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Review Article

Flavone's Worth in the Development of Anticancer Agents

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Abstract

In this review, we report the recent advances in synthetic compounds containing flavones moiety, covering the time span of the last decade. These structures have been investigated in the development of novel compounds with anticancer activity. Therefore, these compounds have been synthesized as target structures by many researchers and were evaluated for their biological activities.

Keywords: Flavone; Pharmacological activity; Anticancer; Flavonoids

Introduction

Flavonoids are the polyphenolic phytochemicals of low molecular weight which are generally obtained from secondary metabolism of plants and are also synthesized in laboratory. These are known to play significant role in different biological processes. They elicit a wide array of properties useful for human health *via* interacting different cellular targets involved in critical cell signalling pathways in the body. Following the French Paradox Concept by the French Epidemiologists in the year 1980, significant escalation was observed towards flavonoid research. Consumption of red wine and a high saturated fat diet was found to be associated with comparatively lower cardiovascular mortality rate in Mediterranean population [1,2].

Flavonoids can be categorised into different classes which have been tabulated in Table 1. All the classes of flavonoids exhibit diverse pharmacological activities, but among them, flavones have been considerably explored. Numerous natural, semi-synthetic and synthetic derivatives of flavones have been synthesized and evaluated for pharmacological effects like antitumor and cytotoxic [3], anti-allergic, antioxidant [4], anti-inflammatory, antiestrogenic and antimicrobial [5]. Oxidative stress is known to be associated with a number of metabolic diseases. Recently, different studies are available in literature showing beneficial of flavones in numerous diseased conditions like cancer, diabetes, Alzheimer's disease and several others. Flavopiridol, derived from synthetic process is commercially available for treatment of different ailments. Naturally, they can be traced in vegetables and fruits which we consume in our daily diet. Naturally occurring flavone moiety with a string of biological activities can serve as a lead for further synthesis of semi-synthetic and synthetic derivatives.

Chemistry

Flavone ($C_{15}H_{10}O_2$) is a class of flavonoids, chemically named as 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one). It comprises of three-ring skeleton, linked as C6-C3-C6, which are denoted as A, B, and C-rings, respectively (Figure 1). Functional groups, hydroxy, carbonyl, and conjugated double bond which are responsible for giving specific reactions. These colourless-to-yellow crystalline substances are soluble in water and ethanol. Yellow color solution is obtained upon their dissolution in alkali. These moderate-to-strong oxygen bases when solubilised in acids result in the formation of oxonium salts with pKa values in the range of 0.8 to 2.45 [6]. Flavones have a planar structure in which its C-O-C bond angle 120.9°. Bond length of C-O is 1.376 Å and its dihedral angle is around 179.2°. Flavone is also known by the names of 2-phenyl-4*H*-chromen-4-one; 2-phenyl-1-benzopyran-4-one. These can react in several ways, including reduction reactions [7], degradation in the presence of base [8], substitution [9,10], oxidation [11], condensation [12], rearrangement [13], reaction with organometallic reagents [14], addition [15-17]. 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 Bakere-Venkataraman rearrangement [18,19], Claisen-Schmidt condensation [20], Ionic Liquid Promoted synthesis [21], Vilsmeier-Haack reaction [22], Allan-Robinson [23], 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 (Scheme 1). 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. In this context, Sashidhara et al. reported an alternate route to synthesize medicinally important flavones. 2-Hydroxy chalcones were obtained *via* condensation between acetophenones and salicylaldehyde. On heating, they undergo oxidative cyclization in the presence of catalytic iodine. This leads to the generation of different flavones under green synthesis conditions (Scheme 2) [24]. Numerous patents published on this moiety are given in Table 2.

Pharmacological Activities of Flavones

Flavones are considered as basic core units which are known to

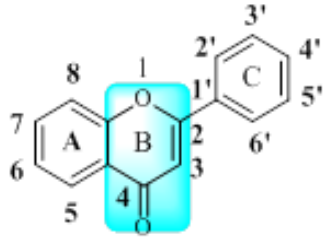
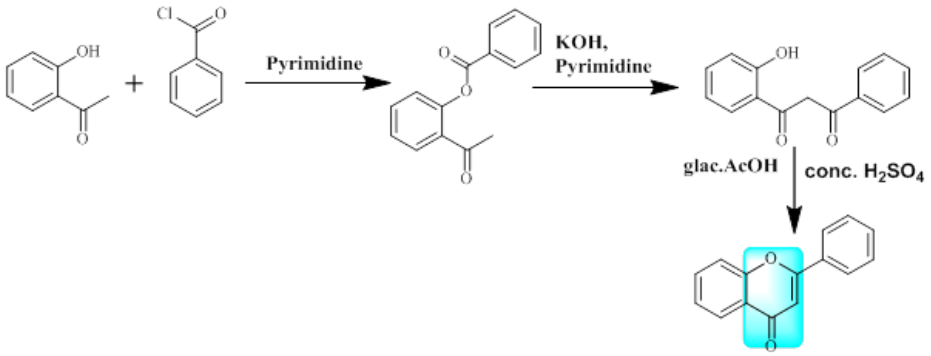


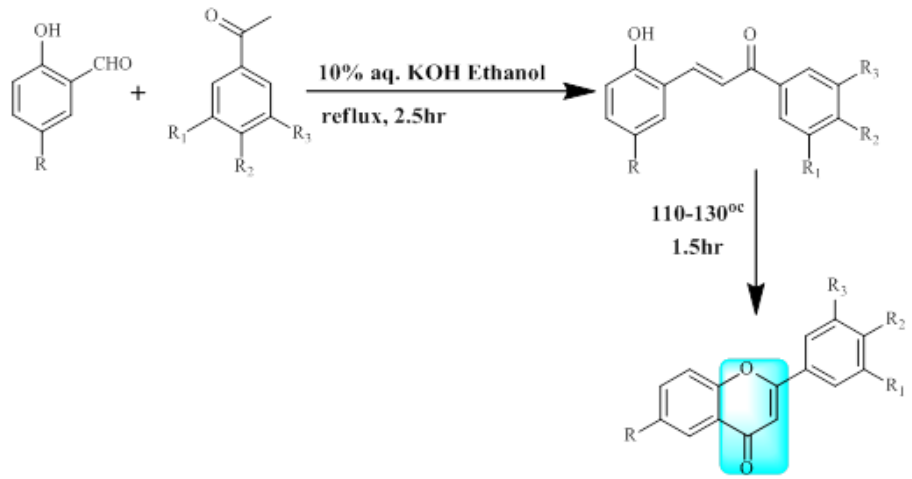
Figure 1: Basic structure of flavone.

S.No.	Class	Example
1	Isoflavones	Genistein, Daidzein
2	Flavones	Luteolin, Apigenin
3	Flavonols	Quercetin, Kaempferol, Myricetin and Fisetin
4	Flavonoid Glycosides	Astragalin, Rutin
5	Flavonolignans	Silibinin
6	Flavanones	Hesperetin, Naringenin
7	Leucoanthocyanidins	Teracacidin
8	Flavans	Catechin, Epicatechin
9	Aurones	Leptosidin, Aureusidin
10	Anthocyanidins	Cyanidin, Delphinidin
11	Neoflavonoids	Coutareagenin, Dalbergin

Table 1: Classification of flavones.



Scheme 1: Synthesis of flavone *via* diketone intermediate.



Scheme 2: Claisen-Schmidt condensation reaction.

act against different targets to demonstrate a broad spectrum of pharmacological activities (Figure 2). Owing to such a broad range of pharmacological activities, medicinal chemists have always shown keen interest in this area and this has led to the discovery of numerous molecules targeting different ailments.

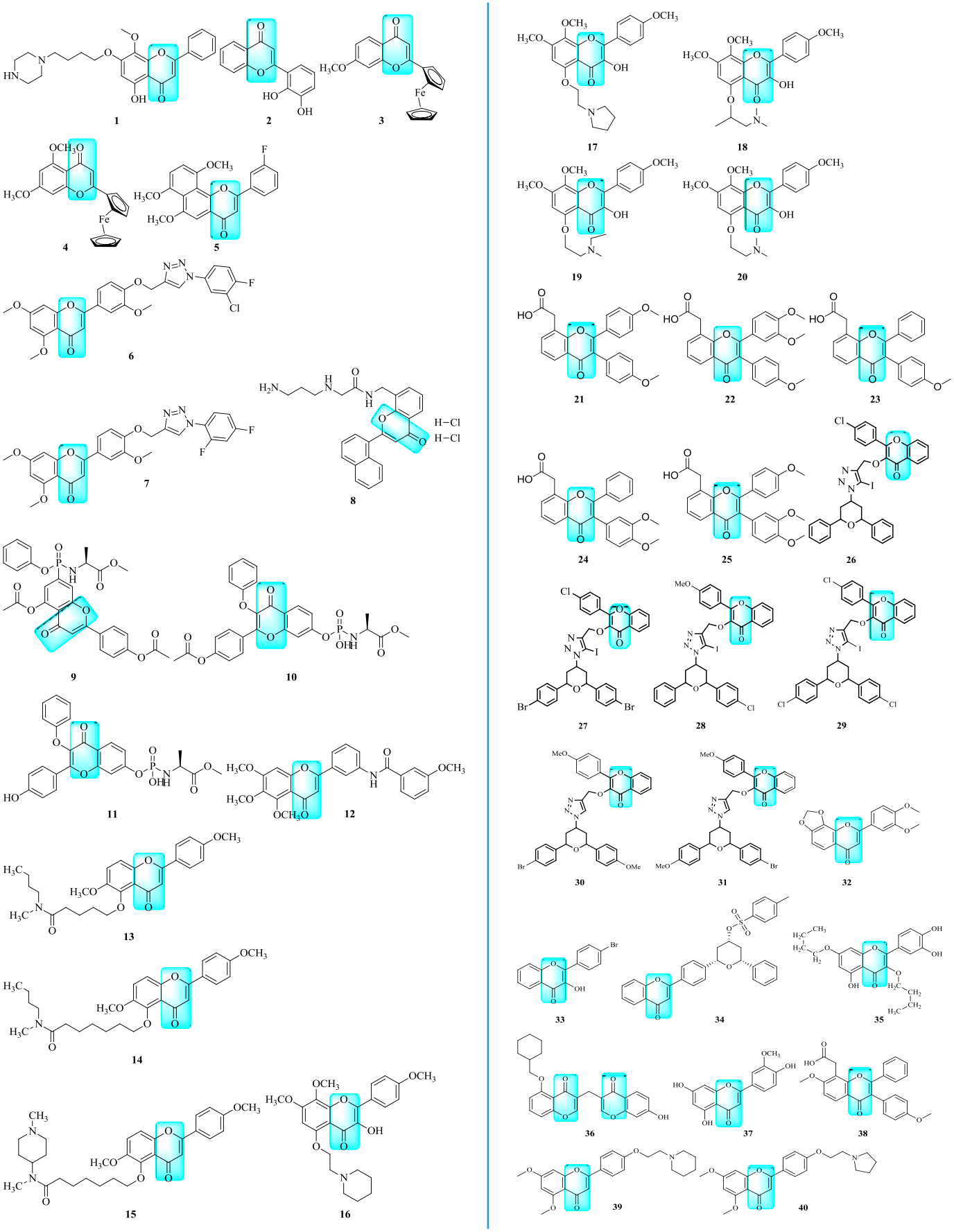
Anti-cancer activity

Cancer, uncontrolled cell division is one of the major causes for mortality and morbidity worldwide. It is characterized by cell proliferation, differentiation, angiogenesis, and loss of apoptosis. Currently available therapy for the treatment of this deadly disease suffers from the major drawback of associated side effects along with emergence of resistance to these drugs. Lack of selectivity towards cancerous cells is also one of the major issues. This results in the continuous engagement in the development of novel anticancer agents [25-46].

Bian et al. synthesized a novel series of wogonin derivatives and evaluated their cytotoxic efficacy against HepG2, BCG-823 and

S.No.	Patent No.	Patent Date	Inventors	Description
1	WO2016125186 A1 [25]	11 Aug, 2016	Pradeep Kumar, Jignesh Kantilal Parikh, Eeshwaraiah Begari	The patent describes novel flavone based egfr inhibitors and process for preparation thereof
2	WO2014018741 A1 [26]	30 Jan, 2014	Keqiang Ye	The patent describes heterocyclic flavone derivatives, compositions, and methods related thereto
3	WO2014048968 A1 [27]	3 Apr, 2014	Benjamin John Maddison, Charlotte Mary Walden, Joy Elizabeth Wilkinson	The patent describes frozen confection comprising valerenic acid and one or more flavones
4	EP2730431 A1 [28]	14 May, 2014	Paul Harry Sandstrom	The patent describes rubber composition and tire with rubber containing flavone
5.	US20140148504 A1 [29]	29 May, 2014	Jae Kwan Hwang, Jaekyung Kim	The patent describes novel use of flavone-based compound.
6.	US8466298 B2 [30]	18 June, 2013	Zhi Yuan, Chunhong Wang, Rongfu Shi, Jing Zhang, Ping Ren, Yingchao Chen	The patent describes high selectively polymeric adsorbent based on the hydrogen bonding interaction and the use there of in isolation and purification of active components from gingko biloba extract
7.	EP2641904 A1 [31]	25 Sep, 2013	Thomas Pietschmann, Sibylle Haid, Juliane Gentzsch, Christina Grethe, Elisabeth Davioud-Charvet, Don Antoine Lanfranchi, Mourad Elhabiri, Xavier Benlloch-Martin	The patent describes Flavone derivatives and their use.
8.	WO2012099449 A2 [32]	26 July, 2012	Jae-Kwan Hwang, Jaekyung Kim,	The patent describes novel use of a lavones-based compound preventing skin wrinkles and aging and improving skin elasticity, and has superior effects of inhibiting loss of skin moisture and thus is effective in skin moisturizing.
9.	WO2009110008 A1 [33]	11 Sep, 2009	Janaswamy Madhusudhana Rao, Muralidhar Gurachar Purohit, Manjulatha Khanapur, Devappa Satyanarayan Nayak, Venkata Srinivas Pullela, Jhillu Singh Yadav,	The patent describes anti-ulcer activity of flavone analogs
10.	US20080176811 A1 [34]	24 July, 2008	Bernadette Geers, Ralf Otto, Albrecht Weiss, Dirk Petersohn, Klaus Rudolf SCHROEDER,	The patent describes Novel flavone glycoside derivatives for use in cosmetics, pharmaceuticals and nutrition
11.	WO2007026251 A2 [35]	8 Mar, 2007	Alain Moussy, Jean-Pierre Kinet	The patent describes use of dual c-kit/fgfr3 inhibitors for treating multiple myeloma
12.	US20060003947 A1 [36]	5 Jan, 2006	Ronald Udell	The patent describes soft gel capsules containing polymethoxylated flavones and palm oil tocotrienols
13.	US20050249803 A1 [37]	10 Nov, 2005	Ronald Udell	The patent describes soft gel capsules containing polymethoxylated flavones and palm oil tocotrienols
14.	US20040109882 A1 [38]	10 June, 2004	Uwe Schonrock, Inge Kruse	The patent describes use of flavones, flavanones and flavonoids for protecting ascorbic acid and/or ascorbyl compounds from oxidation
15.	EP1127572 A3 [39]	2 May, 2003	Hannelore Prof. Dr. Daniel, Uwe Dr. Wenzel	The patent describes use of flavones for treating cycloxygenase-2 mediated diseases
16.	US6596927 B1 [40]	22 July, 2003	Masako Mizutani, Yoshikazu Tanaka, Takaaki Kusumi, Shin-ichi Ayabe, Tomoyoshi Akashi,	The patent describes genes coding for flavone synthases
17.	US20020013481 A1 [41]	31 Jan, 2002	Uwe Schonrock, Inge Kruse	The patent describes use of flavones flavanones and flavonoids for protecting ascorbic acid and/or ascorbyl compounds from oxidation
18.	US20020106388 A1 [42]	8 Sep, 2002	Peter Pugliese	The patent describes formulation of flavones and isoflavones for treatment of cellulite
19.	WO2002087567 A2 [43]	7 Nov, 2002	Najla Guthrie, Elzbieta Maria Kurowska	The patent describes polymethoxylated flavones for treating insulin resistance
20.	WO2002087567 A3 [43]	27 Dec, 2002	Najla Guthrie, Elzbieta Maria Kurowska	The patent describes polymethoxylated flavones for treating insulin resistance
21.	WO2001003681 A2 [44]	18 Jan, 2001	Patrick T. Prendergast	The patent describes use of flavones, coumarins and related compounds to treat infections

Table 2: Patents on flavones.



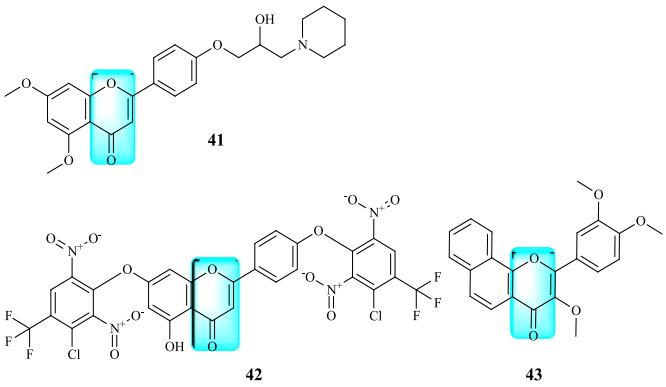


Figure 2: Flavones as anti-cancer agents.

A549 cancer cell lines. Many of them showed cytotoxic effects and compound 1 possessed the highest potency against HepG2, BCG-823 and A549 with IC_{50} values of 1.07 μM, 1.74 μM and 0.98 μM, respectively. Further the quantitative structure-activity relationship (QSAR) study of these synthetic derivatives demonstrated that high solubility and low octanol/water partition coefficient are favourable, and excessive electrostatic properties and refractivity are unfavourable for the cytotoxic activities [47]. Anet al. evaluated novel flavone derivatives which inhibit the production of nitric oxide. Compound 2 showed potent nitric oxide inhibitory activity with IC_{50} vale of 6.29 μM [48]. Peres et al. developed ferrocene embedded into chalcone, aurone and flavone skeletons and assessed their anticancer activity against resistant tumor cells. Compounds 3 and 4 were found to be most potent agents of this series [49]. Horley et al. developed the alpha-naptho flavone derivatives. These compounds were assessed for their inhibition of human CYP1B1 enzyme bound to yeast-derived microsomal. Compound 5 was found to be most active in this series with IC_{50} value 9 nM [50]. Kant et al. developed and synthesized a series of 1,2,3-triazole linked chalcone and flavone hybrid compounds and assessed their cytotoxic activity. Compounds 6 and 7 were found to be most potent [51]. Li et al. synthesis zeda series polyamine conjugates of flavonoids with a naphthalene derivatives and evaluated their anti-hepatocellular carcinoma properties using *in vitro* and *in vivo* assays. Compound 8 was found to be most active inhibitor of *in vitro* tumor cell growth and migration [52]. Li et al. developed a series offlavone-7-phosphoramidate derivatives and assessed their antiproliferative activity. Compounds 9-11 emerged as the potent molecules possessing activity against HepG2 cell line with IC_{50} values of 9.0 μmol/L, 5.5 μmol/L and 6.6 μmol/L respectively [53]. Li et al. synthesized novel flavone derivatives possessing substituted benzamides and evaluated them against human cancer cells. Compound 12 was reported as the most potent compound of the series with 50% of maximal inhibition of cell(GI_{50}) value of 7.06 μM [54]. Singh et al. synthesized 3,5-dihydroxy-7,8-dimethoxy-2-(4-methoxyphenyl)benzopyran-4-one derivatives and determined their anti-cancer potential. Compounds 13-20 showed significant anticancer activity within the range of IC_{50} 2.58-34.86 μM [55]. Yan et al. synthesized 3-arylflavone-8-acetic acid derivatives and evaluated them for anticancer activity against A549 cell lines. Upon evaluation, compounds 21-25 were found to be most active compounds. Those bearing methoxy groups at the 2- or 3-position of the flavone nucleus exhibited higher indirect cytotoxicities against A549 cell lines than DMXAA, and lower cytotoxicities against HPBMCs [56]. Ahmed et al. synthesized a series of flavone-triazole-tetrahydropyran conjugates and evaluated them for treating against human cancer cell line activity. Compounds 26-31 were most active with IC_{50} value in the range of 0.61-1.68 μM [57]. A new series of flavones have been developed by Orlikova et al. was tested against the human leukaemia cells. Upon evaluation, compound 32 was found to be most potent of the series [58]. Burmistrova et al. synthesized a series of flavanols and 3-methyl ether derivatives and tested their anti-cancer potential against the human leukaemia cell lines. Following evaluation, compound 33 was reported as the most active agent with IC_{50} value of 3.3 ± 0.7 μM [59]. Ahmed et al. synthesized a series of flavonoids based novel tetrahydropyran conjugates derivatives and tested their antiproliferative activity against human cancer cell lines. Following evaluation, compound 34 was reported as the most active molecule against HeLa cell line with IC_{50} value of 12.9 ± 1.7 μM [60]. Shi et al. synthesized a series of O-alkylated analogs of quercetin and evaluated their anti-cancer activity. Compound 35 was reported to be the most potent compound of the series [61]. Venkateswararao et al. synthesized a series of bis-chromen one derivatives. The synthesized compounds were evaluated as anti-proliferative agents against human cancer cells. Following evaluation, compound 36 was reported as the most potent against ACHN, HCT15, MDA-MB-231, NCI-H23, NUGC-3 and PC-3 cell lines with IC_{50} values of 2.10, 2.11, 3.22, 2.15, 3.22 and 4.25 μM respectively [62]. Amrutha et al. developed seventeen flavonoids with different substitutions evaluated them for inhibition of nuclear factor-jB (NF-jB) signalling in the invasive breast cancer cell line MDA-MB-231. Compound 37 was reported to be the most potent of this series [63]. Zhou et al. developed and synthesized 7-methoxy-3-arylflavone-8-acetic acids derivatives. These compounds were assessed for their anti-cancer activity. Amongst the synthesized compounds, compound 38 was found to be highly potent against indirect cytotoxicity and higher selectivity [64]. Chen et al. synthesized novel apigenin analogues and evaluated them for their *in vitro* cell proliferation activity. The compounds 39-41 showed most potent antiproliferative effects [65]. Dong et al. synthesized a series of flavone and isoflavone derivatives and determined their anti-cancer activity. Compound 42 demonstrated most potent inhibitory activity *in vitro*. It inhibited the growth of Hela cell and MCF-7 cell lines with IC_{50} values of 4.3 and 4.8 μM [66]. Juvale et al. synthesize the series of flavones and benzoflavones. They reported compound 43 as the most potent candidate, being 50 times selective for BCRP and showing very low cytotoxicity at higher concentrations.

Conclusion

The flavones are important members of the flavonoid family found in fruits, vegetables and synthesized by different routes in the laboratory. They have received considerable interest sue to wide array of pharmacological activities. The main objective of this review is to highlight the significance of flavones moiety as templates fora large number of medicinal agents.

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