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ISOFLAVONES ARE A KEY RESEARCH SCAFFOLD IN MEDICINAL CHEMISTRY: A REVIEW

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Abstract:
Isoflavones showed diverse biological activities particularly associated with anticancer activity due to binding with oestrogen receptors which is related to the inhibition of cell cycle. There are many biological activities attributed to isoflavonoids. The majority of them could be beneficial and some of them may be detrimental, depending on specific circumstances. Isoflavonoids play an important role in human nutrition as health promoting natural chemicals. They belong to plant secondary metabolites that mediate diverse biological functions through numerous pathways. The results of epidemiologic studies exploring the role of isoflavonoids in human health have been inconclusive.
The other activities include urease inhibitory activity, antiparasitic activity, antidiabetc activity, antiviral activity, antibacterial activity, antifungal activity, cardiovascular and skin diseases, osteoporosis and obesity, as well as relief of menopausal symptoms.

Keywords: Isoflavone,Biological Activity, Medicinal Chemistry, Secondary Metabolites

1. Introduction:

Due to a variety of bioprotective properties, including antioxidant[i], antimutagenic[ii], anticarcinogenic[iii], and antiproliferative[iv] activities, primarily evaluated *in vitro*, interest in the potential health advantages of isoflavonoids has developed. Isoflavonoids have traditionally been thought of as dietary antioxidants, or substances that may guard against oxidative stress, which is associated to inflammation and increases the risk of macromolecule damage from free radicals and other related oxygen and nitrogen-based oxidizing agents[v]. They could defend the body against hormone-related cancers like breast, uterine, and prostate cancer. There is growing evidence from human dietary and epidemiologic studies that the role of isoflavonoids in human health is debatable, despite the broad range of health protective abilities that have been attributed to them, such as immunomodulation, risk reduction of chronic diseases including cardiovascular diseases, diabetes, cancer, osteoporosis, and obesity[vi], as well as relief of menopausal symptoms[vii]. While some research supports the

preventive advantages of isoflavonoid supplementation as a natural alternative to oestrogen replacement medication, other studies were unable to show such benefits.

According to reports, flavonoids and isoflavonoids make up the two main classes into which polyphenols are typically separated. Additionally, the B ring of isoflavones is connected to C-3 of the heterocyclic ring, whereas the B ring of flavones is attached to the connected at C-2. Isoflavones, which are naturally occurring secondary plant metabolites and are classified as "phytoestrogen," all have the 3-phenylchroman skeleton. Both Reinsch[viii] and Hlasiwetz[ix] are credited with isolating the first natural isoflavonoid from Ononis spinosa L. in the middle of the nineteenth century. Additionally, Baker *et al*.[x] assigned the complete structure of the first isolated isoflanoid, ononin, as compound around eighty years later.

Additionally, more than 1900 natural isoflavonoids from sources with remarkable chemodiversity have been identified since the isolation of ononin[x]. Additionally, isoflavones' chemodiversity is produced by hydroxylation and the position of the hydroxyl group on the skeleton, methylation, the formation of the methylenedioxy-bridge, prenylation, the dimerization of two isoflavone units, pyranofunctionalization, glycosylation, and the loss of the hydroxyl group at the C-5 position. Furthermore, a significant number of O-linked isoflavone glycosides as well as a number of C-linked isoflavone glycosides have been identified, however only a small number of isoflavone glycosides have been reported possessing both C- and O-glycosylation[x]

Over 800 isoflavones have reportedly been isolated from the family Leguminosae, which is said to be the primary source of natural isoflavonoids. On the other hand, a significant amount of isoflavonoids have been discovered in Papilionoideae, one of the subfamilies of the Leguminosae[xi]. In addition, 225 isoflavonoids from 59 non-leguminous plant groups have been identified[xii]. The following 15 non-leguminous families also include prenylated isoflavones: Cyperaceae, Iridaceae, Zingiberaceae, Asteraceae, Rubiaceae, Convolvulaceae, Nyctaginaceae, Clusiaceae, Ochnaceae, Myricaceae, Moraceae, Urticaceae, Celastraceae, Euphorbiaceae, and Bryaceae, Sapotaceae, and Ochnaceae, three nonleguminous plant families, were shown to have isoflavone dimers or heterodimers[xii]. Other members of the genus that have been reported to contain isoflavones include Iris, Genista, Cytisus, Sophora, Desmodium, Luburnum, Teline, Pueraria, Millettia, Crotalaria, Ulex, Derris, Erythrina, Tephrosia, Lygos, and Trifoliumx[viii,xiv,xv]. Therefore the biological activity of isoflavone and its derivatives are briefly dicussed in the following few pages.

2. Biological Activity:

Numerous biological characteristics of isoflavonoids have been demonstrated, which could explain their potential to prevent cancer. Isoflavones work in a variety of ways, and they seem to employ a variety of methods of action when it comes to preventing cancer. The other activities include Urease inhibitory activity, Antiparasitic Activity, Antidiabetc activity, Antiviral activity, Antibacterial activity, Antifungal activity, cardiovascular and skin diseases, osteoporosis and obesity, as well as relief of menopausal symptoms.**Figure 1.**

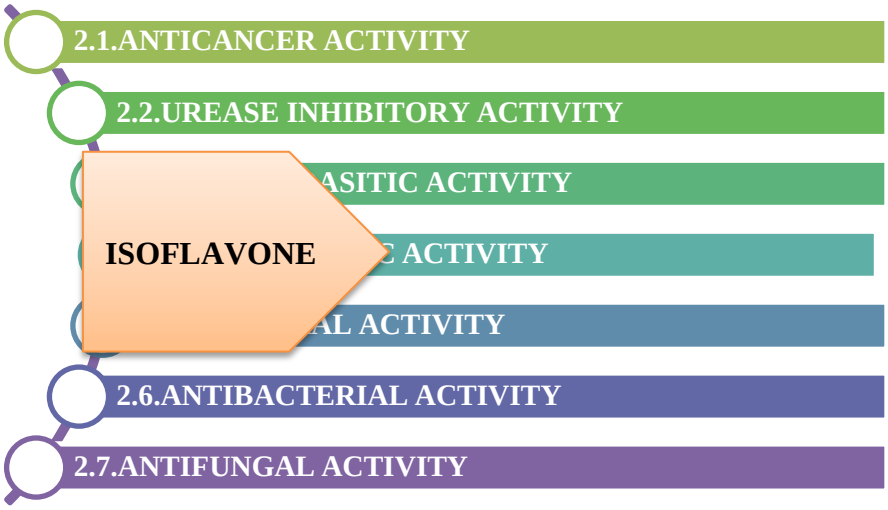


Figure 1

2.1.Anticancer Activity:

Mamoalosi *et al.*[xvi] reported the synthesis of Isoflavone derivatives and evaluated for inhibition of sirtuin 1 (SIRT1) and cell proliferation in MDA-MB-231 triple-negative breast cancer (TNBC) cells. Several isoflavone and benzoylbenzofuran derivatives exhibited potent antiproliferative effects against the MDA-MB-231 cancer cell line. SIRT1 activity was reduced by the majority of isoflavone derivatives to less than 50%. The isoflavone quinones 1, 2, and 3 had the highest activity, with IC_{50} values of 5.58 0.373, 1.62 0.0720, and 7.24 0.823 M, respectively. It's significant that the compound with the highest activity, 6-methoxy-4′,6′-dimethylisoflavone-2′,5′-quinone 2, showed SIRT1 inhibitory activity on par with the reference molecule suramin. The experimental findings were further supported by the in silico docking simulations in the active site of SIRT1, which further investigated the binding orientations of powerful chemicals in the target's active site. **Figure 2.**

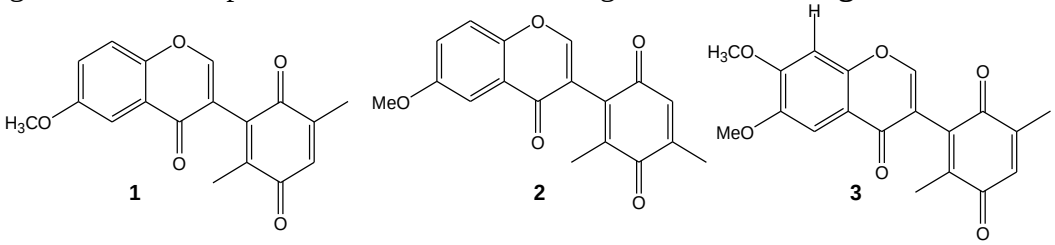


Figure 2. Compounds (1-3)

Because of its structural resemblance to 17-estradiol 5, genistein 4, one of the most common soy isoflavones, has been demonstrated to compete with it for binding to oestrogen receptors, leading to agonistic or antagonistic activity. Both *in vivo* and *in vitro*, it prevents cell proliferation in breast and prostate malignancies. Genistein has been shown to influence the genes essential for the regulation of cell proliferation, cell cycle, apoptosis, oncogenesis, transcription regulation, and cell signal transduction pathways based on gene expression patterns. The activation of the NFB and Akt signalling pathways, both of which are known to maintain a balance between cell survival and apoptosis, has been found to be inhibited by genistein, which is said to increase apoptosis. Through the inactivation of NFB in numerous cancer cell lines, genistein sensitised cancer cells to apoptosis brought on by chemotherapy drugs like docetaxel, gemcitabine, and cisplatin. Based on the structural requirements for the best anticancer impact, Sarkar *et al.*[xvii] synthesised structurally modified derivatives of isoflavone to increase the anticancer activity of genistein, and therefore synthesized that these

artificial isoflavone 6(a-d) variants had greater anticancer efficacy and lower IC_{50} values. In addition, compared to genistein, these isoflavone derivatives increased the amount of apoptosis. These findings imply that synthetic structurally modified isoflavone derivatives and genistein may be effective cancer chemopreventive and therapeutic medicines, either alone or in conjunction with other chemotherapeutic drugs.**Figure 3.**

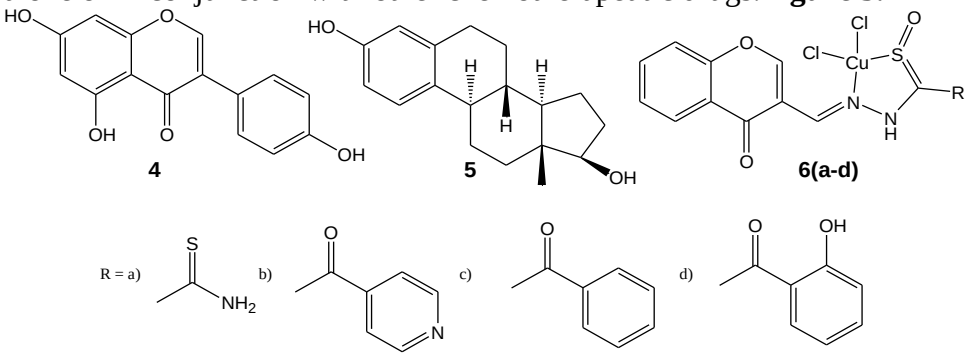


Figure 3. Compounds (4,5,6(a-d))

According to Nguyen *et al*.[xviii] 4′-O-methylgrynullarin **7** and its derivatives **8** exhibited preferential cytotoxicity under nutrient deprived conditions without cytotoxicity under normal nutrient conditions, suggesting that its derivatives may produce novel anticancer agents based on an antiausterity strategy. The Suzuki-Miyaura coupling reaction was used as a key step in the divergent synthesis of 4′-O-methylgrynullarin derivatives, and the evaluation of the synthesised derivatives revealed a clear structure activity relationship. It was discovered that the 6-prenyl moiety and 7-phenolic hydroxyl group on the isoflavone skeleton are essential for preferential cytotoxicity, and that even though the substituent groups on the C-ring are.**Figure 4.**

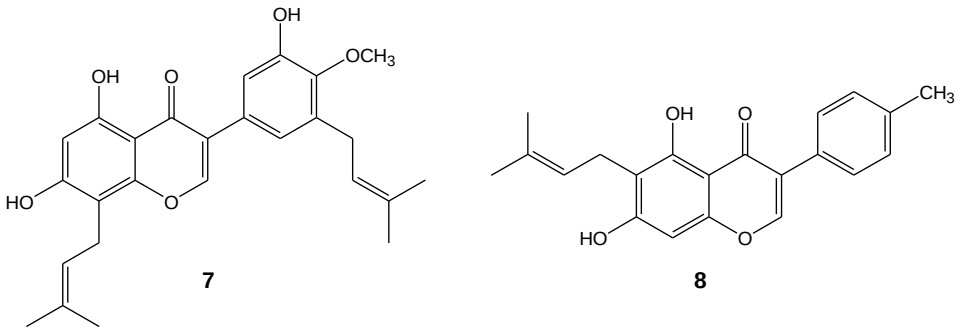


Figure 4. Compounds (7-8)

Phaladi *et al*.[xix] reported that the unanticipated intramolecular cycle involving ring-opening/cyclization, deprotection, and benzoylbenzofuran conversion into isoflavones. This was found during research on how benzoylbenzofurans might change into coumaronochromones. This process provides isoflavones in two significant phases. The transformation was verified through the synthesis of variously substituted isoflavone derivatives 9, and it was then applied to a quick synthesis of glaziovianin A, a potential anticancer lead structure 10.**Figure 5.**

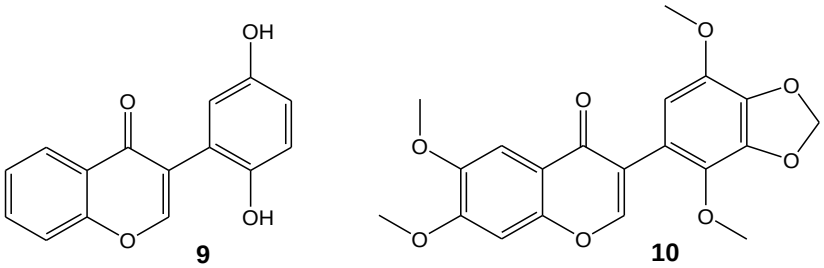


Figure 5. Compounds (9-10)

An important class of oxygen heterocycles includes isoflavonoids. An isoflavone's structure is made up of 3-phenylchromen-4-one skeleton. Isoflavones display a wide range of varied physiologic actions, including anti-inflammatory, antioxidant, and antibacterial properties. The goal of this work is to in silico develop, synthesise, and assess the anticancer activity of isoflavone derivatives. Using the software programmes Argus, Schrodinger, and Molinspiration, twenty analogues were designed in silico. Five of these analogues were chosen for synthesis based on the docking scores. Trypan blue dye exclusion was used to test the anticancer activity. One of the synthetic compounds 11 shown notable antitumor activity. While synthetic isoflavonoid compounds continue to catch the attention of the pharmaceutical industry, natural isoflavonoid compounds have so far shown to be of limited use in clinical settings. These innovative analogues could target anticancer properties particularly and can be thought of as ideal lead molecules for additional study and development[xx].**Figure 6.**

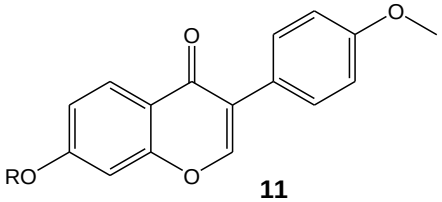


Figure 6. Compound (11)

As inhibitors of the cholesterol ester transfer protein (CETP), Wenbin *et al.*[xxi] synthesized a series of isoflavone amides using isoflavone instead of the scaffold of 2-arylbenzoxazole. Twelve novel substances were synthesized, and the CETP and preadipocyte proliferation-inhibiting effects of each were evaluated. Hamsters were used to conduct additional *in vivo* tests on the most potent compound 12c, for its hypolipidemic potential. The findings show that 12c has positive antihyperlipide- mic and antiproliferative effects on preadipocytes.**Figure 7.**

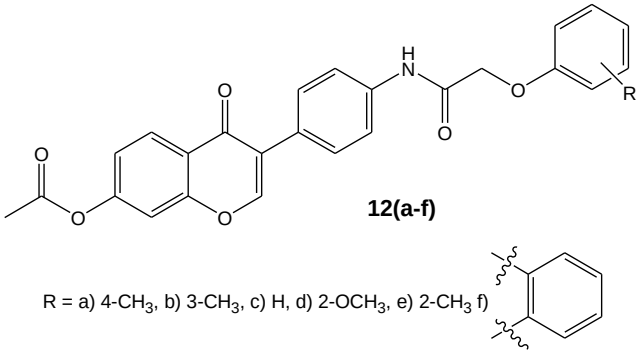


Figure 7. Compound 12(a-f)

2.2.Urease Inhibitory Activity:

Twenty polyphenols were synthesized by Xiao *et al*.[xxii], and their impact on *Helicobacter pylori* urease was assessed. Among them, 7,8,4′-trihydroxyisoflavone (IC_{50} = 0.14 mM) 13 shown strong inhibitory effects and inhibited *Helicobacter pylori* urease in a time-dependent manner. The two ortho hydroxyl groups were crucial for the polyphenol's inhibitory effect, according to the structure-activity relationship of these polyphenols. The inhibitory activity of the isoflavone significantly diminished when the C-ring was disrupted. The carboxyl group was obviously harmful to deoxybenzoin.**Figure 8.**

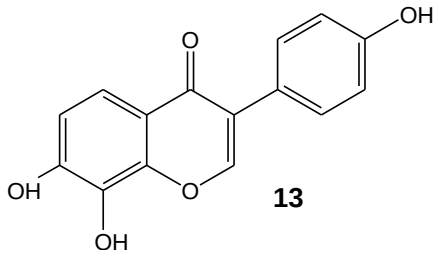


Figure 8.Compound 13

The isoflavones calopogonium isoflavone A, atalantoflavone, 2′,4′,5′,7-tetramethoxyisoflavone, 7-O-methylcuneantin, cabreuvin, and 7-O-methylpseudo- baptigenin were all isolated from the soluble portion of *Calopogonium mucunoides* (Fabaceae) in dichloromethane. Daidzeine, 7-O-methylcuneantin, atalantoflavone, and 16a, 18-dehydroxydegueline have all been isolated from C. mucunoides for the first time, while the others have already been reported. Nine separate compounds were examined for their potential to inhibit urease. Six were discovered to be powerful, though. These include 2′,4′,5′,7-tetramethoxyisoflavone, atalantoflavone, 4′-O-methylderrone, daidzeine, 7-O-methylcuneantin, and 16a, 18-dehydroxy- degueline[xxiii].**Figure 9 and 10.**

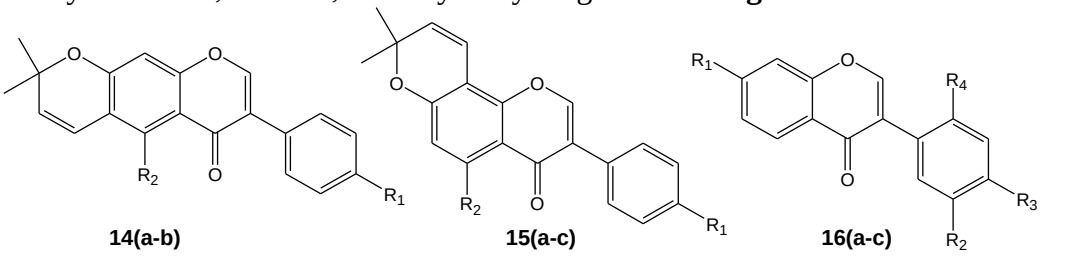


Figure 9.Compounds 14-16(a-c)

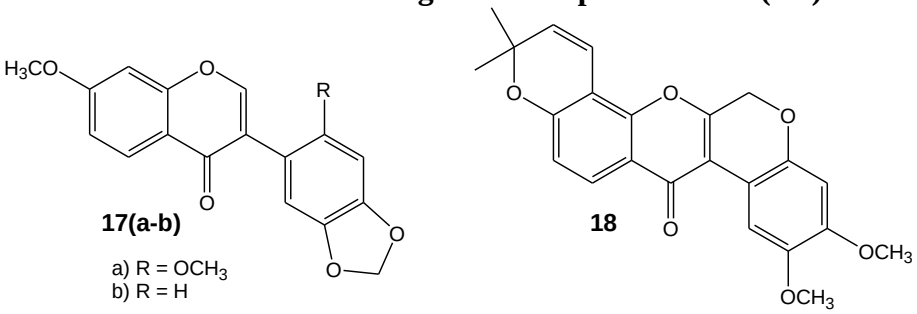


Figure 10. Compounds 17 (a-b),18

2.3.Antiparasitic Activity:

According to Patricia *et al.*[xxiv], the dichloromethane extract of *Cassia fistula* fruits (Leguminosae) was fractionated using bioguided antileishmanial activity, which resulted in the separation of the active isoflavone biochanin A 19, which was identified by spectroscopic techniques. The 50% effective concentration (EC_{50}) value for this compound against Leishmania (L.) chagasi promastigotes was 18.96 g/mL. The EC_{50} value for this compound cytotoxicity against peritoneal macrophages was 42.58 g/mL. Biochanin A also demonstrated anti-Trypanosoma cruzi activity, with an EC_{50} value of 18.32 g/mL and 2.4-fold more efficacy than benznidazole. These findings provide fresh antiprotozoal compounds for upcoming medication development investigations.**Figure 11.**

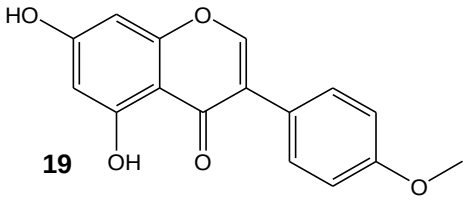


Figure 11. Compound 19

A new isoflavonoid, 5-hydroxy-3-(4-hydroxyphenyl)-8-isopropenyl-8,9-dihydro-4*H*-furo-[2,3-h]-chromen-4-one named derrisisoflavone G 20, four known prenyla- ted flavanones, four known isoflavonoids and two phenolic derivatives have been isolated from crude extracts of *Derris ferruginea* stems, leaves. Compounds were identified using spectroscopic methods whereas an unambiguous structural assignment of 20 was accomplished through hemi-synthesis. Compound 20 exhibited strong *in vitro* antiparasitic activity against *Plasmodium falciparum* and *Leishmania major* but with poor selectivity, whereas 20 significantly inhibited the formation of advanced glycation endproducts (AGEs)[xxv].**Figure 12.**

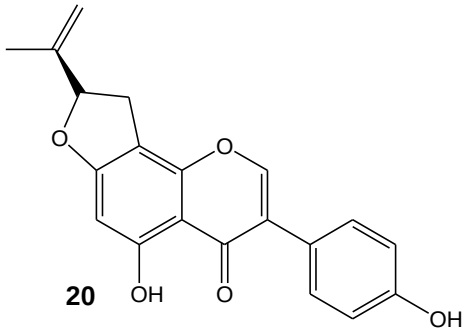
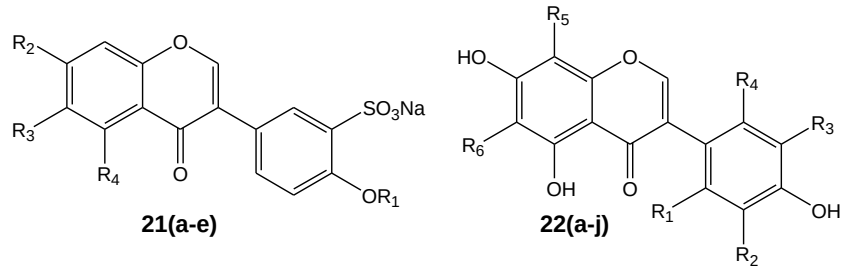


Figure 12. Compound 20

2.4.Antidiabetc Activity:

Li *et al.*[xxvi] reported that, an insulin-resistant (IR) HepG2 cell culture was used to assess the anti-diabetic properties of a collection of new isoflavone derivatives from chickpea. Additionally, a brief discussion of the structure-activity relationships of these derivatives was made. In IR-HepG2 cells, compounds 21c, 22h, and 23b significantly increased glucose uptake. Additionally, the combinations of genistein, 22b, and 22h as well as 23b (combination 1), genistein, and 21c (combination 2) demonstrated stronger anti-diabetic action than the individual substances. There was no difference in the effects of combinations 1 and 2 at the same dosage. Future research may find that combination 2 had better

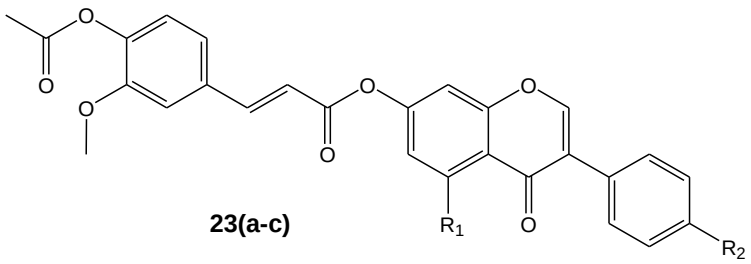
hypoglycemic action since its protective effects were stronger than those of combination 1. This study offers helpful hints for the development and discovery of anti-diabetic medications.**Figure 13 and 14.**



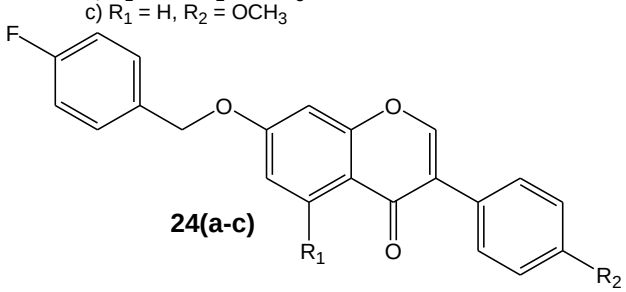
a) R_1 = H, R_2 = OH, R_3 = H, R_4 = OH
b) R_1 = H, R_2 = OH, R_3 = SO_3Na, R_4 = OH
c) R_1 = CH_3, R_2 = OH, R_3 = H, R_4 = OH
d) R_1 = CH_3, R_2 = OH, R_3 = SO_3Na, R_4 = OH
e) R_1 = CH_3, R_2 = OH, R_3 = H, R_4 = H

a) R_1=R_4=R_5=R_6=H, R_2=R_3=isopropyl
b) R_1=R_4=H, R_2=R_3=R_5=R_6=isopropyl
c) R_1=R_3=H, R_2=R_4=R_5=R_6=isopropyl
d) R_1=R_4=R_5=R_6=isopropyl, R_2=R_3=H
e) R_1=R_4=R_5=R_6=H, R_2=R_3=isopropyl
f) R_1=R_4=R_6=H, R_2=R_3=R_5=isopropyl
g) R_1=R_4=H, R_2=R_3=R_5=R_6=isopropyl
h) R_1=R_3=R_4=R_5=R_6=H, R_2=isopropyl
i) R_1=R_4=R_5=R_6=H, R_2=R_3=isopropyl
j) R_1=R_4=R_6=H, R_2=R_3=R_5=isopropyl

Figure 13.Compounds 21(a-e), 22(a-j)



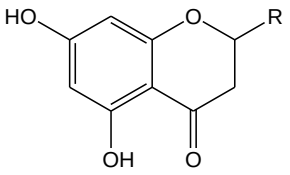
a) R_1 = OH, R_2 = OH
b) R_1 = OH, R_2 = OCH_3
c) R_1 = H, R_2 = OCH_3



a) R_1= OH, R_2 = OH
b) R_1=OH, R_2= OCH_3
c) R_1=H, R_2=OCH_3

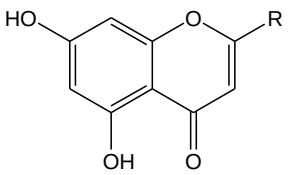
Figure 14. Compounds 23, 24(a-c)

Liu *et al*.[xxvii] reported the synthesis of two series of flavonoids,5,7-dihydroxyflavanones and 5,7-dihydroxyflavones, to investigate the structural components crucial for the antidiabetic activity of flavonoids. Most flavonoids displayed impressive *in vitro* activity when tested for possible antidiabetic action, and compounds 25f, 26d, and 26g were much more efficacious than the positive control, metformin. The structural change at the ring B moiety of the flavonoid skeleton had the biggest impact on the biological activity. According to the findings, 5,7-dihydroxyflavonoids are potential candidates for the creation of fresh anti-diabetic lead compounds.**Figure 15.**



25(a-h)

R = a) Ph, b) 4-Me-Ph, c) 4-CF_3-Ph, d) 3,4-di-Cl-Ph, e) thiophen-2-yl, f) furan-2-yl, g) 3-Cl-4-OH-Ph, h) 3-MeO-4-OH-Ph



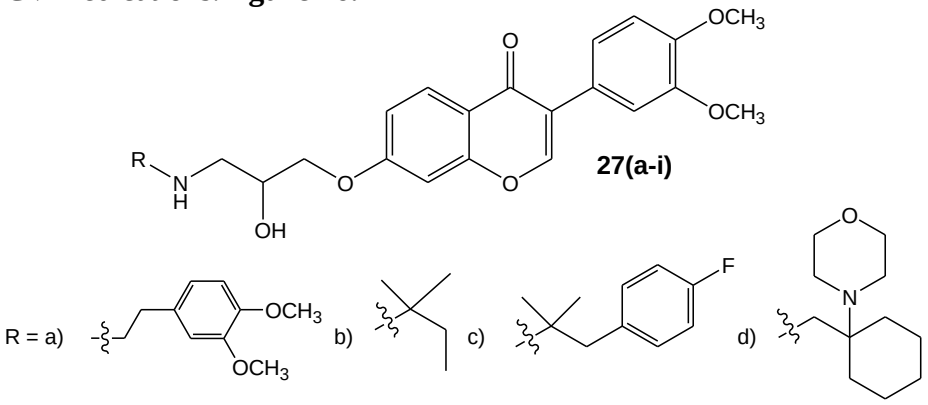
26(a-g)

R = a) Ph, b) 4-CF_3-Ph, c) thiophen-2-yl, d) 4-CN-Ph, e) 4-Me-Ph, f) 3,4-di-Cl-Ph g) furan-2-yl

Figure 15. Compounds 25(a-h), 26(a-g)

2.5. Antiviral Activity:

Some 3-amino-2-hydroxy-propoxy isoflavone derivatives, 27(a-d), were described and evaluated for their anti-hepatitis C virus (anti-HCV) activity. The 7-[(3,4-dimethoxy-phenethyl)amino] group is one of them. -2-hydroxypropoxy} -3-(3,4-dimethoxyphenyl) The most effective antiviral medication was -4H-chromen-4-one 27a, which had an EC_{50} of 6.53 vs. 13.16 M and roughly 2-fold stronger anti-HCV effects than ribavirin. Compound 27a was additionally less cytotoxic than ribavirin. Compared to ribavirin, 27a has a selectivity index (SI) that is roughly 2.6 times higher. Additionally, it was discovered that the compounds 27b, 27c, and 27d have stronger anti-HCV activities than ribavirin. In Ava5 cells, compound 27a was discovered to decrease HCV RNA expression in a dose-dependent manner. In addition, Lee *et al*.[xxviii] discovered that the antiviral action of these substances resulted in HO-1 expression being induced. Compounds 27a, 27b, 27c, and 27d increased Nrf-2 binding activity in order to trigger HO-1 expression using the HO-1 promoter-based study. When combined, compound 27a might function as a prospective lead substance for creating brand-new anti-HCV medications.**Figure 16.**

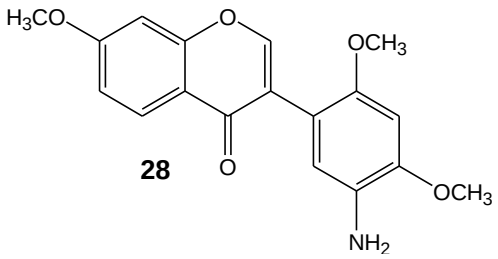


27(a-i)

Figure 16. Compound 27(a-i)

2.6. Antibacterial Activity:

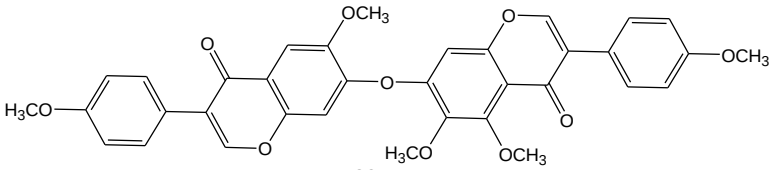
Nawaf, A. M.; Nidal, J. *et al*.[xxix] Aminoisoflavones 28 are synthetic compounds of a class of natural compounds found in plants and nutritional items like those made from soy. By nitrating the parent isoflavone and then reducing it with tin (II) chloride dihydrate, three new aminoisoflavones have been synthesised. After being coupled with L-alanine, these unstable aminoisoflavones produced stable derivatives. Because the parent was unstable, it was hypothesised that these conjugates may be employed 7in chromogenic medium to identify Gram-negative bacteria that produce L-alanyl aminopeptidase. Cleavage of the amide would cause breakdown and the formation of colourful chemicals. However, a variety of bacteria were used for biological testing, despite the fact that a simpler o-aminophenol conjugation did result in black colonies on doped agar plates with *Escherichia coli* strains[xxix].**Figure 17.**



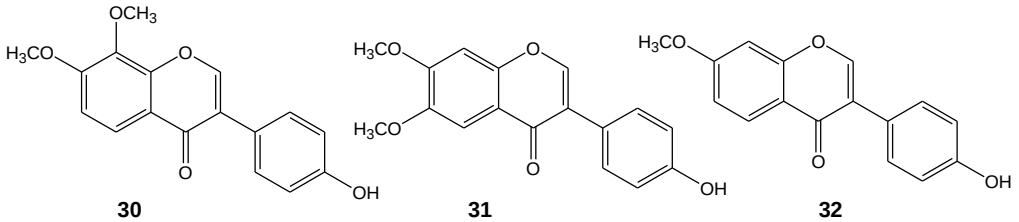
28

Figure 17.Compound 28

Edwige *et al*.[xxx] reported that, a novel bis-isoflavone derivative known as amphiisoflavone 29, as well as isoflavones 8-methoxyisoformononetin 30, 6-methoxyisoformononetin 31, and 32, were obtained from the roots of *Amphimas pterocarpoides*. A known compound, 4,6,7-trimethoxyisoflavone, and two new derivatives, 4-acetoxy-6,7-dimethylisoflavone and 4-O-prenyl-6,7-dimethylisofla- vone, were produced as a result of chemical reactions carried out on compound 31. Antioxidant and antibacterial activities against a variety of bacteria and fungi were assessed for these compounds.**Figure 18.**



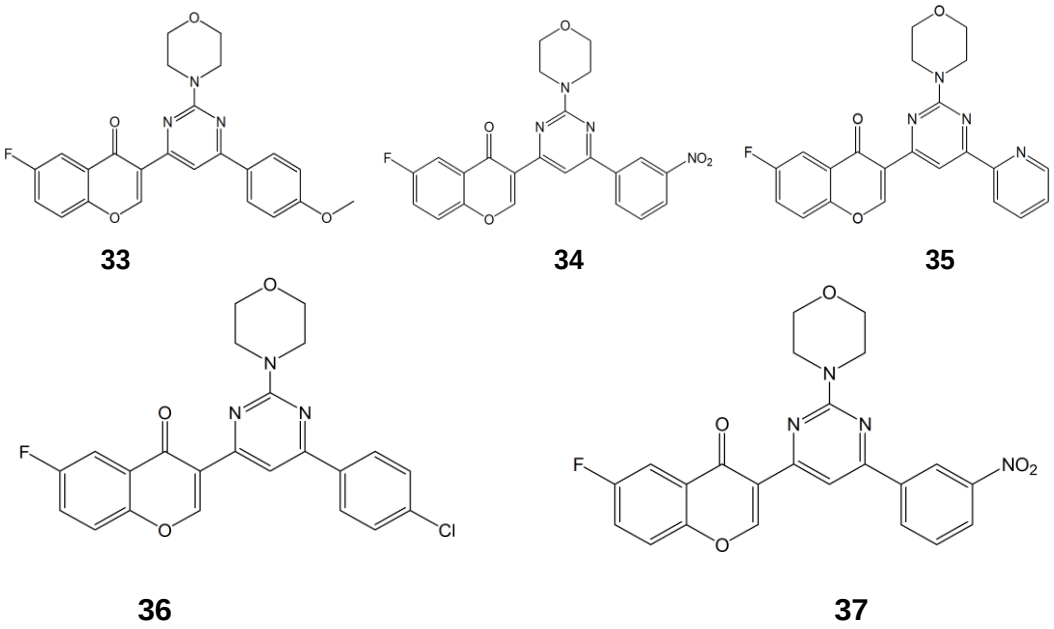
29



30 **31** **32**

Figure 18.Compounds (29-32)

Nagaraj et al.[xxxi] A new series of 6-fluoro-3-(2-morpholino-6-aryl-4-pyrimidinyl)-4H-4-chromenone 4(a-i) were synthesized by the reaction of 6-fluoro-3-[(E)-3-oxo-3-aryl-1-propenyl]-4H-4-chromenone 3(a-i) with 4-morpholinecarboximidamide. The compounds 33-37 were evaluated for their antibacterial activity against Gram-positive bacteria viz.B. subtilis, B.sphaericus and S. aureus.Compounds 33, 34 and 35 showed higher activity towards the Gram-positive bacterial strains. Compounds 36 and 37 showed good inhibition towards B. subtilis and S. Aureus. Gram-negative bacteria P. aeruginosa, K. aerogenes,C.violaceum viz. 4c showed higher activity Against P. aeruginosa, K. aerogenes and 4f showed good activity against C.violaceum.**Figure 19.**



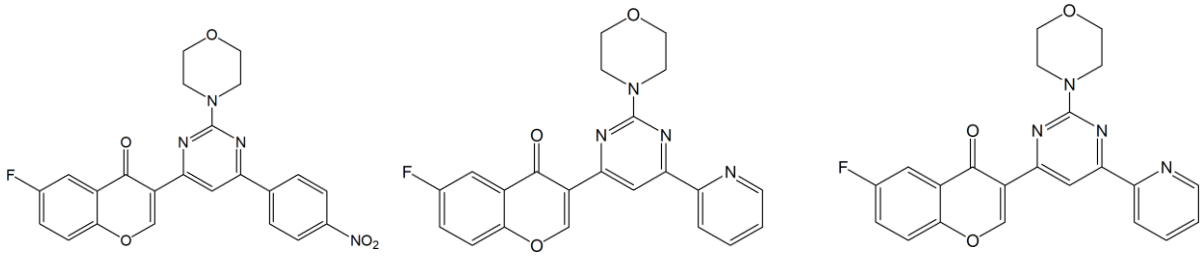
33 **34** **35**

36 **37**

Figure 19. Compounds (33-37)

2.6. Antifungal Activity:

Nagaraj et al.[xxxi] Screened for their antifungal activity against four fungal organisms viz.C.Albicans, A. Fumigatus, T. rubrum and T.Mentagrophytes.The compounds 38, 39 and 40 showed highest activity against all the fungal strains used.**Figure 20**



38 **39** **40**

Figure 20. Compounds (38-40)

3. Conclusion:

This review outlined the biological activities of isoflavones and served as a resourses for both basic and applied research on the subject.These activities included anticancer activity, urease inhibitory activity, antiparasitic activity, antidiabetc activity, antiviral activity, antibacterial activity,antifungal activity.

4. Conflicts of Interest:

There are no conficts to declare.

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