INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

A REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED APIGENIN DERIVATIVES

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ARTICLE INFO

Article history
Received 03/01/2020
Available online
31/01/2020

Keywords
Apigenin,
Flavones,
Different Methods And
Biological Activities.

ABSTRACT

Apigenin belonging to the flavone class that is the aglycon of several naturally occurring glycosides constitute an important class of compounds. In recent year flavone analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. The flavone nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as antiproliferative, antibacterial and antioxidant activities. The present review focuses on the different methods of the substituted apigenin derivative with potential activities that are now in development for the enhancement of bioavailability and therapeutic activity.

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*Please cite this article in press as **Krishna R. Gupta** et al. A Review on Synthesis and Biological Activity of Substituted Apigenin Derivatives. Indo American Journal of Pharmaceutical Research.2020:10(01).*

INTRODUCTION

Flavonoids are phenolic compounds isolated from vascular plants and more than 8150 different flavonoids have been reported. Flavonoids are placed at plant cells or on the surface of various plant organs and plays important role for plants protection and growth as well as acts as antioxidants, antimicrobials, photoreceptors, visual attractors, feeding repellents, and for light screening. Many studies have been reported that flavonoids used as a nutraceutical which exhibit biological and pharmacological activities, including antioxidant, cytotoxic, anticancer, antiviral, antibacterial, cardioprotective, hepatoprotective, neuroprotective, antimalarial, antileishmanial, antitrypanosomal and antiamebial properties. These biological and pharmacological properties are usually due to their free radical scavenging efficacies, metal complexion capabilities, and their plasma protein binding affinity with a high degree of specificity [1].

The basic flavonoid structure contains the flavone nucleus containing 15 carbon atoms derived from a C6 -C3 -C6 skeleton. These flavonoid skeleton is mainly composed of two aromatic rings (commonly designated as A and B), which are linked by a three-carbon chain. The connecting carbon chain combines with an oxygen to form a heterocyclic central or C-ring [2].

Characteristics of flavonoid structure for most effective radical-scavenging activity [3-5]
Examples:

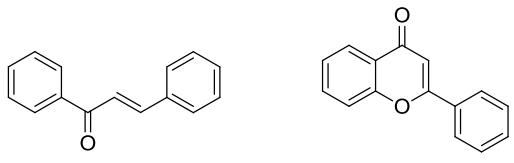
- Great scavenging ability of the catechol is due to (O-dihydroxy) group in the ring.
- A pyrogallol having increase scavenger activity due to (trihydroxy) group in ring B of a catechol, as in myricetin, produces even higher activity. The C2-C3 double bond of the C ring appears to because it confers stability to the phenoxy radical produced.
- In case of most of the flavonoids scavenging activity is due to,
  - The 4-oxo (keto double bond at position 4 of the C ring), especially in association with the C2-C3 double bond, and delocalizing electrons from B ring.
  - The 3-OH group on the C ring, the combination of C2-C3 double bond and 4-oxo group (catechol).
  - 5-OH and 7-OH groups.

The most researchers suggested that flavonoids can used as a major active nutraceutical ingredients in plants. Chemically being a phenolic compound, they can act as potent antioxidants and metal chelators as well as shows anti-inflammatory, anti-allergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities [6]. Flavonoids act as antioxidant through scavenging properties [7, 8].
The various flavonoids have different/ unique scavenging mechanism of action as follows

Table No.1: Reactive oxygen species that can be scavenged or whose formation can be inhibited by flavonoids.

O_2 (Superoxide anion)	One-electron reduction product of O_2 produced by phagocytes, formed in autoxidation reactions (flavoproteins, redox cycling), and generated by oxidases (heme proteins).
HO_2 "-"	Protonated form of O_2. "-"
H_2O_2(Hydrogen Peroxide)	Two-electron reduction product of O_2 formed from O_2 by "-" dismutation or directly from O_2. Reactivity of O_2 and H_2O_2 is amplified in the presence of heme proteins.
OH (Hydroxy radical)	Three-electrons reduction product of O_2 generated by Fenton reaction, transition metal (iron, copper)-catalysed Haber-Weiss reaction; also formed by decomposition of peroxynitrite produced by the reaction of O_2 with NO. (Nitric oxide radical).
	Example: Lipid radical (LO.). "-"
RO. (Alkoxy radical)	Example: Lipid peroxy radical (LOO.) produced from organic hydroperoxide (e.g.
ROO. (Peroxyl radical)	lipid hydroperoxide, LOOH), ROOH by hydrogen abstraction. Singlet oxygen
$1O_2$	

Different classes of flavonoids exhibit different types of biological and pharmacological activities, but among them, the chalcones (Figure 1a) and their ring analogue flavones (Figure 1b) have been considerably undergo consistent research and found that various natural, semi-synthetic and synthetic derivatives of these structures shows wide range of biological activity and it's applications in various therapies [9].



(a) (b)

Figure No.1. The chemical structure of (a) chalcone, (b) flavones.

Flavonoid

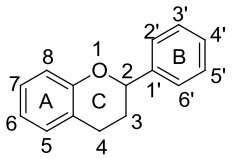


Figure No.2: Basic structure of flavonoid.

Flavonoids are an important class of natural products; particularly, they belong to a class of plant secondary metabolites having a polyphenolic structure, widely found in fruits, vegetables and certain beverages. They are benzo-γ-pyrone derivatives consisting of pyran ring. Dietary flavonoids differ in the arrangements of hydroxyl (-OH), methoxy (-OCH_3) and glycosidic side groups, and in the conjugation between the A- and B- rings [10]. Flavonoids exhibit various beneficial effects like anti-cancer [11], anti-viral, anti-inflammatory [12], anti-HIV [13], anti-tumor [14], anti-oxidant [15] and anti-diabetic [16].The classification of flavonoids in given below:-

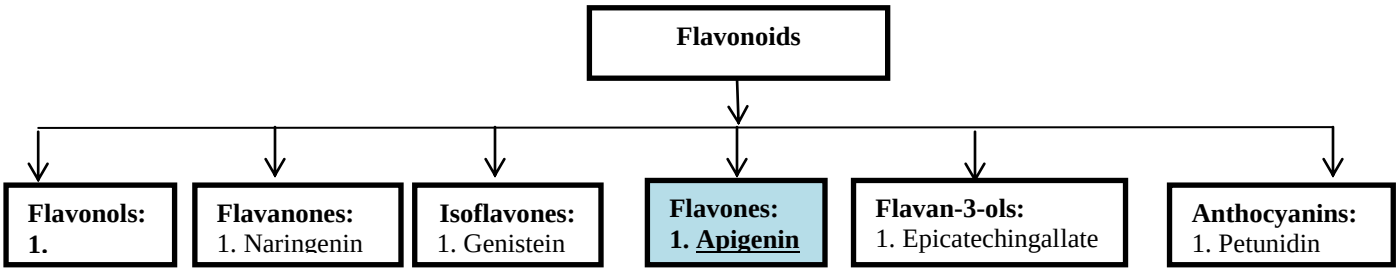


Figure No.3: Different Classes of Flavonoides.

FLAVONES

These can react in several ways, including reduction reactions, degradation in the presence of base, substitution, oxidation, condensation, rearrangement, reaction with organometallic reagents, addition. Several synthetic methods have been developed and modified to obtain products of high yield, purity and of the desired quality. Flavones can be synthesized by various synthetic schemes like Baker-Venkataraman rearrangement, Claisen-Schmidt condensation, Ionic Liquid Promoted synthesis, Vilsmeier-Haack reaction, Allan-Robinson, Wittig reaction, Fries rearrangement and modified Schotten-Baumann reaction. At present, synthesis of majority of the flavones is based on Baker-Venkataraman method. This method is based on the conversion of o-hydroxy acetophenone into phenolic ester, which then undergoes intramolecular Claisen condensation in the presence of a base to yield β-diketone. It is finally cyclized into flavones by an acid-catalyzed cyclodehydration. Traditionally, flavones were synthesized *via* Baker-Venkataraman-rearrangement but these reactions involve the use of strong bases, acids, long reaction time which ultimately results in low yields [17].

Apigenin (AP)

Structure of Apigenin

Apigenin belongs to the flavones class of flavonoids with a variety of common name such as APe; Chamomile; Apigenol; Spigenin; Versulin; 4',5,7-Trihydroxyflavone.Apigenin is a class II drug having low molecular weight (270.24g) with a very high melting point (347.5^{0}C). It found to be insoluble in water but soluble in dil. potassium hydrochloride and dimethylsulfoxide [18]. For this reason food borne AP, AP-7-O-glucoside used to increase water solubility *via* bond formation with carbohydrate group [19]. Apigenin structure contains hydroxyl (-OH) groups at positions C-5 and C-7 of A-ring and C-4′ of B-ring [20].

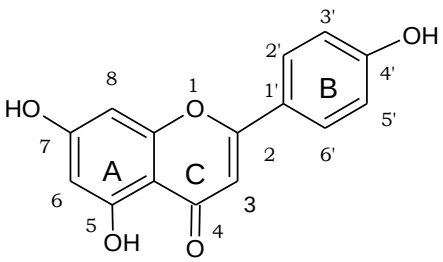


Figure No.4: Chemical structure and numbering pattern for Apigenin:5,7-dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.

It is classified as class II drug of the Biopharmaceutical classification system (BCS) due to its low lipid (0.001–1.63 mg/mL in nonpolar solvents) and water (2.16 µg/mL in water) solubility [19, 21]. Apigenin shows various cytostatic and cytotoxic effects on the various cancer cells, prevents the atherogenesis, type 2 diabetes and its complication, osteoporosis, and collagen-induced arthritis [22].

Some apigenin derivatives found as a naturally occurring plant metabolic residue such as Vitexin and isovitexin, naturally occurring C-glycosylated derivatives of apigenin having potent anti-diabetic, anti-Alzheimer's disease (anti-AD), and anti-inflammatory activities. Apigenin its C-glycosylated derivatives act as anti-diabetic activity due to their inhibitory activities against RLAR, HRAR, PTP1B and AGEs formation.

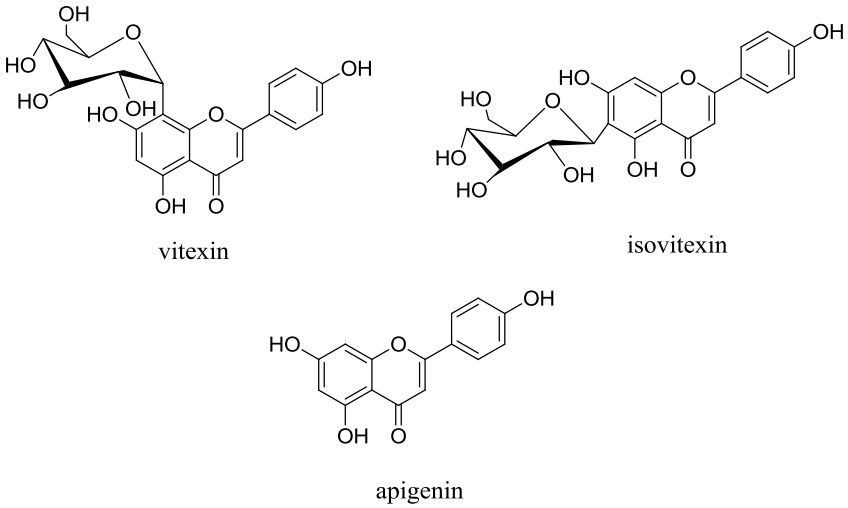


Figure No.5: Structures of apigenin and its C-glycosylated derivatives.

Apigenin and its two C-glycosylated derivatives such as vitexin and isovitexin have been reported that they have anti-diabetic, anti-AD, and anti-inflammatory activities, but till date no systematic study explain how the location of C-glycosylation at C-8 position on the aglycone affects biological activities of apigenin. The order of sequence of AChE and BChE inhibitory potential was found to be isovitexin > vitexin > apigenin. Therefore, C-glycosylation at C-8 position responsible for the inhibitory action of apigenin against BACE1; however absence of this functional group drastically decreases apigenin affinity against BACE1 which is evidenced by isovitexin and apigenin. Also glucopyranose shows additional electron withdrawals property in ring-A therefore electron density is drawn into the A-ring. Also differences in sugar moieties played an important role in enzyme inhibitor interactions resulting in varying degrees of potency towards different enzymes used in this study [23].

Apigenin derivatives or natural analogues:

Apigenin is a flavones class derivative with three hydroxyl substituent having chemical name (4′, 5, 7,-trihydroxyflavone). Removal of these substituted hydroxyl group gives basic structure of flavones (a). Apigenin can be mono-substituted flavones derivative separately at positions 4′, 5 and 7, resulting in the formation of different compounds 4′-hydroxyflavone (b), 7-hydroxyflavone (c), and 5-hydroxyflavone (d). Further hydroxylation can generate three dihydroxy-flavones 4′,7-dihydroxyflavone (e), 4′,5-dihydroxyflavone (f), and 5,7-dihydroxy flavones (g) shown in Figure No.3. Apigenin has seven possible derivatives/analogues generated from the selective hydroxyl substitutions at positions 4′, 5, and 7 of the basic flavonoid skeleton [24].

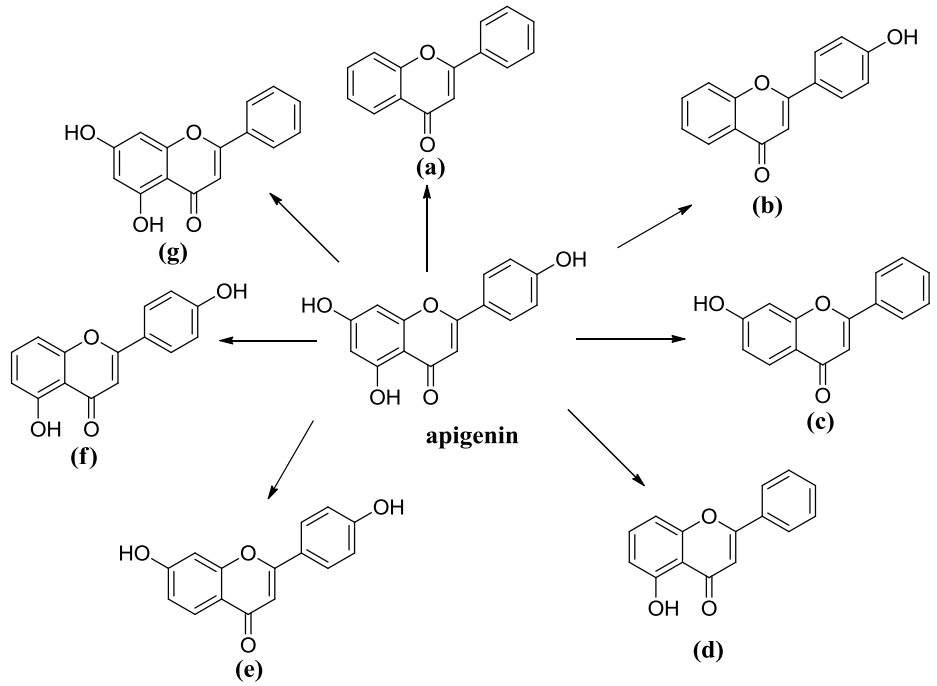


Figure No.6: Apigenin derivatives and natural analogues.

Microbial production of Apigenin:

Recently Microbial production of plant secondary metabolites has become an attractive part of production. Microorganisms such as Escherichia coli and Saccharomyces cerevisiae have been engineered and used as host engineering machinery for synthesis of final products similarly which was utilized biological pathways for the synthesis of several plant metabolites in plants. Apigenin is found in various plants part, fruits and vegetables but parsley and celery used as rich source of Apigenin. Genkwanin is synthesized from apigenin by 7-Omethylation of POMT7 identified only in Daphne genkwa. Apigenin is synthesized from p-coumaric acid by four enzymes (4CL, CHS, CHI, and FNS; Figure No.7). In E. coli, conversion of naringenin chalcone to naringenin occurs spontaneously and, therefore, the CHI that catalyzes this step is not required. Introduction of (Os4CL, PeCHS, and FNS) enzymes into E. coli and tested if BAP1 synthesized apigenin from p-coumaric acid and obtained culture filtered were analyzed by HPLC and mass spectrometry showed that apigenin was synthesized [25].

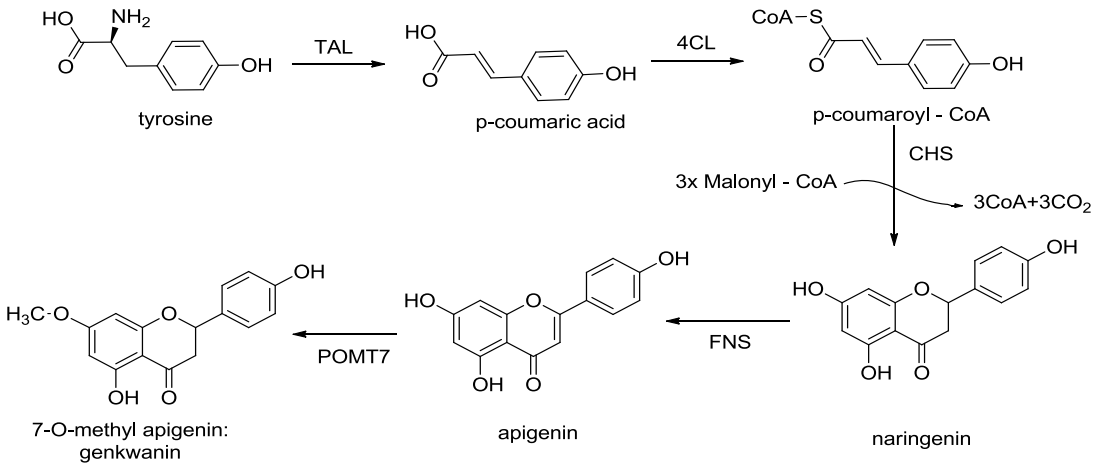


Figure No.7: Biosynthesis pathway of 7-O-methylapigenin (genkwanin) from tyrosine. TAL, tyrosine ammonium lyase; 4CL, 4-coumarate CoA ligase; CHS, chalcone synthase; FNS, flavone synthase; POMT7, apigenin 7-Omethyltransferase.

Need of Synthetic derivatives of Flavon- Apigenin:

- **Poor Bioavailabilty:** Flavonoids has poor bioavailability due to rapid metabolism via UDP-glucuronosyltransferases (UGTs). Apigenin and genistein are metabolized more rapidly in intestine than in liver through the involvement in UGTs proved by the yeast cells expressing UGT1A isoform isolated from rats. Flavonoids are efficiently metabolized by UGT1A deficient Gunn rats because of compensatory up-regulation of intestinal UGT2B and hepatic anion efflux transporters, which increases their disposition and limited their bioavailabilities [26].
- **Pure Apigenin and its own side effects:** It was reported that apigenin induces a process called autophagia (a kind of cellular dormancy) that may well explain its chemopreventive properties, but at the same time it induces resistance against chemotherapy [27].
- **Solubility issues:** AP belongs to BCS class II with poor aqueous solubility and high permeability in intestine (due to their high hydrophilicity). AP was found to possess maximum solubility 2.16 μg/mL at pH 7.5 resulting in low dissolution and poor bioavailability [28].
- **Multi-drug resistance as a drawback of synthetic drugs**: Because of extensive use of antibiotics leads to multi-drug resistance. These leads development of urgent global needs for finding new antimicrobial drugs as well as more suitable natural source to overcome multi-drug resistance. Therefore natural resources such derived flavonoids was reported to have potential antimicrobial activity [29].

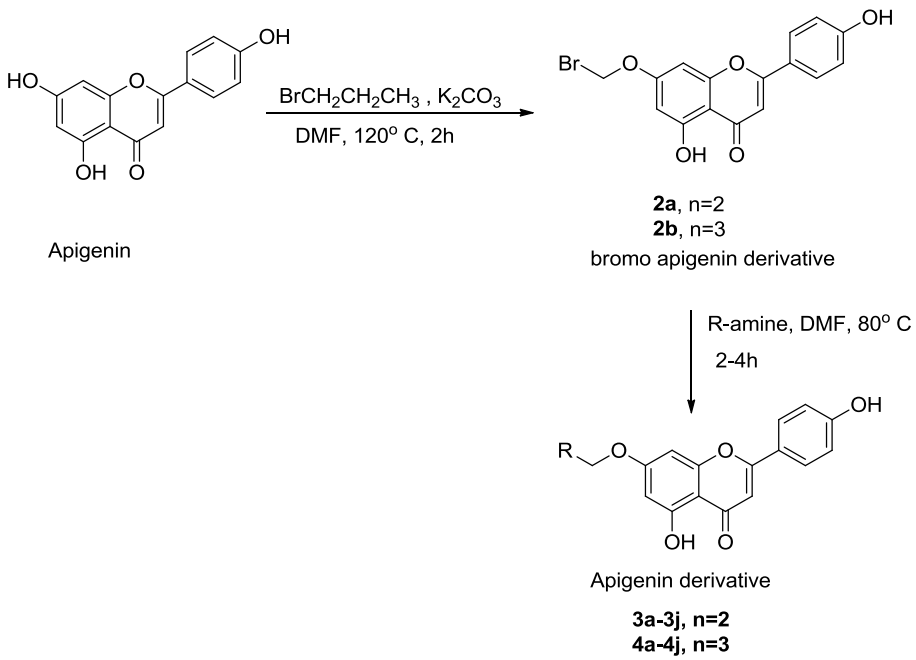
Literature survey reported that various substitution, complexation done to overcome drawbacks of pure apigenin. In our review article reported the data of need of substitution and their effects on pharmacological actions. Synthetic derivatives of apigenin were synthesized by substitution of ring system or complexation to enhance their lipophilicity and thus bioavailability. Also the obtained data revels that this substituted derivative can be used in various antimicrobial or chemotherapy. Literature survey reveals that AP has potent biological activity but have low solubility and bioavailability. The main objective of this review is to study different derivatives of AP to overcome its drawback i.e. low solubility and bioavailability.

Synthesis and biological activity:

Several methods for the synthesis and pharmacological properties of substituted apigenin reported in the literature.

Synthesis of C-7-modified apigenin derivatives:

Apigenin derivative [5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one], 3a–3j and 4a–4j, were synthesized with the help of 2 or 3 carbon spacer at C-7 position between apigenin and alkyl amines moiety to enhance their lipophilicity. Synthesized derivatives were evaluated for their anti-bacterial and anti-proliferative activities. Among these derivatives, 4a-4j which contains a C_3 spacer between AP and the different amines, displayed greater anti-proliferative activity than 3a-3j [30].



Apigenin

2a, n=2
2b, n=3
bromo apigenin derivative

Apigenin derivative

3a-3j, n=2
4a-4j, n=3

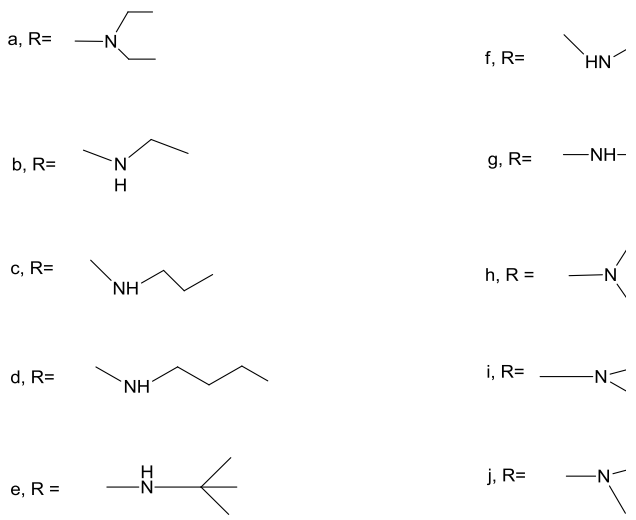


Figure No.8:- Schematic diagram showing Synthesis of C-7-modified apigenin derivatives.

Synthesis of Nitrogen-containing Apigenin 8-aminomethylated Apigenin derivative:

Nitrogen-containing apigenin 8-aminomethylated apigenin analogs **4a**–**j** was synthesized via Mannich reactions and evaluated for their anticancer, antibacterial, and antioxidant agents from plant-derived flavonoids. Bioactivity assays showed that all the synthesized compounds exhibited greater compared with the parent apigenin. Among these apigenin analogues, compound **4j** was found to be the most active and showed increased biological activities were due to the introduction of aminomethyl groups into the C-8 position of the parent apigenin [31].

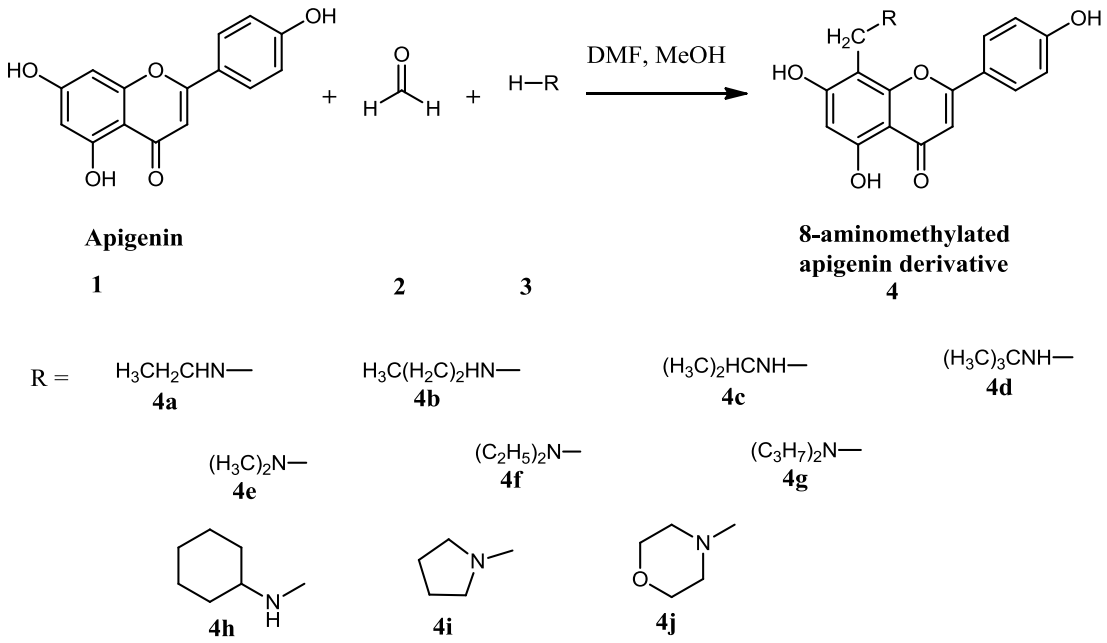


Figure No.9:- Synthetic route of compounds 4a to 4j.

Synthesis of Novel triazole analogs of apigenin-7-methyl ether:

Novel triazole analogs of apigenin-7-methyl ether (compound 1) were isolated from the ethanolic extract of leaves of Aquilaria sinensis. The novel triazole analog was synthesized by using propargyl bromide in presence of base K_2CO_3 to give compound 2. Obtained Compound 2 reacted with different substituted organic azides under click chemistry conditions to give 1,2,3-triazole as a Apigenin substituted product. A synthesized novel triazole analog of the bioactive apigenin-7-methyl ether was evaluated for its anticancer activity against three human ovarian cancer cell lines. A total of eight novel triazole derivatives were synthesized and screened for their anticancer activity. The results showed that the apigenin-7-methyl ether novel derivative 3d may prove an important lead molecule for the treatment of ovarian cancer [32].

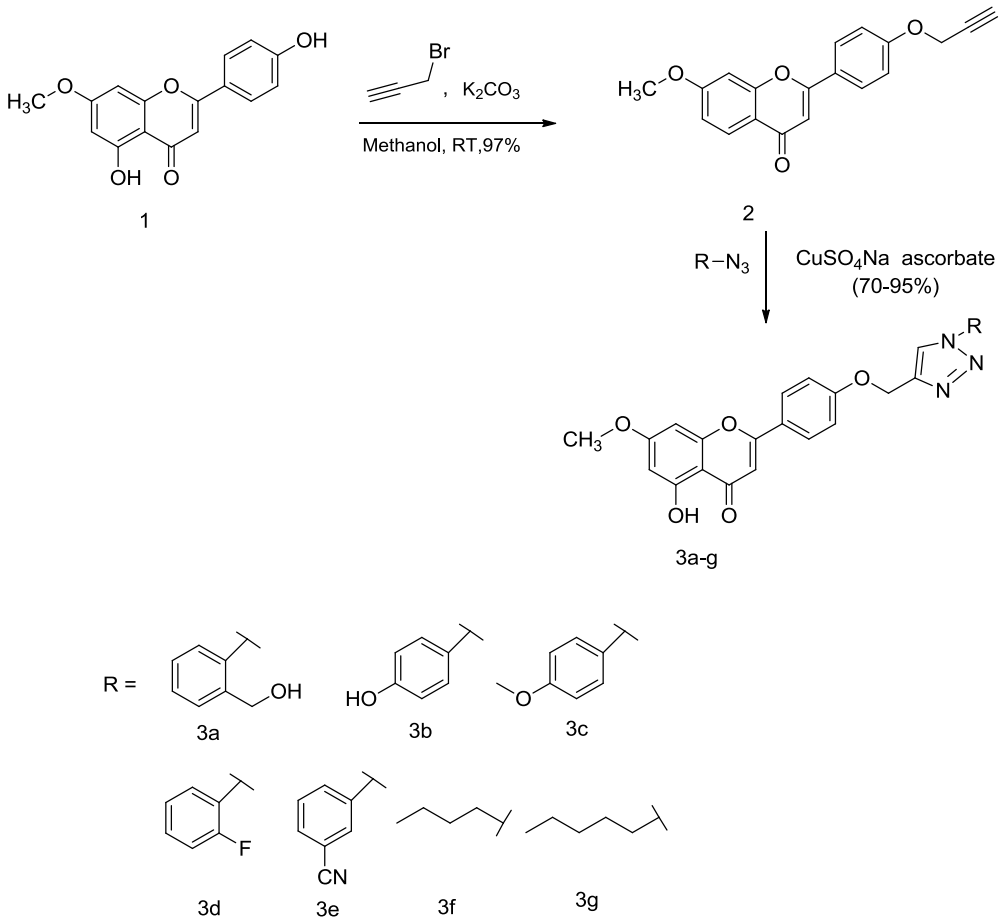


Figure No.10:- Schematic diagram showing different steps for the synthesis of novel triazole analogs of apigenin-7-methyl ether.

Synthesis of protoapigenone from Apigenin:

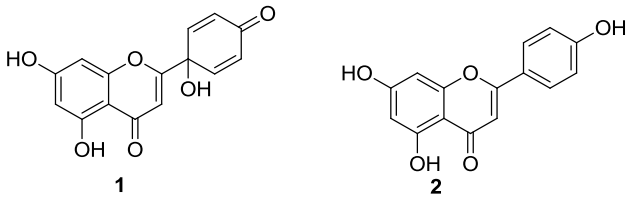


Figure No.11: Structures of protoapigenone (1) and apigenin (2).

The apigenin derivatives such as protoapigenone from apigenin were synthesized by two different methods:

Conventional heating method:-

By decreasing the concentration of 1 mg/mL used as the starting material to improve the yield of Apigenin could be improved significantly but below this concentration did not provide further increases in the yield. This synthesis reaction was highly dependent on the solvent used such as non-nucleophilic polar solvent like cetonitrile widely used. Acetone:water (9:1, v/v) and THF:water (9:1, v/v), the reaction failed to give higher yield but when reasercher used EtOAc saturated with water gave traces of 1, while 1,1,1,3,3,3-hexafluoro-isopropanol:water (9:1, v/v) resulted gives half the yield of that obtained using the ACN:water mixture. Low energy microwave heating (70uC, 1 min, 500 W) found to be increased yield by more than two-folds as compared to room temperature. The TFA (trifluoroacetic acid) derived from the PIFA ([bis(trifluoroacetoxy)iodo]benzene commonly referred to as PIFA) leads to decreases the pH and prevents 1 from quick decomposition, but was reported to be sensitive to acidic environments. Therefore it was purified quickly. Due to neutralizing the TFA undergo ionizable phenolic hydroxyl groups which lead to alteration in purification process.

Micro assisted Reaction:-

In microwave-assisted oxidation of 2 (1 mg/mL in acetonitrile:water 9:1, v/v) with 2 eq. of PIFA, which gives 31% practical yield from 100 mg of starting material. New 19-O-alkylflavone analogs were synthesized by using apigenin or b-naphthoflavone. The obtained derivatives were tested for in-vitro cytotoxic activity on six human cancer cell lines (HepG2, Hep3B, Ca9-22, A549, MCF-7 and MDA-MB-231). SAR study of the 19 O-alkyl-protoapigenone derivatives proved that the substitution of side-chain like 19-O-butyl ether was found to exert significantly stronger activity against three of the cell lines (Hep3B, MCF-7 and MDA-MB-231) than its non-substituted analog, protoapigenone itself. But b-naphthoflavone derivatives bearing the same pharmacophore on their B-ring showed decreased cytotoxic activities having O-alkyl side-chain at position 19, comparing to that of the non-substituted compound. For both starting materials 2 and 10, further derivatives were also synthesized by replacing water with various alcohols to obtain the corresponding 19-O-alkyl ethers, as shown in Figure 13[33].

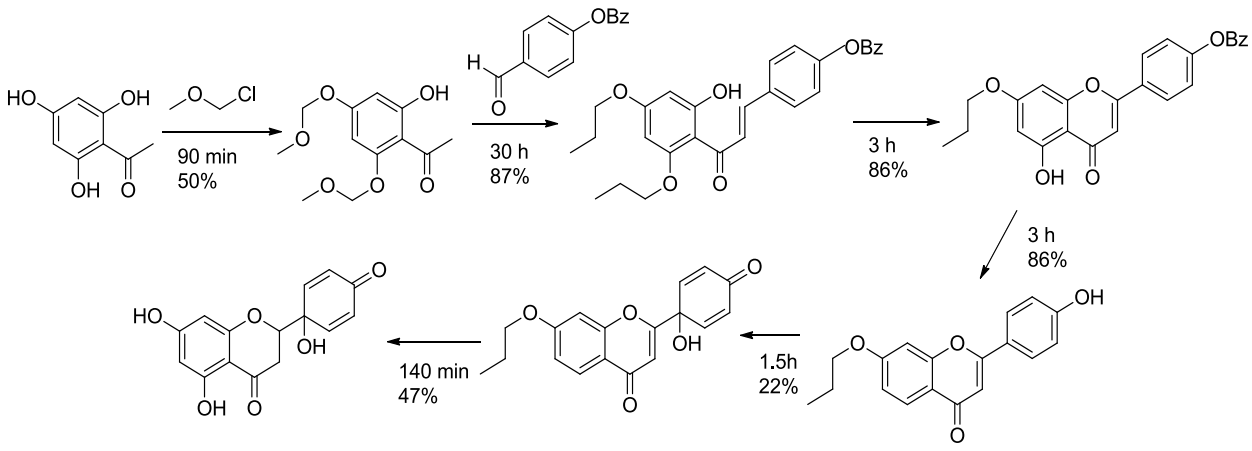
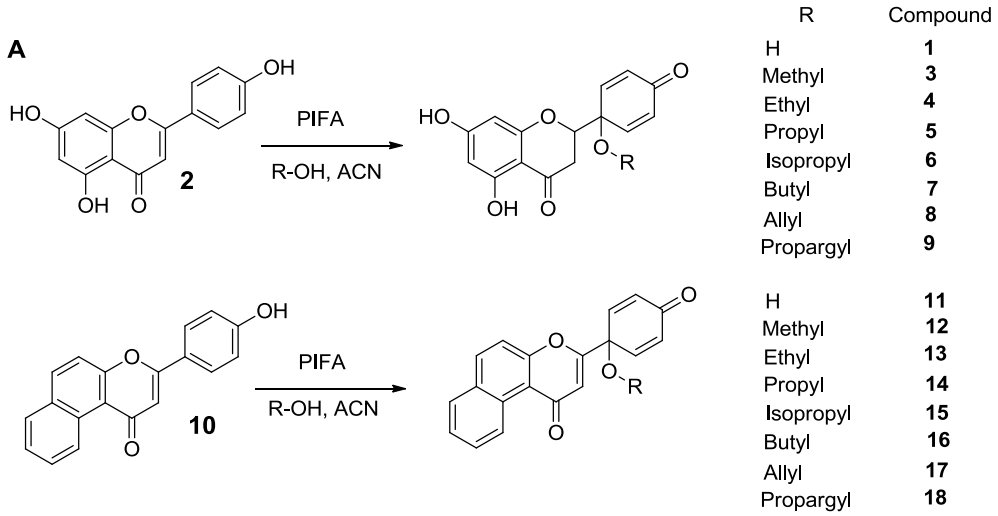


Figure No.12: The total-synthesis of protoapigenone as reported previously. Reaction times and isolated yields are shown for each reaction step. Purification of each intermediate product was performed by column chromatography on silica.



R	Compound
H	1
Methyl	3
Ethyl	4
Propyl	5
Isopropyl	6
Butyl	7
Allyl	8
Propargyl	9
H	11
Methyl	12
Ethyl	13
Propyl	14
Isopropyl	15
Butyl	16
Allyl	17
Propargyl	18

Figure No.13: The reaction of 2 and 10 with PIFA in presence of water or various alcohols.

It was reported that protoapigenone derivatives with longer aliphatic side chain results in beneficial on the activity comparing to that of the non-substituted protoapigenone, amongs them protoapigenone 19-O-butyl ether (7) was found to be the most promising one substitution.

Synthesis of nicotinic acidified and isonicotinic acidified apigenin derivatives:

Nicotinic acidified apigenin derivative was synthesized by using dry $CHCl_2$ in the presence of dehydrating agents. For this 0.2 mmol nicotinic was mixed with 0.1 mmol apigenin and refluxed for 24 h in presence of catalyst such as dicyclohexyl-carbodiimide/4-dimethylaminopyridine (DCC/DMAP). Then unreacted DCC and DMAP in reaction mixture were separated with the help of aqueous hydrochloric acid solution. The synthesized compound was separated using silica gel (100 mesh) column wit/h methanol:carbon tetrachloride:acetic acid (1:10:1) and dried them respectively. The reaction of Nicotinic acidified Apigenin shown in figure No.14.

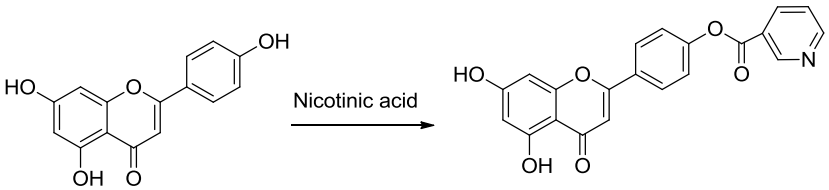


Figure No.14: Synthesis of nicotinic acidified apigenin. Reagents and conditions: nicotinic acid 0.2 mmol, apigenin 0.1 mmol, DCC 0.13 mmol, DMAP 0.05 mmol, 28 °C, reflux for 24 h

Similarlly isonicotinic acidified apigenin was used the same method as that of nicotinic acidified apigenin shown in figure No.15. Apigenin nicotinic acid derivative and apigenin isonicotinic acid derivative reported to have specifically antibacterial activity towards *Acinentober* and antitumor activities such as HepG2 [34].

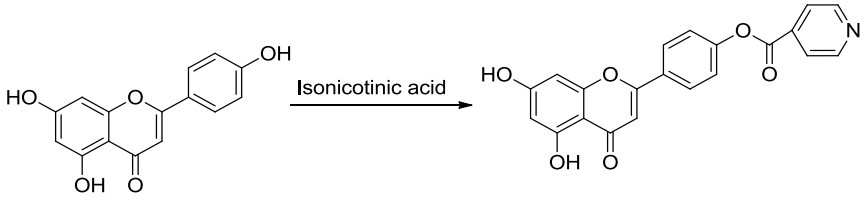


Figure No.15: Synthesis of isonicotinic acidified apigenin. Reagents and conditions: isonicotinic acid 0.2 mmol, apigenin 0.1 mmol, DCC 0.13 mmol, DMAP 0.05 mmol, 28 °C, reflux, for 24 h

Synthesis of Copper (II) Complexes with Apigenin:

Nowadays, copper (II) complexes attract most attention of reaserchers due to their possible medical uses as antitumor agents as well as acts as metal complexing agent with bioactive ligands, involving natural product ligands. Naturally occurring compounds have served as a major source of drugs for centuries which in combination with copper formed new Cu-coordination novel drugs. Many flavonoids are natural chelators and flavonoid metal complexes were reported to have higher cytotoxic activity than those of the parent flavonoids, such as quercetin, morin, and chrysin. On this basis, researchers Synthesized Cu-Apigenin complex [Cu $(Apg)_2(H_2O)_2$]having yellow-green ccoloured compound. It was synthesized by using an ethanolic solution of Apigenin (0.2 mmol) was added to a aqueous solution of $CuCl_2$. $2H_2O$ (0.12 mmol) and was adjusted pH to 7-8 with ammonia solution. The mixture was refluxed with stirring for 12 hours and yields brown precipitate formed during reflux. Allowed to cool to room temperature and filtered. The solid was washed with water and ethanol, and then air-dried for 2 days. The difference in inhibition rates (cytotoxicity activity) of the Cu(II) complexes of apigenin was due to flavone planar structure of Apigenin [35].

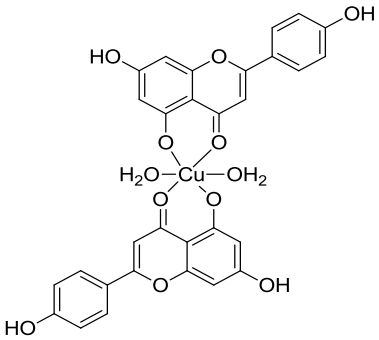


Figure No.16: Complex of Copper (II) and Apigenin.

SUMMARY AND CONCLUSION

On the basis of review of literature, it is concluded that, various substituted apigenin derivatives were synthesized using structural modifications and chain homologation with the objective to increase lipophilicity and therapeutic activity. All the synthesized Substituted derivatives of apigenin evaluated for their antioxidant, antimicrobial and antiproliferative activity. All the synthesized derivatives have greater antioxidant and antimicrobial activity than standard apigenin.

The results suggest those susbstited apigenin derivatives are the excellent template for designing and further development of molecules that possesses antioxidant, antimicrobial and antiproliferative activity. Further experiments are needed to elucidate their SAR and mechanism of action. Also all synthesized derivative by various schemes can be tested various other cancer cell lines to explore their anticancer activity and set the small concentration dose.

The study has encouraged us to continue the development and testing of AP derivative on cell line and also find also find out other therapeutic potential of these derivatives.

ABBREVIATIONS

AP – Apigenin
TFA - trifluoroacetic acid
PIFA - ([bis(trifluoroacetoxy)iodo]benzene
DCC - N, N′-Dicyclohexylcarbodiimide

ACKNOWLEDGEMENT

The authors are thankful to our HOD Mr. R. T. Lohiya, Department of Pharmaceutical Chemistry for their valuable guidance and illimitable enthusiasm throughout the time.

Conflict of Interests: None

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