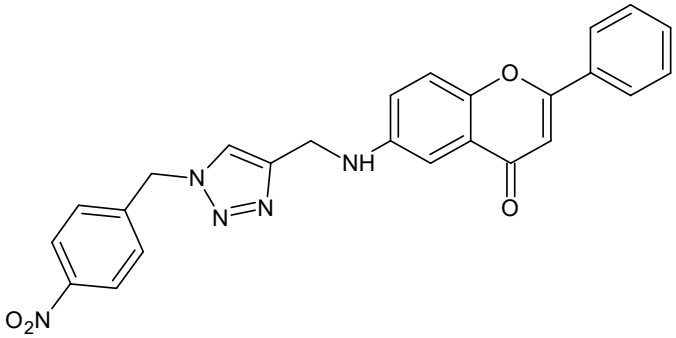


Figure 13

Jaroslaw Poplonski et al 2018 a series of Xanthohumol-derived compounds with cyclized prenyl groups was synthesized and evaluated. *Invitro* antiproliferative activity of cancer cell line prostate (PC-3, colon (HT-29) and breast cancer (MCF-&) was evaluated by using SRB assay. A non-natural 2,3-dehydroisoxanthohumol, which exhibited activity is comparable to cisplatin. Flavone tested compounds (Figure 14), (Figure15) and (Figure 16) have showed high antiproliferative activity. [34]

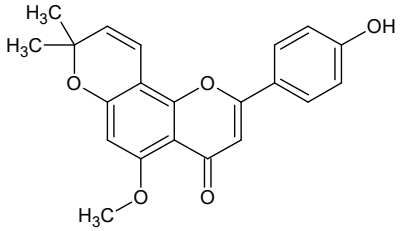


Figure 14

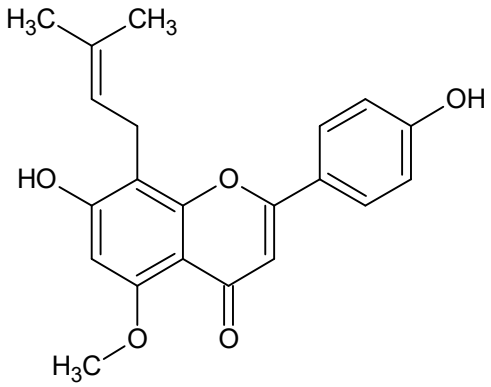


Figure 15

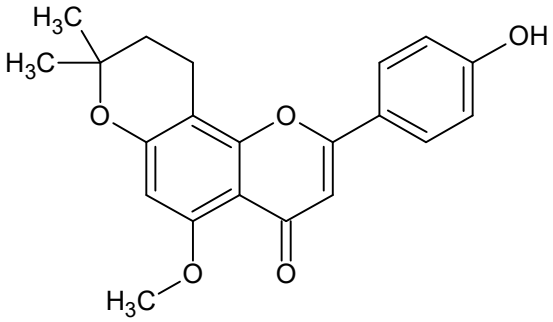


Figure 16

Cytotoxicity activity

Ahmed Kamal et al synthesized new PBD-flavone hybrid is evaluated by *invitro* cytotoxicity of hybrids increase in linker chain length reduces the DNA binding affinity and three carbon chain spacers of (Figure 17) 7-Methoxy-8-{3-[2-phenyl-4-oxo-4H-[1]benzopyran-6-yloxy]propoxy}=(11aS)-1,2,3,11atetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5-one showed a strong effect to Ht-29, HCT-15, HOP-62 cell lines by using solforhodamine B using a standard drug. [35]

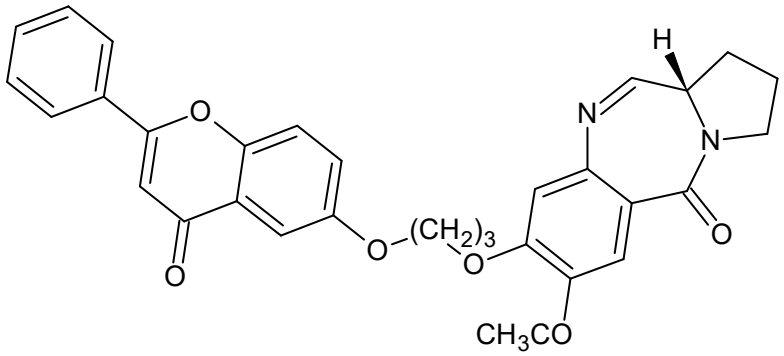


Figure 17

Krisztina Konya et al *invitro* cytotoxicity of the Buchwald-Hartwig reaction for amination of bromo or triflyloxy-substituted flavone but only on hexylamine was used as nitrogen source under microwave activation. Compound (Figure 18) 7-{[1-carboxyl-3-

methylbutyl]amino}flavone was showed 9.2 µM activity against CCRF-CEM (T-lymphoblastic leukemia). [36]

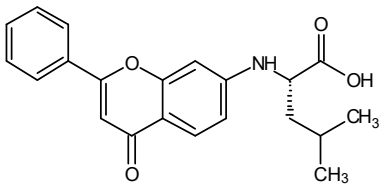


Figure 18

Anti-inflammatory activity

Yong Sup Lee et al repurposing hybrids of 5,6,7-trimethoxyflavone **(40)** (Figure 19) of anti-inflammatory activity of most promising compounds **(40a)** with X-Y = CONH, $R_1 = CH_3O$, R_2 = 3,4,5-triCH_3O and **(40b)** with X-Y = CONH, R_1 = OH, R_2 = 3,4,5-triCH_3O are evaluated by IC50 value is 2.75 and 2.11 µM with a dose dependent inhibitor of LPS-stimulated NO production in RAW 264.7 macrophages. Compound **(40a)** mosloflavone are more effective inhibitor than 49b had TMF moiety. *Insilico* docked compound **(40b)** are p48- α MAPK inhibitor of proinflammatory mediators are induced the production of NO, PGE3, IL-6, TNF-α and IL-1β at the low 1µM concentration by 44.76, 35.71, 53.48, 29.39 and 41.02% respectively. [37]

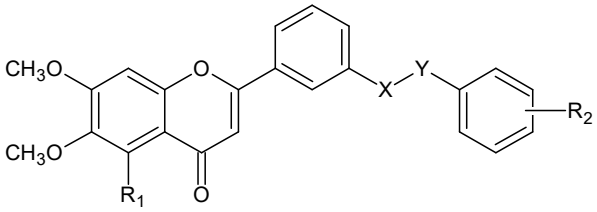


Figure 19

Compound	X-Y	R_1	R_2
40a	CONH	CH_3O	3,4,5-triCH_3O
40b	CONH	OH	3,4,5-triCH_30

Antidiabetic activity

Ram Pratap et al synthesized hybrid with oxypropanolamine moiety was evaluated for their antidiabetic activity on STZ-induced diabetic rats in db/db mice. Compound (Figure 20) 3′,5′-Dibenzyloxy-7-[3-tert-butylamino-2-hydroxypropoxy]-flavone have more promising activity by using a standard drug as fenofibrate. Compounds are compared to same doses of standard lipid lowering drug fenofibrate, lowering in cholesterol, TG concentration, and low-density lipoprotein level. [38]

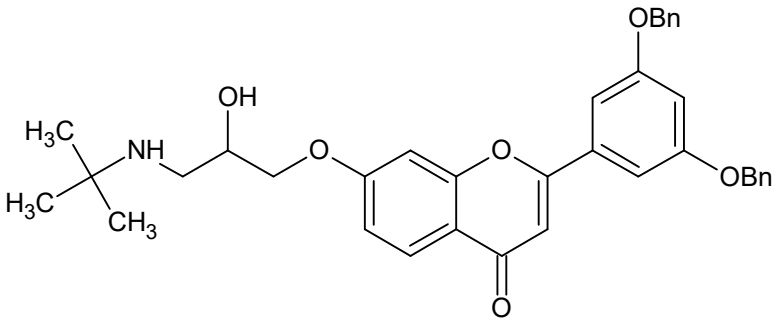


Figure 20

Kui Lu et al a natural product of 8-(6”-umbelliferyl)-apigenin, a hybrid structure of apigenin and coumarin was synthesized. In anti-diabetic activity of compound (Figure 21) 5’,7’ -dihydroxy-2’-(4-hydroxyphenyl)-7-methoxy-2H,40H-[6,8’-bichromene]-2,4’-dione have showed most potent of IC50 value of 10 μM. [39]

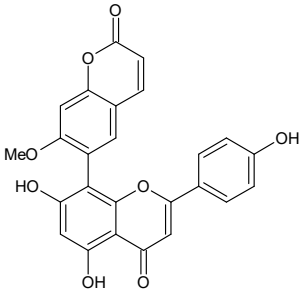


Figure 21

Anti-HIV-1N activity

N. Alves et al 2006 a studied of thirty-two flavone compounds by anti-HIV-1 integrase activity. The stepwise discriminant analysis (SDA), principal component analysis (PCA) and Hierarchical cluster analysis (HCA) methods are used to classify. The compound (Figure 22) is more active and intense region of negative electrostatic potential with 93.3% than the compound twenty-two is inactive and a more attractive cation-binding site. They showed two groups of active and inactive molecules against anti-HIV 1N activity. [40]

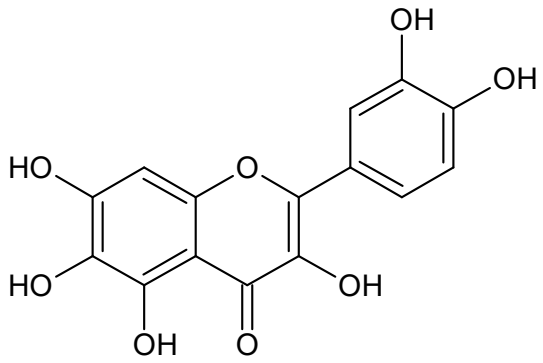


Figure 22

Antimycobacterial activity

Yerrabelly Jayaprakash Rao et al 2018 synthesized triazole and isoxazole moity at seven and eight position of 6-formyl-7-hydroxy flavone. The compound (Figure 23) 9-Methyl-10-phenylpyrano[2,3 :5,6]chromeno[,3-c]isoxazole-8(4H)-one derivatives showed moderate antimycobacterial activity with 41.7% BCG value of inhibitor by using a turbidometry assay. [41]

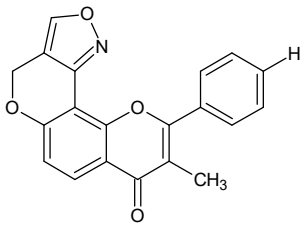


Figure 23

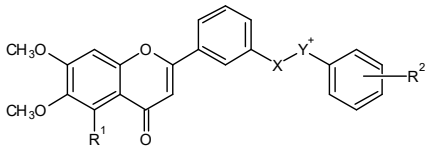


Figure 23

Compound	X-Y	R_1	R_2
49a	CONH	CH_3O	3,4,5-triCH_3O
49b	CONH	OH	3,4,5-triCH_30

Conclusion

Variety of flavonoids found in the nature possesses their own physical, chemical and physiological properties. Since the majority of people are exposed to flavonoids on a regular basis, their effect on human health is significant. The current situation reveals that multiple experimental investigations of the diverse biological activities of flavonoids have been conducted. Even while our research sheds light on the various bioactivities of these flavonoids, it is important to recognize that some elements, such as various pharmacokinetic/pharmacodynamic parameters and toxicological studies, have not yet been fully explored. Therefore, more thorough research is required to comprehend the processes underlying the actions of these flavonoids and their potential consequences on human health. Despite these restrictions, this review work offers important new information on the possible health advantages of these flavonoids. Their actions across various health areas have shown promise for the creation of new therapeutics and functional food additives. In conclusion, this research lays the groundwork for future research into the therapeutic potential of these flavonoids, highlighting the necessity of further, in-depth research to fully harness their positive impacts on human health.

ACKNOWLEDGMENT

The authors are thankful to the management of C.L.Baid Metha College of Pharmacy, Thoraipakkam, and Chennai for providing the necessary facilities to carry out this work successfully.

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Middleton Jr E. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. The flavonoids: advances in research since 1986. 1993:337-70.

2.Martens S, Preuß A, Matern U. Multifunctional flavonoid dioxygenases: flavonol and anthocyanin biosynthesis in Arabidopsis thaliana L. Phytochemistry.2010 Jul 1;71(10):10409

3. Dixon RA, Pasinetti GM. Flavonoids and isoflavonoids: from plant biology to agriculture and neuroscience. Plant Physiology. 2010 Oct 1;154(2):453-7.

4. Desta KT, Lee WS, Lee SJ, Kim YH, Kim GS, Lee SJ, Kim ST, Abd El-Aty AM, Warda M, Shin HC, Shim JH. Antioxidant activities and liquid chromatography with electrospray ionization tandem mass spectrometry characterization and quantification of the polyphenolic contents of Rumex nervosus Vahl leaves and stems. Journal of separation science. 2016 Apr;39(8):1433-41.

5. Hundsdörfer C, Stahl W, Müller TJ, De Spirt S. UVA photoprotective properties of an artificial carotenylflavonoid hybrid molecule. Chemical research in toxicology. 2012 Aug 20;25(8):1692-8.

6. Šmejkal K. Cytotoxic potential of C-prenylated flavonoids. Phytochemistry Reviews. 2014 Mar;13(1):245-75.

7. Liao SY, Chen JC, Qian L, Shen Y, Zheng KC. QSAR, action mechanism and molecular design of flavone and isoflavone derivatives with cytotoxicity against HeLa. European journal of medicinal chemistry. 2008 Oct 1;43(10):2159-70.

8. McLean L, Soto U, Agama K, Francis J, Jimenez R, Pommier Y, Sowers L, Brantley E. Aminoflavone induces oxidative DNA damage and reactive oxidative species-mediated apoptosis in breast cancer cells. International journal of cancer. 2008 Apr 1;122(7):1665-74.

9. Kant R, Kumar D, Agarwal D, Gupta RD, Tilak R, Awasthi SK, Agarwal A. Synthesis of newer 1, 2, 3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities. European journal of medicinal chemistry. 2016 May 4;113:34-49.

10. Mbachu OC, Howell C, Simmler C, Malca Garcia GR, Skowron KJ, Dong H, Ellis SG, Hitzman RT, Hajirahimkhan A, Chen SN, Nikolic D. SAR Study on Estrogen Receptor α/β Activity of (Iso) flavonoids: Importance of Prenylation, C-Ring (Un) Saturation, and Hydroxyl Substituents. Journal of Agricultural and Food Chemistry. 2020 Sep 18;68(39):10651-63.

11. Lee-Hilz YY, Boerboom AM, Westphal AH, van Berkel WJ, Aarts JM, Rietjens IM. Pro-oxidant activity of flavonoids induces EpRE-mediated gene expression. Chemical research in toxicology. 2006 Nov 20;19(11):1499-505.

12. Zhang D, Xie L, Jia G, Cai S, Ji B, Liu Y, Wu W, Zhou F, Wang A, Chu L, Wei Y. Comparative study on antioxidant capacity of flavonoids and their inhibitory effects on oleic acid-induced hepatic steatosis in vitro. European journal of medicinal chemistry. 2011 Sep 1;46(9):4548-58.

14. Shcherbakov KV, Artemyeva MA, Burgart YV, Evstigneeva NP, Gerasimova NA, Zilberberg NV, Kungurov NV, Saloutin VI, Chupakhin ON. Transformations of 3-acyl-4H-polyfluorochromen-4-ones under the action of amino acids and biogenic amines. Journal of Fluorine Chemistry. 2019 Oct 1;226:109354.

15. Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. The Journal of nutritional biochemistry. 2002 Oct 1;13(10):572-84.

16. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. The scientific world journal. 2013 Oct;2013.

17. Eugster CH, Märki-Fischer E. The chemistry of rose pigments. Angewandte Chemie International Edition in English. 1991 Jun;30(6):654-72.

18. Gupta J, Gupta A, Gupta AK. Flavonoids: its working mechanism and various protective roles. International Journal of Chemical Studies. 2016;4(4):190-8.

19. Fossen T, Andersen ØM. Spectroscopic techniques applied to flavonoids. Flavonoids: chemistry, biochemistry and applications. 2006:37-142.

20. Markham KR, Mabry TJ. Ultraviolet-visible and proton magnetic resonance spectroscopy of flavonoids. InThe flavonoids 1975 (pp. 45-77). Springer, Boston, MA.

21. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacology & therapeutics. 2002 Nov 1;96(2-3):67-202.

22. Croft KD. The Chemistry and Biological Effects of Flavonoids and Phenolic Acids a. Annals of the New York Academy of Sciences. 1998 Nov;854(1):435-42

23. Xiao ZP, Wang XD, Wang PF, Zhou Y, Zhang JW, Zhang L, Zhou J, Zhou SS, Ouyang H, Lin XY, Mustapa M. Design, synthesis, and evaluation of novel fluoroquinolone–flavonoid hybrids as potent antibiotics against drug-resistant microorganisms. European journal of medicinal chemistry. 2014 Jun 10;80:92-100.

24.López-Rojas P, Janeczko M, Kubiński K, Amesty Á, Masłyk M, Estévez-Braun A. Synthesis and antimicrobial activity of 4-substituted 1, 2, 3-triazole-coumarin derivatives. Molecules. 2018 Jan 18;23(1):199.

25. Rane RA, Sahu NU, Gutte SD, Mahajan AA, Shah CP, Bangalore P. Synthesis and evaluation of novel marine bromopyrrole alkaloid-based hybrids as anticancer agents. European journal of medicinal chemistry. 2013 May 1;63:793-9.

26. Xiao CF, Tao LY, Sun HY, Wei W, Chen Y, Fu LW, Zou Y. Design, synthesis and antitumor activity of a series of novel coumarin–stilbenes hybrids, the 3-arylcoumarins. Chinese Chemical Letters. 2010 Nov 1;21(11):1295-8.

27. Hassan AH, Lee KT, Lee YS. Flavone-based arylamides as potential anticancers: Design, synthesis and in vitro cell-based/cell-free evaluations. European journal of medicinal chemistry. 2020 Feb 1;187:111965.

28. Wei M, Xie M, Zhang Z, Wei Y, Zhang J, Pan H, Li B, Wang J, Song Y, Chong C, Zhao R. Design and synthesis of novel Flavone-based histone deacetylase inhibitors antagonizing activation of STAT3 in breast cancer. European journal of medicinal chemistry. 2020 Nov 15;206:112677.

29. Habashneh AY, El-Abadelah MM, Zihlif MA, Imraish A, Taha MO. Synthesis and Antitumor Activities of Some New N1-(Flavon-6-yl) amidrazone Derivatives. Archiv der Pharmazie. 2014 Jun;347(6):415-22.

30. Corbett TH, Bissery MC, Wozniak A, Plowman J, Polin L, Tapazoglou E, Dieckman J, Valeriote F. Activity of flavone acetic acid (NSC-347512) against solid tumors of mice. Investigational new drugs. 1986 Sep;4(3):207-20.

31. Sang Z, Wang K, Shi J, Cheng X, Zhu G, Wei R, Ma Q, Yu L, Zhao Y, Tan Z, Liu W. Apigenin-rivastigmine hybrids as multi-target-directed liagnds for the treatment of Alzheimer's disease. European journal of medicinal chemistry. 2020 Feb 1;187:111958.

32. Dong Y, Zhang X, Liu M, Yang Y, Guo T, Mao Y, Zhang J, Fu X, Zhao Y, Chen J, Dong L. Hybrid molecules of scutellarein and tertramethylpyrazine's active metabolites for ischemic stroke. Bioorganic & medicinal chemistry letters. 2019 Oct 1;29(19):126608.

33. Sowjanya T, Rao YJ, Murthy NY. Synthesis and antiproliferative activity of new 1, 2, 3-triazole/flavone hybrid heterocycles against human cancer cell lines. Russian Journal of General Chemistry. 2017 Aug 1;87(8):1864-71.

34. Popłoński J, Turlej E, Sordon S, Tronina T, Bartmańska A, Wietrzyk J, Huszcza E. Synthesis and antiproliferative activity of minor hops prenylflavonoids and new insights on prenyl group cyclization. Molecules. 2018 Apr;23(4):776.

35. Kamal A, Ramu R, Khanna GR, Saxena AK, Shanmugavel M, Renu MP. Synthesis and evaluation of new pyrrolo [2, 1-c][1, 4] benzodiazepine hybrids linked to a flavone moiety. Arkivoc. 2005(3).

36. Pajtás D, Kónya K, Kiss-Szikszai A, Džubák P, Pethő Z, Varga Z, Panyi G, Patonay T. Optimization of the synthesis of flavone–amino acid and flavone–dipeptide hybrids via Buchwald–Hartwig reaction. The Journal of organic chemistry. 2017 May 5;82(9):4578-87.

37. Hassan AH, Yoo SY, Lee KW, Yoon YM, Ryu HW, Jeong Y, Shin JS, Kang SY, Kim SY, Lee HH, Park BY. Repurposing mosloflavone/5, 6, 7-trimethoxyflavone-resveratrol hybrids: Discovery of novel p38-α MAPK inhibitors as potent interceptors of macrophage-dependent production of proinflammatory mediators. European journal of medicinal chemistry. 2019 Oct 15;180:253-67.

38. Verma AK, Singh H, Satyanarayana M, Srivastava SP, Tiwari P, Singh AB, Dwivedi AK, Singh SK, Srivastava M, Nath C, Raghubir R. Flavone-based novel antidiabetic and antidyslipidemic agents. Journal of medicinal chemistry. 2012 May 24;55(10):4551-67.

39. Pan G, Zhao L, Xiao N, Yang K, Ma Y, Zhao X, Fan Z, Zhang Y, Yao Q, Lu K, Yu P. Total synthesis of 8-(6 ″-umbelliferyl)-apigenin and its analogs as anti-diabetic reagents. European journal of medicinal chemistry. 2016 Oct 21;122:674-83.

40. Lameira J, Medeiros IG, Reis M, Santos AS, Alves CN. Structure–activity relationship study of flavone compounds with anti-HIV-1 integrase activity: A density functional theory study. Bioorganic & medicinal chemistry. 2006 Nov 1;14(21):7105-12.

41. Rao YJ, Sowjanya T, Thirupathi G, Murthy NY, Kotapalli SS. Synthesis and biological evaluation of novel flavone/triazole/benzimidazole hybrids and flavone/isoxazole-annulated heterocycles as antiproliferative and antimycobacterial agents. Molecular diversity. 2018 Nov;22(4):803-14.