



# IJRM

INTERNATIONAL JOURNAL OF RESEARCH METHODOLOGY

An Official Publication of Human Journals



Human Journals

Vol.:1, Issue:4

**Review Article**

© All rights are reserved by Prafulla M. Sable et al.

## Flavones as Attractive Target for a Research



### IJRM

INTERNATIONAL JOURNAL OF RESEARCH METHODOLOGY  
An Official Publication of Human Journals



**Lata C. Potey<sup>1</sup>, Prafulla M. Sable\*<sup>1</sup>, Satish Kosalge<sup>2</sup>**

<sup>1</sup> University Department of Pharmaceutical Sciences,  
Nagpur, Maharashtra, India

<sup>1,2</sup> Hi-tech College of pharmacy Chandrapur,  
Maharashtra, India

**Keywords:** Flavones; Antimicrobial; Anticancer; Antioxidant; Anti-HIV; Anti-Alzheimer.

### ABSTRACT

Flavones are present in variety of medicines and natural products. Due to the flexible and unique structure it shows wide variety of pharmacological activities. This review covers the general methods for the synthesis and biological activities of various synthetic derivatives of flavonoids. This will help the readers in developing the most target compound after going through the various biologically active flavonoids.



HUMAN JOURNALS

[www.ijrm.humanjournals.com](http://www.ijrm.humanjournals.com)

## 1. INTRODUCTION

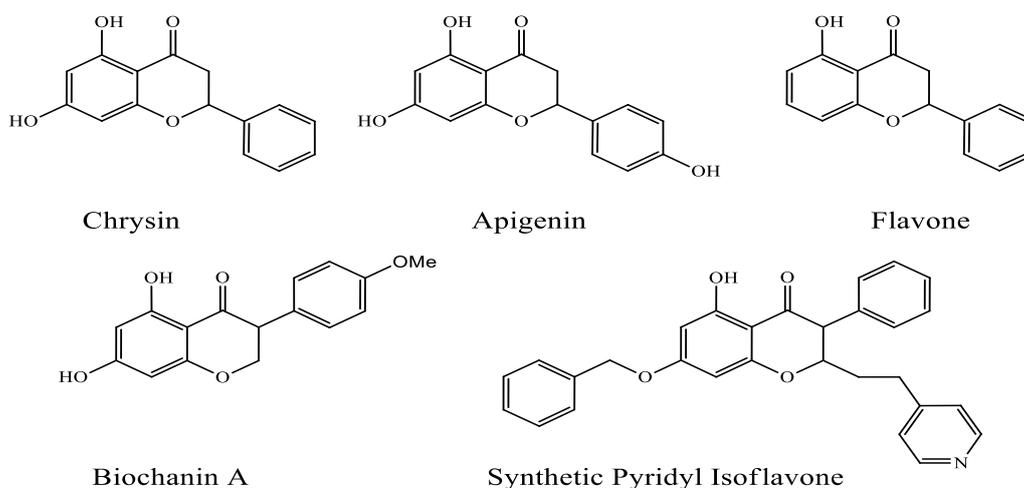
Flavones are also known as phenyl benzopyran, having C6-C3-C6, with 15 Carbon skeleton, depending on the linkage of phenyl ring on benzopyran (Chromone) moiety they have been divided naturally into three types, flavonoids (2-phenyl benzopyran), Isoflavonoids (3-phenyl benzopyrans), neoflavonoids (4-phenyl benzopyrans).[1] [Figure 1]



**Figure 1: Classes of flavonoids on basis of position of aromatic ring.**

They are naturally occurring oxygen containing heterocyclic compounds that are abundant in nature, especially found in plants. The name flavonoid has derived from Greek word, Flavus - meaning yellow color. Flavonoids are class of secondary metabolite in plants and fungus and are most important plant pigments/co-pigments responsible for coloration in flowers. [2]

Flavonoids are a group of polyphenolic compounds are mainly found in cereals and herbs. Naturally occurring flavones include Apigenin (4',5,7-trihydroxyflavone), Luteolin (3',4',5,7-tetrahydroxyflavone), Tangeritin (4',5,6,7,8-pentamethoxyflavone), Baicalein (5,6,7-trihydroxyflavone), Scutellarein (5,6,7,4'-tetrahydroxyflavone).



**Figure 2: Naturally occurring flavonoids**

We consume flavonoids in our daily diet and have positive impact on our health. In the West, the estimated daily intake of flavones is in the range 20–50 mg per day. Flavones intake in the form of dietary supplements and plant extracts has been increasing day by day. Quercetin is a well known flavone for its antioxidant, anti-inflammatory [3] anticancer, [4] and others so many biological activities. [3]

Flavone shows wide variety of biological activities such as anti-cancer, anti-inflammatory, anti-microbial, Alzheimer's Disease, anti-malarial, antioxidant, gastro-protection and  $\alpha$ 1-adrenoceptor ( $\alpha$ 1-AR) antagonists etc. This review is dealing with various biological activities of flavonoids and overview about their synthesis.

## 2. Synthesis of Flavonoids

The importance of flavones in the chemical community grew impressively when structurally diverse flavones were found to possess significant biological activities.

From many more decades the flavonoids had been synthesizing by various methodologies Satyajit Saha *et. al*, recently in 2018 has reported various methods such as Kostanecki-Robinson (1900), Auwer synthesis (1908), Allan Robinson (1924), Algar Flynn Oyamadas, (1934), Baker Venkatraman (1934), Claisen Schmidth (1962).[2]

### 2.1 Kostanecki-Robinson Method.

A. Samat *et, al*, prepare 3-benzoyl-2-benzylchromones from the substituted O-hydroxyphenyl- $\beta$ -diketones and an acid anhydride by the Kostanecki Robinson method This old and efficient method involving the Baker– Venkataraman rearrangement to prepare the flavones more efficiently.[4] The scheme is given in [Figure 3]

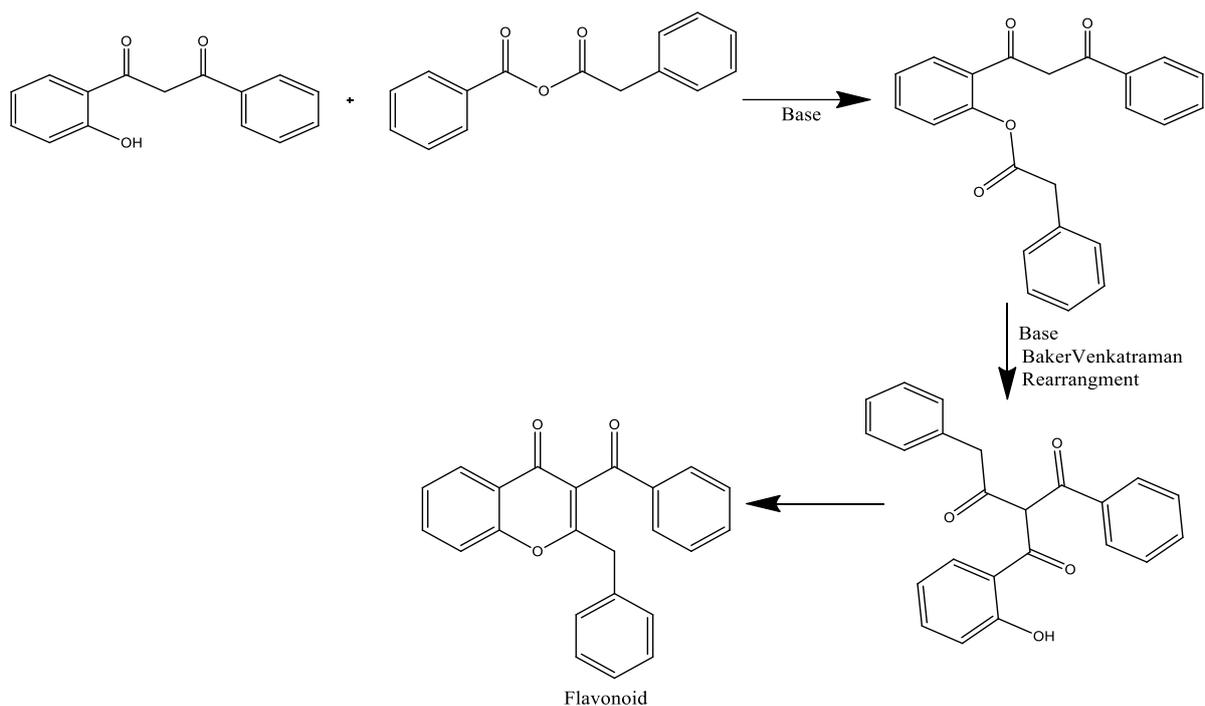


Figure 3: Synthesis of Flavones by Kostanecki-Robinson Method

## 2.2 Auwer's Method

Auwer et, al, in 1908 reported the synthesis of benzopyran-4-ones **4** (flavones) from benzofuran-3-ones **1** and yield was (30%). [5]

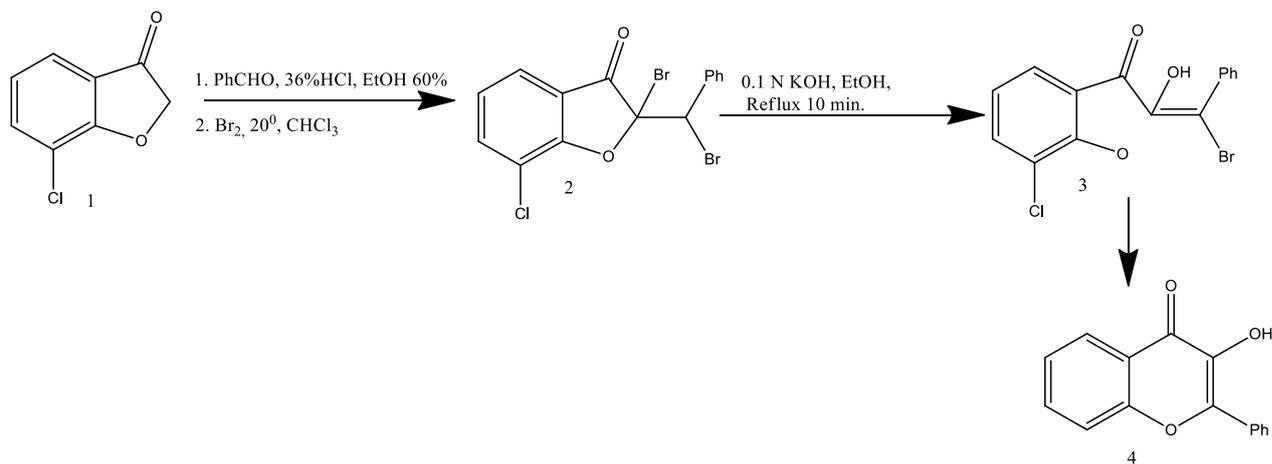
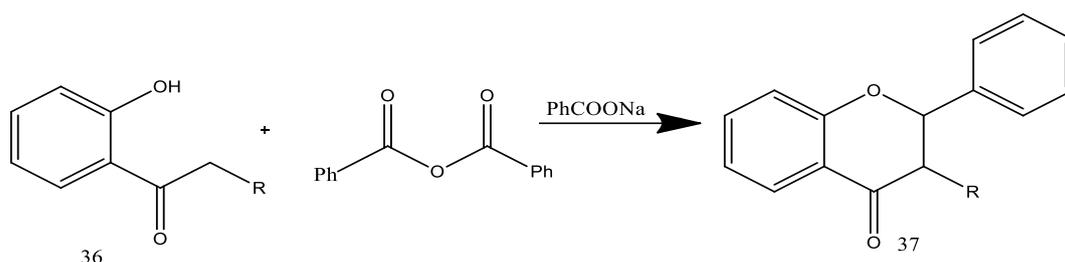


Figure 4: Synthesis of flavones by Auwer Method.

### 2.3 Allan Robinson Method

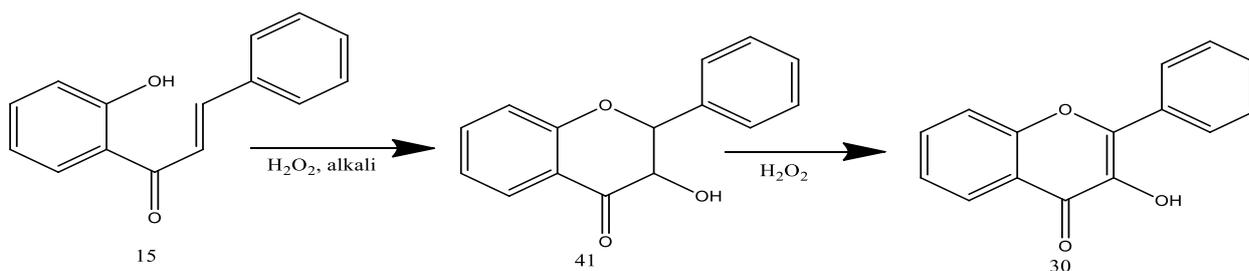
Allan & Robinson in 1924 has reported the synthesis of flavone **37** from O-hydroxyaryl ketone **36** and an anhydride of aromatic acid in presence of sodium salt of the corresponding aromatic carboxylic acid anhydride [Figure 5]. In future structurally modified flavonoids can be synthesized. In this method 2-hydroxyacetophenone **36** reacts with aryl anhydride to give 1,3 dicarbonyl compound which under basic condition undergo intramolecular cyclocondensation to generate flavone **37**. [6]



**Figure 5: Synthesis of flavonoids by Allan Robinson method**

### 2.4 Algar Flynn and Oyamadas Method

The Algar Flynn and Oyamada has reported this in 1934 for the synthesis of flavones whereby chalcones **15** undergo an oxidative cyclization to form 3-hydroxy flavones **30** in presence of alkaline  $H_2O_2$ . [Figure 6] [7, 8]



**Figure 6: Synthesis of flavonoids by Algare Flynnne Oyamada**

### 2.5 Baker–Venkataraman rearrangement

The first application of the Baker–Venkataraman rearrangement towards the synthesis of flavones was by Venkataraman himself, when he attempted the synthesis of  $\alpha$ -naphthaflavone from naphthyl derivative. Subsequently, a variety of flavones have been synthesized which exploit the rearrangement. For example, aroyl-5-hydroxyflavones have been synthesized under a microwave-assisted Baker–Venkataraman transposition In their work, a new and successful

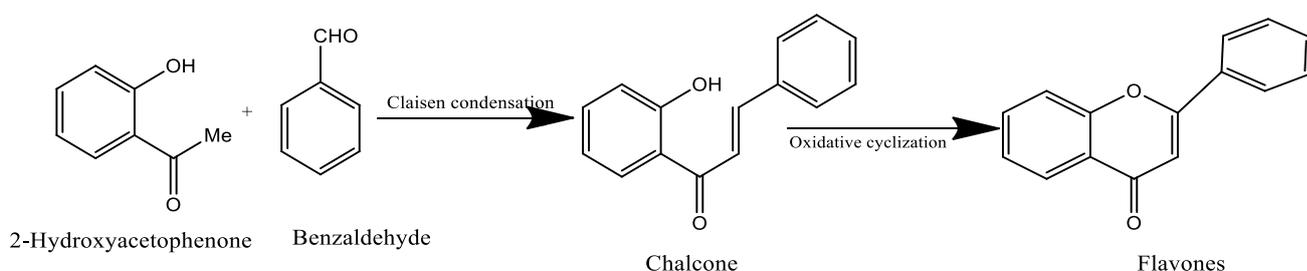
method was established wherein microwave irradiation was shown to selectively induce a Baker–Venkataraman rearrangement of 2', 6'-diaryloxyacetophenones to give the corresponding 3-aryl-5-hydroxy flavones, in very short reaction times (10 min) and good yields (68–72%). Conversely, under classical thermal conditions these reactions afforded 5-hydroxyflavones 30 only as by-products. [9, 10] [Figure 7]



**Figure 7: Baker Venkatraman rearrangement for the synthesis of flavonoid**

## 2.6 Claisen Schmidt Condensation

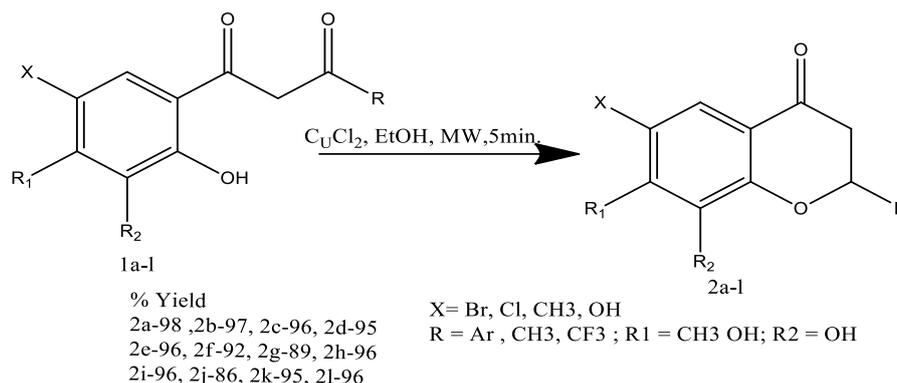
Claisen-condensation developed in 1962, is one of the well known synthetic methodology that was first applied for the synthesis of flavones. This is a two-step process where chalcones are formed first from the reaction of 2-hydroxy acetophenone and benzaldehyde under basic condition followed by their oxidative cyclization to flavone. Various Lewis and Brønsted acid/base catalysts have been utilized for this oxidative cyclization. [11] [Figure 8]



**Figure 8: Claisen condensation for the synthesis of Flavonoids**

## 2.7 Microwave Assisted Synthesis

The author George W. Kabalka *et, al*, has reported, the high yield synthesis of flavones and chromones (Figure 8). In the their study, the intermediate 1,3-propanediones **1a–l** were synthesized in 5 min via dehydrative cyclization to the corresponding flavones and chromones **2a–l** in ethanol, in the presence of CuCl<sub>2</sub> under microwave irradiation. The percent yield of the compounds is given below.



**Figure 9: Microwave assisted synthesis of flavones**

A simple method for the synthesis of flavonoids has been reported by using heterogeneous catalyst molecular iodine loaded neutral alumina under microwave irradiation.[13]

### Biological Activities of Flavonoids

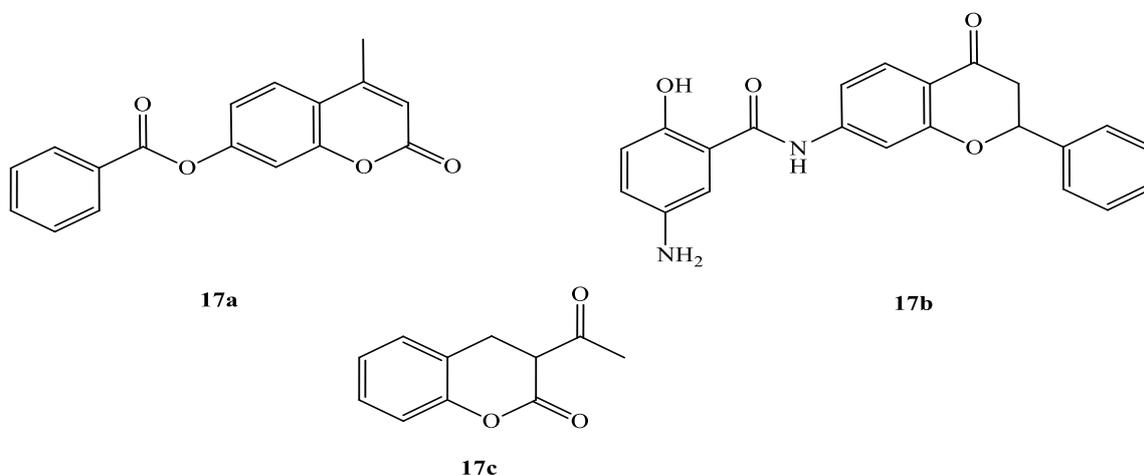
The flavone nucleus is an important scaffold used in the preparation of pharmaceutical agents, since both natural and synthetic derivatives are known to be responsible for a large variety of biological and pharmacological activities, including antitumor, anti-inflammatory, antiviral, and antioxidant etc. Many researches on flavones and its derivatives have suggested that dietary flavones and its analogs are responsible for various biological activities. Nowadays researcher group is pursuing drug design and discovery efforts exploiting flavones as core templates. [14]

### 3.1 Antimicrobial Activity

The flavonoids show antibacterial activity. Several high-quality investigations have examined the relationship between flavonoid structure and antibacterial activity. In addition, numerous research groups have sought to elucidate the antibacterial mechanisms of action of selected flavonoids. The activity of quercetin, for example, has been at least partially attributed to inhibition of DNA gyrase. It has also been proposed that sophoraflavone G and (–)-epigallocatechin gallate inhibit cytoplasmic membrane function, and that licochalcones A and C inhibit energy metabolism. Other flavonoids whose mechanisms of action have been investigated include robinetin, myricetin, apigenin, rutin, galangin, 2,4,2'-trihydroxy-5'-methylchalcone and lonchocarpol A.[15]

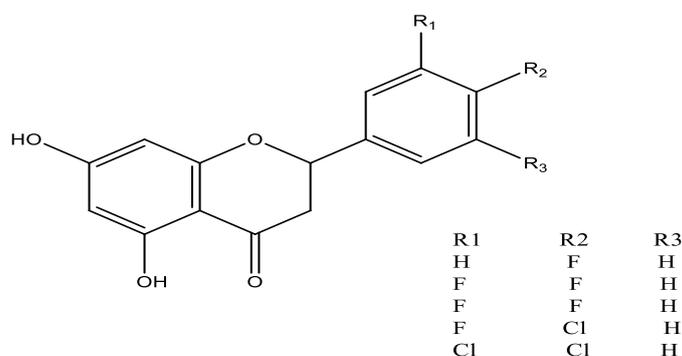
The author Jayashree BS *et al* in 2011 has proposed in their work the synthesis of a series of novel flavone analogues which has been confirmed by various spectrochemical methods and

evaluated them for antioxidant potency and screened for antimicrobial activity. They have been concluded that the compounds (17b) and (17c) have shown antibacterial activity. [16] [Figure 6]



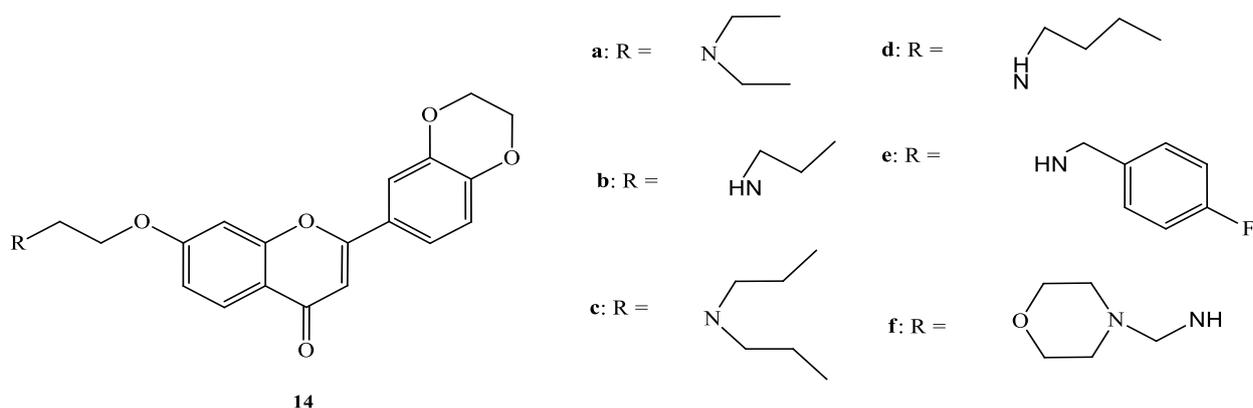
**Figure 10: Novel flavonoids with antimicrobial activity**

In 2016 the author Zhang, X., *et al* has been reported the synthesis of a series of 5, 7-dihydroxyflavanone derivatives and evaluated them for antimicrobial efficacy against Gram-negative, Gram-positive bacteria and yeast. In paper author concluded that most of the halogenated derivatives exhibited the best antimicrobial activity against Gram-positive bacteria, the yeast *Saccharomyces cerevisiae*, and the Gram-negative bacterium *Vibrio cholerae* and when they has been tested cytotoxicities of these compounds on HepG2 cells using a cell viability assay. In result and discussion they have been shown that all the halogenated derivatives were low toxic. This study suggests that halogenated flavanones might represent promising pharmacological candidates for further drug development. [17] [Figure 7]



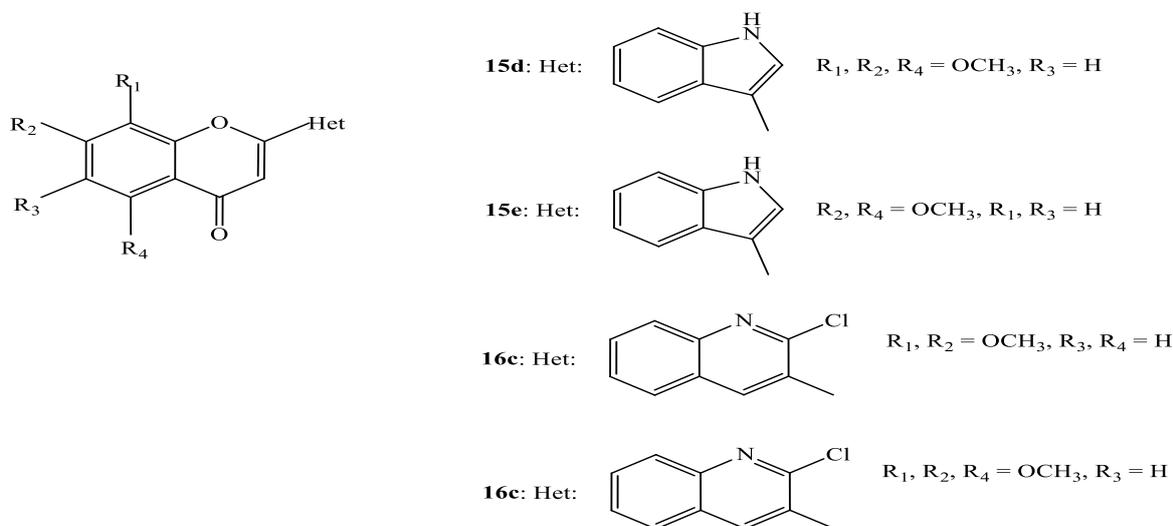
**Figure 11: Series of 5, 7-dihydroxyflavanone derivatives with antimicrobial efficacy**

The author Lv PC *et al* has synthesized a series of luteolin derivatives (**14a-f**) and evaluated for antibacterial activity against *B. Subtilis*, *S. aureus*, *p. fluorescens* and *E.coli*. The compound 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-hydroxy-7-(2-(3-morpholinopropylamino)ethoxy)-4H-chromen-4-one (**14f**) displayed significant activity against all the strain with MIC of 1.562, 3.125, 3.125 and 6.25  $\mu\text{M}$ . [18] [Figure 8]



**Figure 12: Series of Luteolin derivatives with antimicrobial activity**

Author Venkatesan P *et al* reported that the biological activity of flavone has been enhanced by introducing heteroaryl moiety in C-2 position of chromone derivatives. Synthesis of 2-(1H-Indol-3-yl)-4H-chromen-4-one derivatives (**15**) and 2-(2-chloroquinolin-3-yl)-4H-chromen-4-one derivatives (**16**) were synthesized from corresponding chalcone and evaluated for antimicrobial activity against *S. aureus*, *B.subtilis*, *E.coli* and *S. typhi*. (**15d**), (**15e**), (**16c**) and (**16d**). They have been concluded that all flavonoids with heteroaryl moiety had been shown appreciable activity against all the tested microorganisms. [19] [Figure 9]

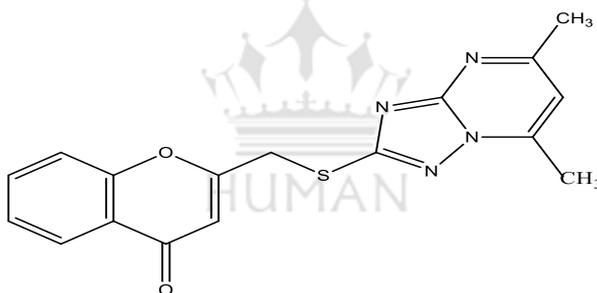


**Figure 13: Heteroaryl Chromone derivatives with antimicrobial activity**

### 3.2 Antiproliferative activity

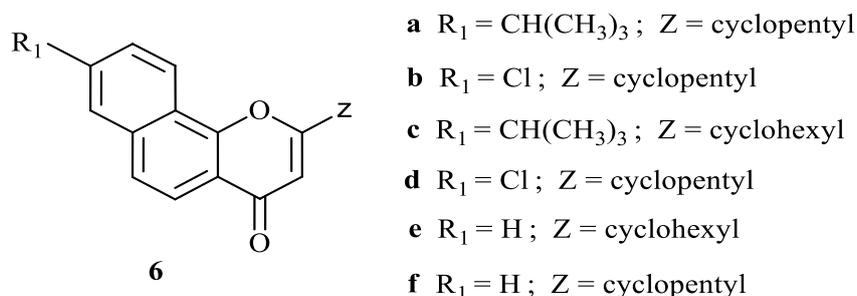
Flavonoids have important chemo preventive and chemotherapeutic effects on cancer. [20] Attention has been focused on their potential anticancer effect for decades. For example, flavopiridol was identified as the first cyclin-dependent kinase inhibitor, and it is currently being tested in Phase II clinical trials. On the other hand, many studies have indicated that functional thioether groups can enhance the antitumor activity. The flavonoid scaffold with a flexible, thio-methyl linkage might be an effective strategy for discovering novel flavonoids with potential bioactivity. [21]

The author W. Huang, Q. Chen, W.C. Yang, G.F. Yang et, al, reported the synthesis a new lead structure with flavonoid moiety and evaluated for antiproliferative activities against six cancer cell lines, HCCLM-7, Hela, MDA-MB-435S, SW-480, Hep-2, and MCF-7 by the MTT-based assay. Compared with the positive control 5-fluorouracil. Compounds successfully identified as the most promising candidates, due to their higher potency and broad-spectrum bioactivity with IC50 values in the range of 0.43  $\mu$ M – 6.7  $\mu$ M. [22] [Figure 10]



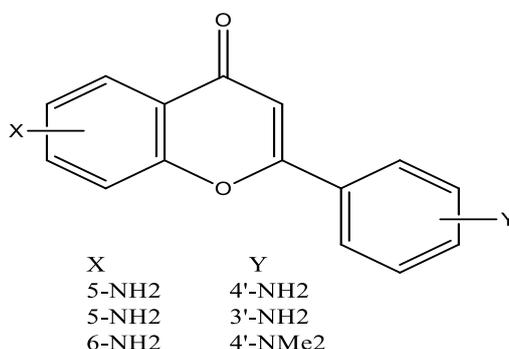
**Figure 14: Novel flavonoids with antiproliferative activity**

In 2010 to prove the anti proliferative activity the author Huachen Liu *et al* reported the synthesis and structure activity relationship of 2-Phenyl-benzo[h]chromen-4-one (**6a-f**) as novel anti proliferative agents. Anti proliferative assays showed that the synthesized derivatives possess notable activity against hepatocarcinoma cells (HepG-2) [23] [Figure 11]



**Figure 15: 2-Phenyl-benzo[h] chromen-4-ones as novel anti proliferative agents**

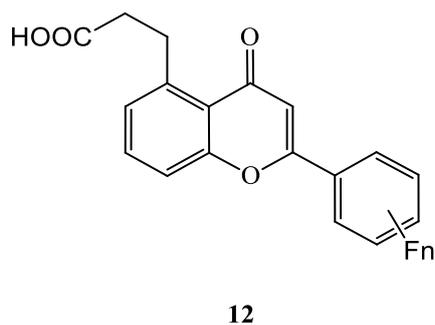
As well the author Tsutomu Akama, et *al* also reported synthesis of novel amino substituted flavone derivatives and evaluated for anticancer activity for breast cancer by antiproliferative activity against estrogen receptor positive and estrogen responsive human breast cell line MCF-7. In which 5, 4 Diaminoflavone derivatives were more active and did not shown activity against estrogen negative human cell line HeLaS<sub>3</sub>, WiDr, MDA-MB. [24] [Figure 12] Figure 12: 2-Phenyl-benzo[h] chromen-4-one as novel anti proliferative agents



**Figure 16: Novel amino substituted flavone derivatives with antiproliferative activity**

One of the most serious diseases in the world is cancer due to its high mortality rate. The incidence of cancer has increased continuously not in developing countries but also in developed countries of Europe and United States. The incidence of cancer and mortality due to cancer is decreased by chemotherapy, immunosuppressant and radiations but the number of deaths due to cancer is greater than heart diseases in persons with age less than 85 years. Different studies have demonstrated that some flavonoids inhibit the growth of cancer cell lines. The anti-proliferative effect in estrogen depending tumor cells is related to the anti estrogenic properties of different flavonoids, In some in vitro studies flavonoids have been reported to affect cell signaling and in the progression of cell cycle. [25]

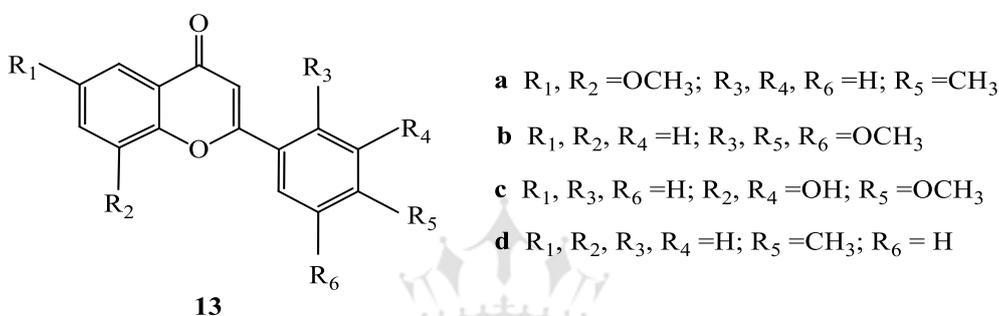
Aristoff *et al* reported the design and synthesis of various substituted fluorinated flavone acetic acid derivatives (**12a-j**) as a new class of anticancer agents. The compounds were screened for inhibition of the P450 enzymes aromatase and 17 $\alpha$ -Hydroxylase/ C17, 20-Lyase. [Figure 13].



- |                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>a</b> Fn = 2-Fluoro            | <b>g</b> Fn = 3,4-Difluoro        |
| <b>b</b> Fn = 2,6-Difluoro        | <b>h</b> Fn = Pentafluoro         |
| <b>c</b> Fn = 2,3,4,5-Tetrafluoro | <b>i</b> Fn = 3,4,5-Fluoro        |
| <b>d</b> Fn = 3-Fluoro            | <b>k</b> Fn = 2,3-Fluoro          |
| <b>e</b> Fn = 4-Fluoro            | <b>j</b> Fn = 2,3,5,6-Tetrafluoro |
| <b>f</b> Fn = 3,5-Difluoro        |                                   |

**Figure 17: Acetic acid derivatives of flavonoids with anticancer activity.**

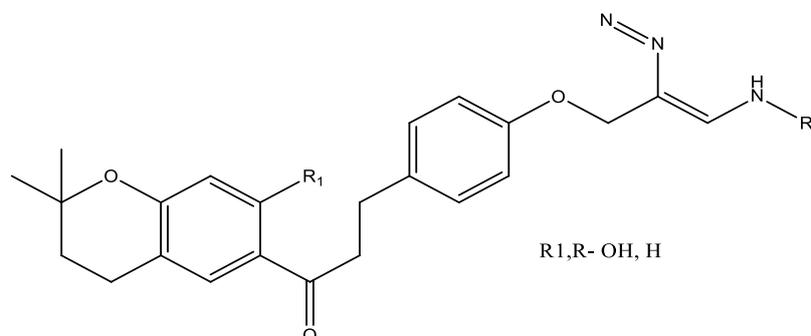
Sohel Mostanhan *et al* have been synthesized flavone derivatives (**13a-c**) as cytotoxic agents. Compounds (**13c**) and (**13d**) show good cytotoxic activity. [26][Figure 14]



- |   |
|---|
| <b>a</b> R <sub>1</sub> , R <sub>2</sub> =OCH <sub>3</sub> ; R <sub>3</sub> , R <sub>4</sub> , R <sub>6</sub> =H; R <sub>5</sub> =CH <sub>3</sub> |
| <b>b</b> R <sub>1</sub> , R <sub>2</sub> , R <sub>4</sub> =H; R <sub>3</sub> , R <sub>5</sub> , R <sub>6</sub> =OCH <sub>3</sub>                  |
| <b>c</b> R <sub>1</sub> , R <sub>3</sub> , R <sub>6</sub> =H; R <sub>2</sub> , R <sub>4</sub> =OH; R <sub>5</sub> =OCH <sub>3</sub>               |
| <b>d</b> R <sub>1</sub> , R <sub>2</sub> , R <sub>3</sub> , R <sub>4</sub> =H; R <sub>5</sub> =CH <sub>3</sub> ; R <sub>6</sub> = H               |

**Figure 18: Novel flavonoids with anticancer efficacy**

Yakaiah Chinthala, *et, al* synthesized a series of novel chalcone-triazole derivatives and screened for in vitro anticancer activity on the human cancer cell lines IMR32 (neuroblastoma), HepG2 (Human hepatoma) and MCF-7 (Human breast adenocarcinoma), DU-145 (Human prostate carcinoma), and A549 (Human Lung adenocarcinoma). [27] [Figure15]

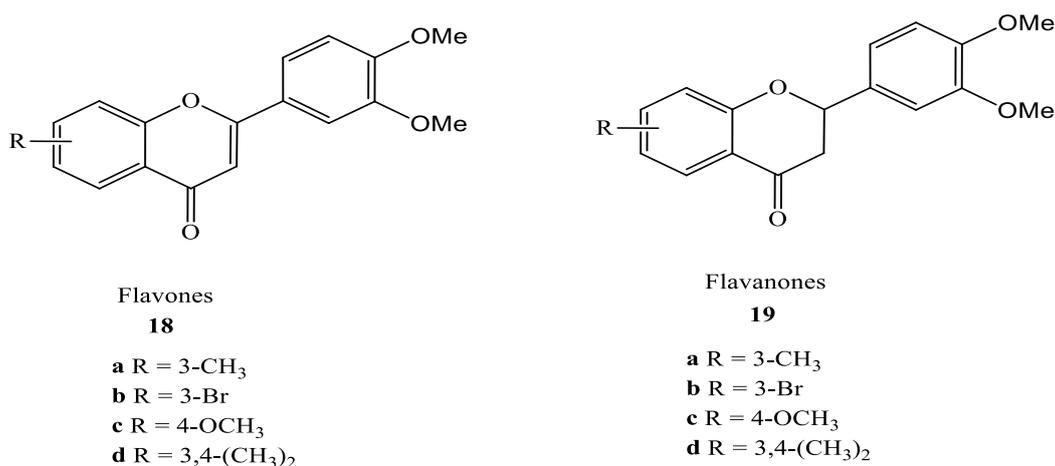


**Figure 19: Novel chalcone-triazole derivatives with in vitro anticancer activity**

### 3.3 Antimalarial activity

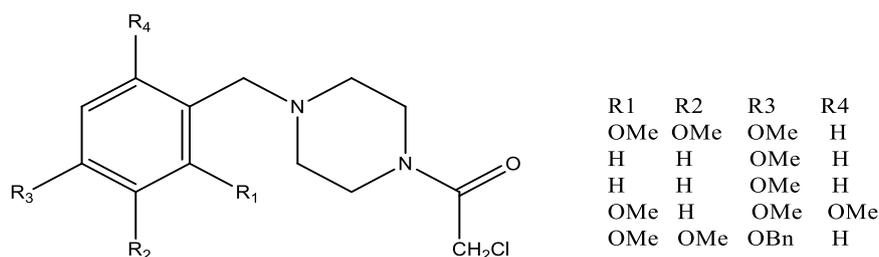
Malaria is a protozoan disease that is transmitted to humans by bites of female Anopheles mosquitoes. There are five Plasmodium parasite species that are capable of human infection: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The majority of malaria mortality in Africa occurs due to *P. falciparum* infections, while considerable morbidity can be caused by *P. vivax* infections, particularly in South America and Southeast Asia. Quinine was the first effective treatment for malaria caused by *P. falciparum* and remained the drug of choice until the late 1940s, when other drugs such as chloroquine and later on pyrimethamine artemisinin, mefloquine, etc. replaced it. Unfortunately, resistance of the Plasmodium parasite against frequently used antimalarial drugs such as chloroquine and artemisinin is ever-increasing and urges scientists to find new approaches to treat and prevent malaria infections. Since there is currently no licensed malaria vaccine available to make people immune, chemotherapy still offers the best solutions. Novel strategies in antimalarial treatment include the optimization of therapies with available drugs (e.g. artemisinin combination therapy), flavonoids is the best choice by researcher due to structural similarity with reported antimalarial drugs. [28]

The author Lim SS *et al* designed and synthesized four derivatives for each of flavones (**18a-d**), flavanones (**19a-d**) and evaluated for *in vitro* antimalarial activity against *P. falciparum* strain FCR-3. Among the flavonoids derivatives tested, the most active compounds were 3'-methyl-substituted flavanones (**19a**) and (**18a**) showing 100% inhibition against *P. falciparum* at the final concentration of 5.0 µg/ml and 5.2 µg/ml, respectively.[29] [Figure 16]



**Figure 20: 3'-methyl-substituted flavanones with antimalarial activity**

The author Gwenola Auffret, *et al* synthesized a series of 27 flavonoid derivatives containing a piperazinyl chain have been synthesized and tested for their antiparasmodial activity. Diverse substitution patterns on piperazinyl and flavone moieties were examined and found to affect the activity differently. The most active compounds, which have a 2,3,4-trimethoxybenzylpiperazinyl chain attached to the flavone at the 7-phenol group, showed in vitro activity against chloroquine-sensitive (Thai) and -resistant (FcB1,K1) Plasmodium falciparum strains in the micromolar to submicromolar range. One of them was active when given orally in a Plasmodium yoelii nigeriensis infected mouse model. [30][Figure 17]

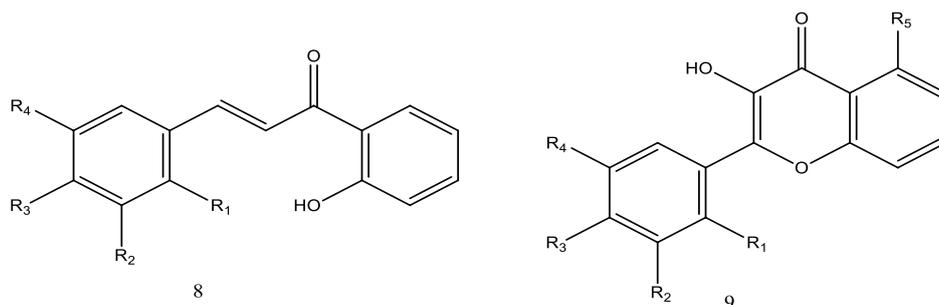


**Figure 21: Piperazinyl derivative of flavonoid with antimalarial activity**

### 3.4 Anti HIV activity

It has been shown that HIV I proteases are inhibited by various flavonoids including demethylated gardenin A and 3, 2-dihydroxyflavone. Among 28 flavonoids tested flavones showed better antiviral activity as compared to flavanones in the selective inhibition of HIV-1 and HIV-2 and other related immunodeficiency virus infections [31].

The author Amy L. Cole, Sandra Hossain, Alex M. Cole, *et al*, reported the synthesis of a series of chalcone, flavone, coumaranone and other flavonoid compounds which were screened for their anti HIV-1 activity in two cell culture models using TZM-bl and PM1 cells. Within the systems evaluated, the most promising compounds contained either an  $\alpha$ - or  $\beta$ - hydroxy-carbonyl motif within their structure (e.g., 8 and 9). Efficacious substituents were identified and used to design new HIV inhibitors with increased potency and lower cytotoxicity. [32][Figure 18]

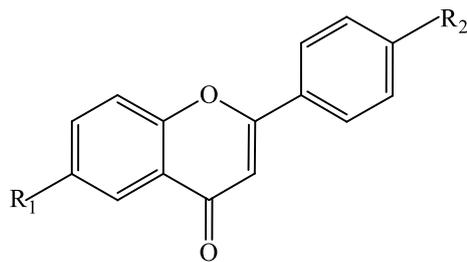


**Figure 22: New HIV inhibitors having flavonoid moiety**

### 3.5 Anti-Alzheimer

Alzheimer disease (AD) is a deadly neurodegenerative brain disorder characterized by dementia, cognitive impairment, and memory loss. It has been estimated that 36 million people were living with dementia in the world in 2010 and that the number will double every 20 years, leading to more than 115 million people with AD in 2050. Although the etiopathogenesis of AD still remains unknown, in the last decades, several factors that are involved in the onset of AD have been identified. Among them, low levels of acetylcholine, oxidative stress and  $\beta$ -amyloid ( $A\beta$ ) deposits play significant roles in AD [fl]. Because of the multipathogenesis of AD, new therapeutic strategies are being developed to arrest and reverse the progress of AD, one strategy is to develop novel anti-AD agents with multiple potencies. This is the case of the multi-target-directed ligand (MTDL) approach. In this regard, a lot of interest has recently regained the natural product such as flavonoids. [33]

*In vivo* imaging of  $\beta$ -amyloid aggregates in the brain may lead to early detection of Alzheimer's disease and monitoring of the progression and effectiveness of the treatment. For such purpose Ono M et al. developed novel  $^{18}\text{F}$ -labeled amyloid imaging probes based on flavones (**11a-f**) as a core structure. [34] Fluoropegylated (FPEG) flavone derivatives were designed and synthesized. All derivatives had varied affinity for  $\beta$ -amyloid aggregated ranging from 5 to 321 nm. In brain sections of AD model mice, FPEG flavones with the dimethylamino group intensely stained  $\beta$ -amyloid plaques. [Figure 19]



11

- a: R<sub>1</sub> = FCH<sub>2</sub>CH<sub>2</sub>O; R<sub>2</sub> = N(CH<sub>3</sub>)<sub>2</sub>
- b: R<sub>1</sub> = (FCH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>; R<sub>2</sub> = N(CH<sub>3</sub>)<sub>2</sub>
- c: R<sub>1</sub> = FCH<sub>2</sub>CH<sub>2</sub>O; R<sub>2</sub> = NHCH<sub>3</sub>
- d: R<sub>1</sub> = (FCH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>; R<sub>2</sub> = NH<sub>2</sub>
- e: R<sub>1</sub> = F; R<sub>2</sub> = NH<sub>2</sub>
- f: R<sub>1</sub> = F; R<sub>2</sub> = NHCH<sub>3</sub>

**Figure 23: Novel flavonoids in Alzheimer disease**

### 3.6 Antioxidant Activity

Oxidative stress in human arises from an imbalance in the antioxidant status, that is, production of excessive Reactive Oxygen Species (ROS) during cellular metabolism versus living cell's own defense and repair mechanisms. This oxidative stress plays a crucial role in the age-associated diseases such as cardiovascular and cerebrovascular diseases, some forms of cancer and Parkinson's and Alzheimer's diseases. (ROS) Superoxide free radical, hydrogen peroxide, hydroxyl free radical and single oxygen, play a pivotal role in oxidative damage. Fortunately, antioxidants may prevent and/or relieve oxidative stress-related diseases through delaying or reducing such oxidative damage. [35] It is well-recognized that antioxidants can be classified into two types, namely enzymatic antioxidants and non-enzymatic antioxidants. Enzymatic antioxidants act as the first defense line in human body such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, while non-enzymatic antioxidants including synthetic and natural antioxidants are considered to be the second defense line. polyphenols are capable of exhibiting excellent antioxidant property due to their high radical scavenging capacity which is based on availability of specific hydroxyl groups and probability of stabilization of resulting phenolic radicals through hydrogen bonding or extended electron delocalization Flavonoids are documented to be one of the major quantities of polyphenols ingested from the diet, especially plant-based foods such as green tea, soy bean, and onion. Structural modification of flavonoids with addition hydroxyl group have shown good antioxidant activity. [36]

Sreeparna Das *et, al*, a series of flavonoid analogues and screened for the in vitro antioxidant activity through their ability to quench 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical. The

activity of these compounds, measured in comparison to the well-known standard antioxidants. [37]

## CONCLUSION

This review is based upon the synthesis of modified flavonoids as it shows various biological activities. We have attempt for the development and evolution of research on flavonoids and conclude that today flavonoids have become attractive target for the research in Pharmaceutical field

## Conflict of Interest

Author's donot have any conflict of interest

## REFERENCES

1. Jannie P. J. Marais, The science of flavonoids, Springer science business media 2006.
2. Satyajit Saha, Rajpratap Kshtriya (2018), In memory of Prof. Venkatraman: Recent Advances in the Synthetic Methdology of Flavones, Tetrahedron 74, 811-833.
3. MarijaLesjak, IvanaBeara (2018) Antioxidant and anti-inflammatory activities of quercetin and its derivatives, Journal of Functional Foods, 40, 68-75.
4. V. Rossollin, V. Lokshin, A. Samat, R. Guglielmetti, Reinvestigation of prototropic photochromism: 3-benzoyl-2-benzylchromones, Tetrahedron 59 (2003) 7725–7731.
5. Auwers K, Synthesis of flavones, Chem Ber, 1908, 41, 4233.
6. Allan J, Robinson R., Synthesis of novel flavonoids, J Chem Soc Trans. 1924, 125, 2192-2195.
7. Flynn Algar, J. Proc Roy Irish Acad. 1934, 42B, 1-4.
8. Oyamada T. J Bull Chem Soc Jpn. 1935, 10, 182-186
9. Yue Liu, Zhen-Gang, (2017), Effects of quercetin on proliferation and migration of human glioblastoma U251 cell, Biomedicine & Pharmacotherapy, 92, 33-38.
10. Snape, Timothy James and Ameen, Dana (2014), Mechanism and application of Baker Venkatraman acyl migration reaction, Synthesis 47(2), 141-158
11. Koneni V. Sashidhara, ManojKumar, AbdheshKumar, (2012), A novel route to synthesis of flavones from salicylaldehyde and acetophenone derivatives, Tetrahedron Letters, 53, 18, 2355-2359.
12. George W. Kabalka, Arjun R. Mereddy, Microwave-assisted synthesis of functionalized flavones and chromones, Tetrahedron Letters, 46, 37, 2005, 6315-6317
13. Swapnil R. Sarda, Wamanrao N. Jadhav,(2009), I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>-Asuitable heterogeneous catalyst for the synthesis of flavonoids by microwave irradiation, International Journal of Chemtech Research, 1,3,539-543.
14. Shashank Kumar and Abhay K. Pandey, (2013) Chemistry and Biological Activities of Flavonoids: An Overview, The Scientific World Journal (2013), 16
15. T.P. Tim Cushnie, Andrew J. Lamb, (2006), Antimicrobial activity of flavonoids International Journal of Antimicrobial Agents, 27, 2,181.
16. B. S. Jayashree, Abhishek Kumar, (2011), Synthesis, Characterization and Antimicrobial activity of novel flavones, Pharmacology online, Newsletter, , 963-973
17. Zhang, X., Khalidi, O., Kim, S.Y., Wang, R., Schultz, V., Cress, B.F., Gross, R.A., Koffas, M.A.G., Linhardt, R.J.(2016), Synthesis and biological evaluation of 5,7-dihydroxyflavanone derivatives as antimicrobial agents, Bioorganic & Medicinal Chemistry Letters.

18. Lv PC, Li HQ, Xue JY, Shi L and Zhu HL, (2009), Synthesis and biological evaluation of novel luteolin derivatives as antibacterial agents. *Eur. J. Med. Chem.*, 44, 908-914.
19. Venkatesan P and Maruthavanan T, (2011), Synthesis of substituted flavone derivatives as potent antimicrobial agents. *Bull. Chem. Soc.*, 25(3), 419-425.
20. Demetrio Raffa, Benedetta Maggio, Maria Valeria Raimondi, Fabiana Plescia, Giuseppe Daidone, (2017), Recent discoveries of anticancer flavonoids, *European Journal of Medicinal Chemistry*.
21. W. Huang, Q. Chen, W.C. Yang, G.F. Yang, (2013), Efficient Synthesis and Antiproliferative Activity of Novel Thioether-Substituted Flavonoids, *European Journal of Medicinal Chemistry*.
22. Huachen Liu, Aijun Dong, Chunmei Gao, Chunyan Tan, Zhenhua Xie, Xuyu Zu, Long Qu and Yuyang Jiang, (2010), New synthetic flavone derivatives induce apoptosis of hepatocarcinoma cells, *Bioorg. Med. Chem.*, 18, 6322–6328.
23. Tsutomu Akama, Yasushi Shida, Toru Sugaya, Hiroyuki Ishida, Katsushige Gomi and Masaji Kasai, (1996), Novel 5-Aminoflavone Derivatives as Specific Antitumor Agents in Breast Cancer. *J. Med. Chem.* 39, 3461-3469.
24. W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, A. Jemal, X.Q. Yu, J. He, (2016) Cancer statistics in China, 2015, *CA Cancer J. Clin.* 66 115-132.
25. Sohel Mastahar, Sayed Alam and Azizul, (2006), Cytotoxic and antimicrobial activities of some synthetic flavones, *Indian J. Chem.*, 45B, 1478-1486.
26. Y. Chinthala, S. Thakur, S. Tirunagari, S. Chinde, A.k. Domatti, N.K. Arigari, K.V.N.S. Srinivas, S. Alam, J.K. Kumar, F. Khan, A. Tiwari, P. Grover, (2015), Synthesis, docking and ADMET studies of novel chalcone triazoles for anti-cancer and anti-diabetic activity, *European Journal of Medicinal Chemistry*.
27. Vandekerckhove, S., D'hooghe, M., (2014) Quinoline-based antimalarial hybrid compounds, *Bioorganic & Medicinal Chemistry*.
28. Lim SS, Kim SH and Dong-Ung, (2007), In vitro Antimalarial Activity of Flavonoids and Chalcones. *Bull. Korean Chem. Soc.*, 28(12), 2495-2497.
29. Gwenola Auffret, (2007), Synthesis and antimalarial evaluation of a series of piperazinyl flavones *Bioorganic & Medicinal Chemistry Letters* 17, 959–963.
30. Cabrera, C., Giménez, R., & López, M. C. (2003). Determination of tea components with antioxidant activity. *Journal of Agricultural and Food Chemistry*, 51(15), 4427-4435.
31. Evans, W. C. (2009). *Trease and Evans' Pharmacognosy*: Elsevier Health Sciences.
32. Cole, A.L., Hossain, S., Cole, A.M., Phanstiel, O., (2016), Synthesis and Bioevaluation of Substituted Chalcones, Coumaranones and other Flavonoids as anti-HIV agents, *Bioorganic & Medicinal Chemistry*.
33. Wen Luo, Ting Wang, Chen Hong, Ya Chen Yang, Ying Chen, Juan Cen, Song Qiang Xie, ChaoJie Wang, Design, Synthesis and Evaluation of 4 Design, Synthesis and Evaluation of 4-Dimethylamine Flavonoid Derivatives Flavonoid Derivatives Derivatives as Potential Multifunctional as Potential Multifunctional Anti-Alzheimer agents Alzheimer agents, *European Journal of Medicinal Chemistry* (2016).
34. Ono M, watanabe R, Kawashima H and Kawai T, (2009): <sup>18</sup>F-labeled flavones for in vivo imaging of  $\beta$ -amyloid plaques in Alzheimer's brains., *Bioorg. Med. Chem.*, 17, 2069-2076.
35. Ahamd, A., Kaleem, M., Ahmed, Z. & Shafiq, H., (2015), Therapeutic Potential of Flavonoids and Their Mechanism of Action against Microbial and Viral Infections-A Review, *Food Research International*
36. K. Li, H. Fan, P. Yin, L. Yang, Q. Xue, X. Li, L. Sun, Y. Liu, (2017), Structure-activity relationship of eight high content flavonoids analyzed with a preliminary assign-score method and their contribution to antioxidant ability of flavonoids-rich extract from *Scutellaria baicalensis* shoots, *Arabian Journal of Chemistry*,.
37. Sreeparna Das, Indrani Mitra, Shaikh Batuta, Md. Niharul Alam, Kunal Roy, Naznin Ara Begum, (2014), Design, synthesis and exploring the quantitative structure–activity relationship of some antioxidant flavonoid analogues, *Bioorganic & Medicinal Chemistry Letters*,.