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INSIGHTS INTO VARIOUS NOVEL SYNTHETIC STRTAEGIES FOR FLAVONE DEVELOPMENT: PHARMACOLOGICAL IMPORTANCE

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ABSTRACT: Flavones make up one of the biggest subgroups of the secondary metabolite class of flavonoids, which has more than 9000 known structural variations. It is shown that they are present in practically all plant tissues naturally. In the literature, many flavone aglyca and their O- or C-glycosides have been described. Numerous potential uses exist for flavones due to their wide range of biological activities in plants and their numerous interactions with other species. These include plant breeding, ecology, agriculture, human nutrition, and pharmacology, in addition to plant breeding. Flavones are abundant polyphenols of plant origin that have been extensively studied for their pharmacological properties. Flavones are a subclass of flavonoids with their structural basis in 2-phenylchromen-4-one (flavus = yellow). Cereals and plants are the primary sources of flavones. Since flavones are physiologically active substances, several synthetic techniques have been developed. We have attempted to include a variety of synthetic methods for the synthesis of flavones in this update. Claisen-Schmidt condensation and Baker-Venkatraman synthesis are two well-known techniques for creating flavones. It is widely known that derivatives of flavones exhibit a wide range of pharmacological actions. This study paves the way for thorough biochemical and molecular characterizations as well as the creation of direct metabolic engineering techniques for modifying flavone production in plants to increase their nutritional and/or medicinal value.

INTRODUCTION: Drugs have traditionally been made from natural substances, mostly plant-based substances, and a significant fraction (30–40%) of the medications used in contemporary medicine are made either directly or indirectly from natural substances. The search for new drugs is also highly interested in natural ingredients. They enable the detection of key molecules of interest for the creation of novel therapeutic medicines due to their wide variety in nature.

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Additionally, they offer the biochemical and molecular tools required to decipher intricate cellular and molecular mechanisms of capable of organizing in the majority of pathological and physiological events. In conclusion, there has been an increase in interest around the globe in using phytopharmaceuticals as supplementary or alternative medicine, either for the treatment or prevention of numerous diseases, in current history.

Approximately 80% of the planet's population is said to rely mostly on plants for their therapeutic needs. Particularly, flavones are regarded as being one of the most significant natural products and among the substances that are utilised the most frequently globally [1]. Flavones **Fig. 1** are a subclass of flavonoid containing a backbone of 2-phenylchromen-4-one (from the Latin flavus,

which means "yellow"). The anti-cancer, anti-inflammatory, anti-microbial, antioxidant, anti-osteoporatic, anti-diabetic, anti-estrogenic, anti-allergic, and metal chelating activities of flavones, one of the most significant groups of plant secondary metabolites, are well documented. Due to the vast range of biological effects of this class of chemicals, much synthetic research has been done on them and more than 4000 chemically unique flavonoids have been discovered in plants.

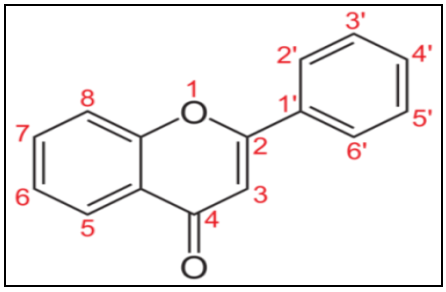

FIG. 1: STRUCTURE OF A FLAVONE

However, fresh developments in synthetic chemistry have led to the creation of a number of crucial compounds for medicine. The production of flavones, their derivatives, and other flavone analogues, which have the potential to cure a variety of diseases and maladies, is summarised in this article. Further flavonoids comprise isoflavonoids and neoflavonoids, which are generated from the 3-phenylchromen-4-one and 4-phenylcoumarin structures, respectively. Due to the ketone content of all three flavonoid families, anthoxanthins (flavones and flavonoids) are widely distributed in yellow plant pigments. The heterocyclic chemicals that make up the flavonoid family in nature are called derivatives of flavone (2-phenylchromen). The biological activity of flavone has been enhanced by the addition of a heteroaryl component to the C-2 position of chromone variants [2].

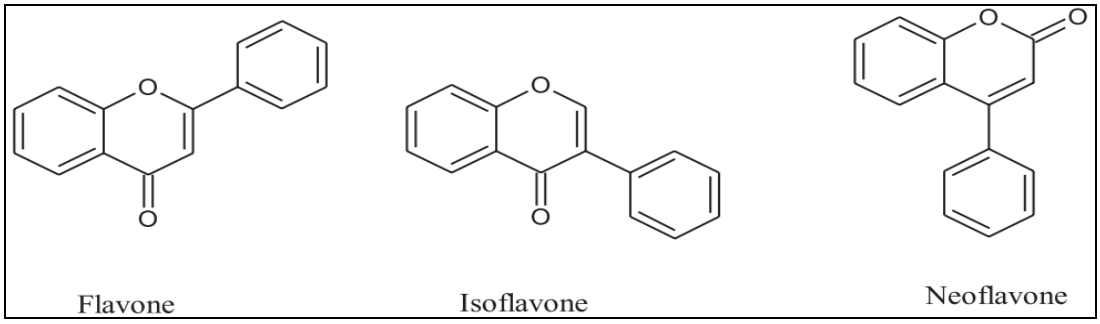

FIG. 2: MAJOR POLYPHENOLIC SUBSTANCES IN VARIOUS PLANT SPECIES

A polyphenolic substance called flavones is present in a variety of plant species. Flavonoids, which come in the forms of flavonols, flavones, isoflavones, flavonones, and biflavones **Fig. 2**, are found in foods including tea, red wine, apple, tomato, cherry, onion, thyme, parsley, grapes, fruit, orange, and lemon as well as soybeans and other legumes. Since they are widely distributed and have a low toxicity compared to other chemical categories of substances, flavonoids have caught the interest of synthetic chemists. Research suggests that flavones inhibit proliferation while causing little to no harm to healthy cells [3-5].

Flavones such as kaempferol, nobiletin, artonin A, semiglabrin, *etc*. **Fig. 3** are a family of compounds that may one day be employed to create low-cost anti-cancer, anti-inflammatory [6], anti-osteoporotic [7], anti-diabetic [8] and other medicines, according to a study of the literature.

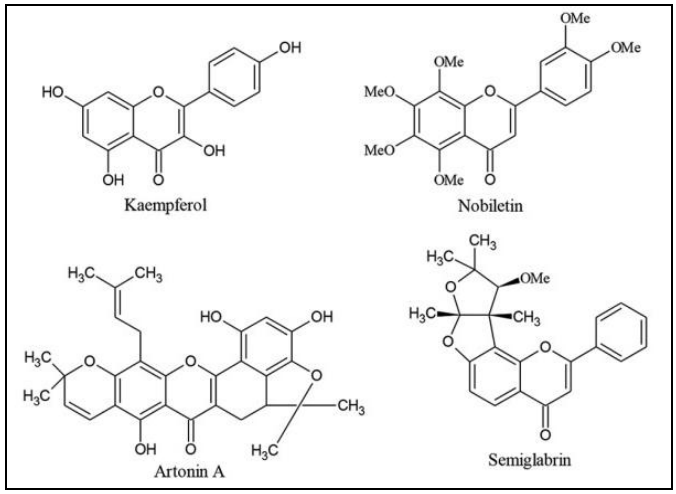

FIG. 3: THERAPEUTICALLY ACTIVE FLAVONES

Synthetic Strategies of Flavones: Traditional methods for making flavones include the Baker-Venkatraman rearrangement and Claisen-Schmidt condensation, which involve converting 2-hydroxyacetophenones into benzoyl esters,

followed by base-based rearrangement to 1,3-diphenylpropane1,3-diones, which can then be cycled under acidic conditions to produce flavones **Fig. 4**.

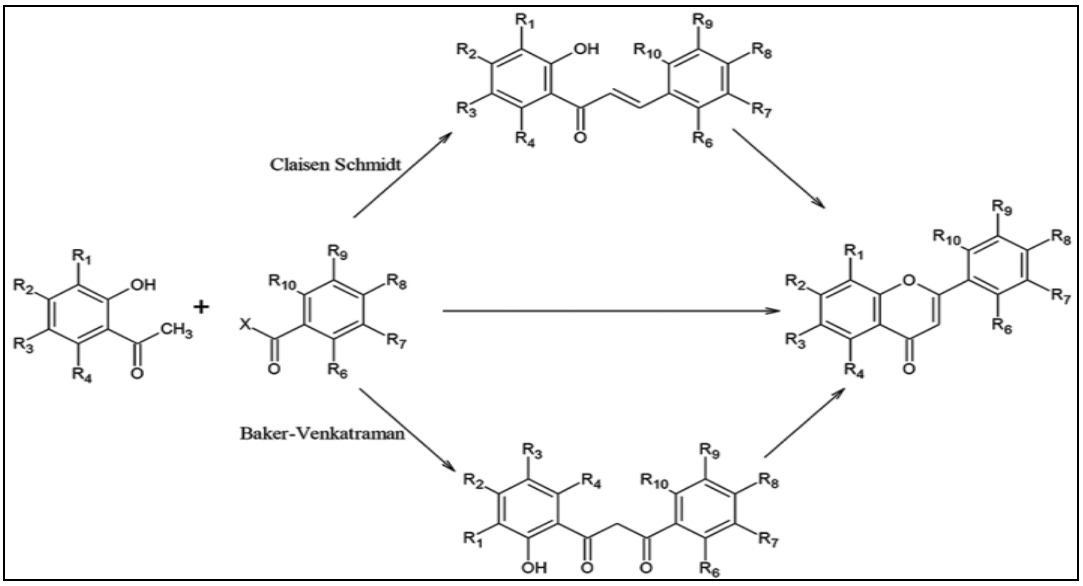

FIG. 4: BASIC REACTIONS FOR THE SYNTHESIS OF FLAVONES

On the other hand, hydroxychalcone can go through oxidative cyclization to produce a flavone ring when it is generated from 2-hydroxyacetophenone and benzaldehyde under Claisen-Schmidt conditions **Fig. 5.**

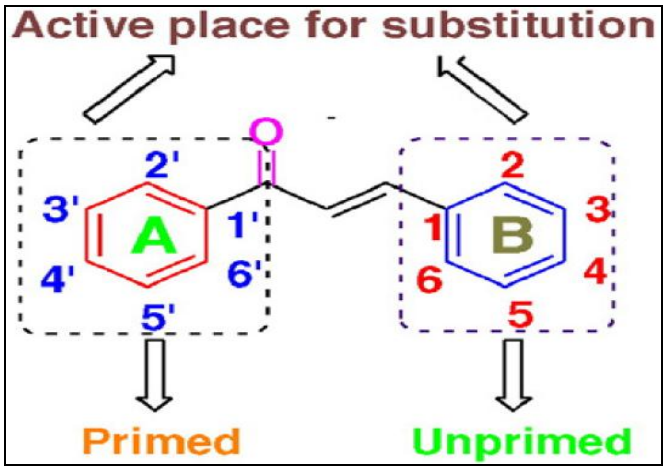

FIG. 5: STRUCTURE OF CHALCONE

Following are several of the fundamental plans for the synthesis of flavones.

From 2-hydroxy Acetophenone and Aromatic Aldehyde Derivatives:

General Procedure for the Synthesis of Substituted Chalcone:

Method 1: In a mortar and pestle, 24 mM of aryl aldehyde (1.2 equivalent) was added and it was continuously triturated while NaOH powder was added in little amounts. With continuous trituration, 20 mM of 2-hydroxy acetophenone (1 equivalent) was added. Continuous trituration resulted in the formation of a solid yellow mass. TLC was used to observe the response. To get crude chalcone, the newly produced yellow solid was promptly washed with hot methanol.

Method 2: EtOH was used to dissolve 2-hydroxy acetophenone (1 equivalent), benzaldehyde derivatives (1.2 equivalent), and KOH pallet (3 equivalent). Until TLC indicated that the reaction was complete, the reaction mixture was stirred at RT for 6 to 12 hrs.

After working up the reaction, the fluid was poured over crushed ice and acidified with weak HCl (pH 5). Chalcone was obtained by recrystallizing the solid from diluted ethanol.

General Procedure for the Synthesis of all Substituted Flavones: In radial basis function, 5 mM of synthetic 2-hydroxy arylchalcone and 6 mL of DMSO were introduced.

The reaction mixture was then given a catalytic quantity of I_2 and the mixture was heated on an oil bath at 110°C for 2 to 6 hrs. TLC signalled that the reaction was finished. After working up the reaction, the liquid was poured over crushed ice, and extra I_2 was taken out by gradually adding sodium thiosulfate solution.

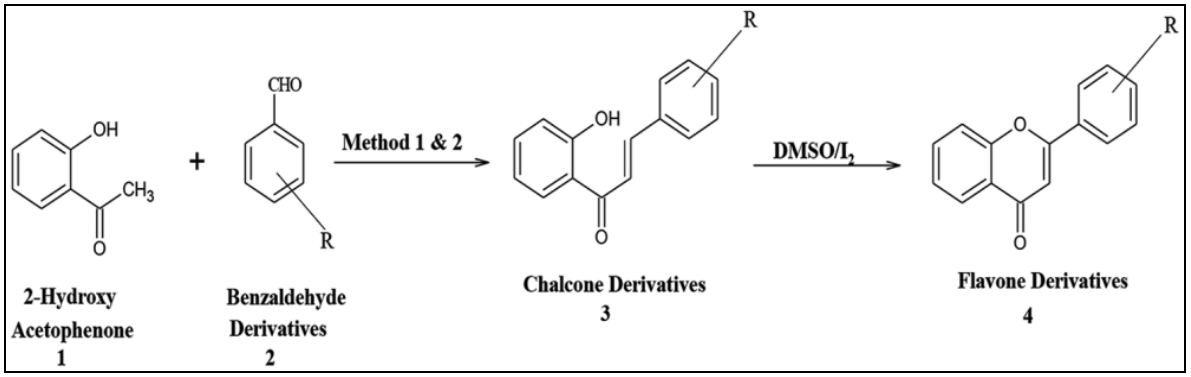

FIG. 6: SYNTHESIS OF CHALCONE BY TRITURATION AND CONVENTIONAL METHOD AND FLAVONES

Suction filtration was used to remove the precipitate and the solid was then recrystallized from diluted ethanol to produce crystallized flavone **Fig. 6** [9].

From 1, 3-benzoxazine Derivatives: The flavone moiety is located at the third position in a number of 6- and/or 8-substituted 1,3-benzoxazines. The compounds were created by reducing 6- or 8-substituted salicylaldehydes with aminoflavone, cyclizing the resultant aminoflavone precursors with $CHCl_3$/HCHO to obtain the necessary 1,3-benzoxazine skeleton, and finally reducing the substances [10].

General Procedure for the Preparation of 6-(2H-1, 3 – benzoxazine - 3(4H) – yl – 2 – phenyl - 4H -chromen-4-one Derivatives:

Step 1: 20 mL of ethanol were used to make 6-aminoflavone (0.001 M), which was then transferred to a flask with a flat bottom. Until it was entirely dissolved, the mixture was cooked in a water bath. To the resulting mixture, salicylaldehyde (0.001 M) was gradually added before it was refluxed for 4 hrs. From chloroform and petroleum ether (1:1), Schiff's base was separated, filtered, dried, and recrystallized to produce orange microcrystalline powder **Fig. 7**.

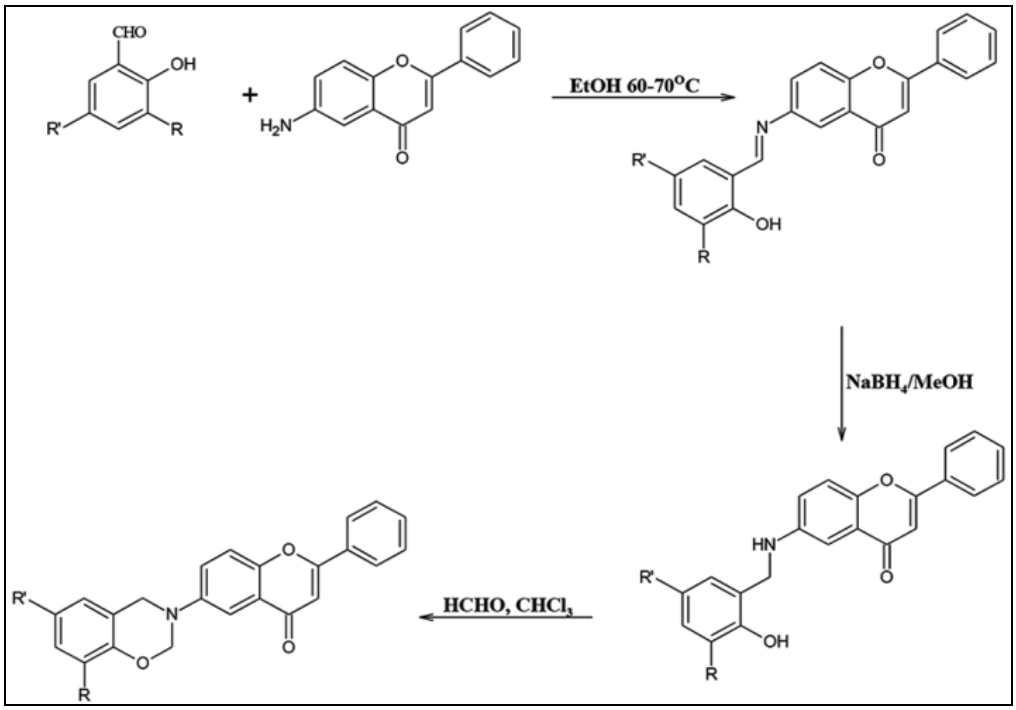

FIG. 7: SYNTHESIS ROUTE OF 6 - (2*H*) - 1, 3 – BENZOXAZINE – 3 (4*H*)-YL)-2-PHENYL-4*H*-CHROMEN-4-ONE DERIVATIVES

Step 2: By gently heating, compound 1 (0.001 M) was dissolved in 20 mL of methanol. After adding sodium borohydride (0.02 M), the mixture was agitated for one hour. For 10 to 15 minutes, the mixture was heated to 40 °C. The methanol evaporated at a lower pressure. To get a pale

yellow microcryatalline powder of compound, the residue was washed with water, dried and recrystallized from chloroform and petroleum ether (1:1). From diketone intermediate and claisen-schmidt condensation reaction: Other names for flavone include 2-phenyl-4*H*-chromen-4-one and 2-phenyl-1-benzopyra-4-one. They may react by a variety of processes, such as reduction reactions [11], base-induced degradation [12], substitution [13, 14], oxidation [15], condensation [16], rearrangement [17], reactivity with organometallic reagents [18], and addition [19, 20, 21]. To produce items with high yields, purity, and the necessary quality, a number of synthetic processes have been created and updated. The Baker-Venkataraman rearrangement [22, 23], Claisen-Schmidt condensation [24], Ionic Liquid Promoted Synthesis [25], Vilsmeier-Haack reaction [26], Allan-Robinson [27], Wittig reaction, Fries rearrangement, and Modified Schotten-Baumann reaction are a few examples of synthetic methods that can produce flavones.

Most flavones are currently synthesised using the Baker-Venkataraman process. This procedure works by converting o-hydroxy acetophenone to phenolic ester, which is subsequently converted to β-diketone *via* intramolecular Claisen condensation in the presence of a base. By way of an acid-catalyzed cyclodehydration, it is ultimately cyclized into flavones (Scheme 4). Flavones were previously produced via the Baker-Venkataraman rearrangement; however this method calls for the use of strong bases, acids, and lengthy reaction times, all of which reduce yields. In this regard, Sashidhara *et al.* reported a different method to synthesis flavones of therapeutic importance. Salicylaldehyde and acetophenones were condensed to create 2-hydroxy chalcones. In the presence of catalytic iodine, they undergo oxidative cyclization when heated. As a result, several flavones are produced under green synthesis circumstances **Fig. 8** [28].

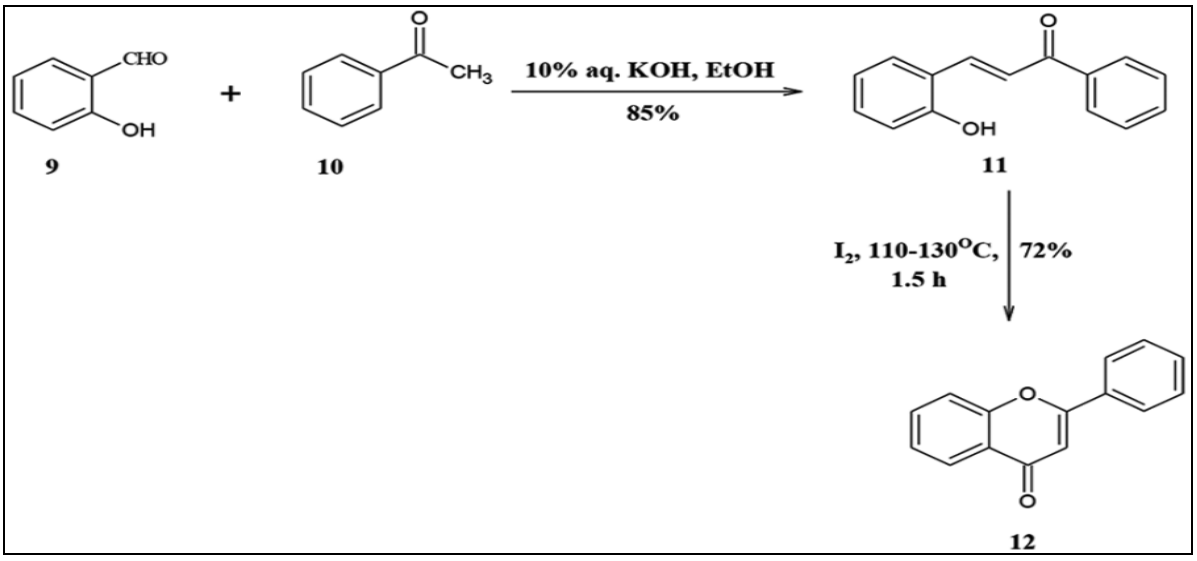

FIG. 8: CLAISEN-SCHMIDT CONDENSATION REACTION

From 2'-allyloxy-α, β-dibromochalcones: As a follow-up to earlier research [29], the synthesis of 2'-allyloxy-α, β-dibromochalcones, which results in the corresponding 3-bromoflavones, has caught the attention of researchers. Previously, the allyl group of 2'-allyloxy chalcones was smoothly removed by the DMSO-I_2 reagent, followed by cyclization and dehydrogenation to produce flavones. The elimination of HBr and subsequent dehydrogenation to produce 3-bromoflavones are anticipated by α, β-dibromochalcones. By treating 2'-hydroxy chalcones with allyl bromide for 24 hrs at room temperature while adding potassium carbonate and dimethylsulfoxide, 2'-allyloxy chalcones were created. In 24 hrs, 2'-allyloxy-α,β-dibromochalcones (1) were produced at room temperature by brominating 2'-allyloxy chalcones with bromine water in the presence of acetic acid. In the presence of dimethylsulfoxide, the reaction of 2'-allyloxy-α, β-dibromochalcones (1) with iodine (1 mM) was predicted to proceed through the stages of deallylation, cyclization, debromination and dehydrogenation to produce 3-bromoflavones (5).

However, it comes as a surprise to see that at the conditions described, 2'-allyloxy-α, β-dibromochalcones (1) were successfully converted to flavones (2) with a high yield **Fig. 9**.

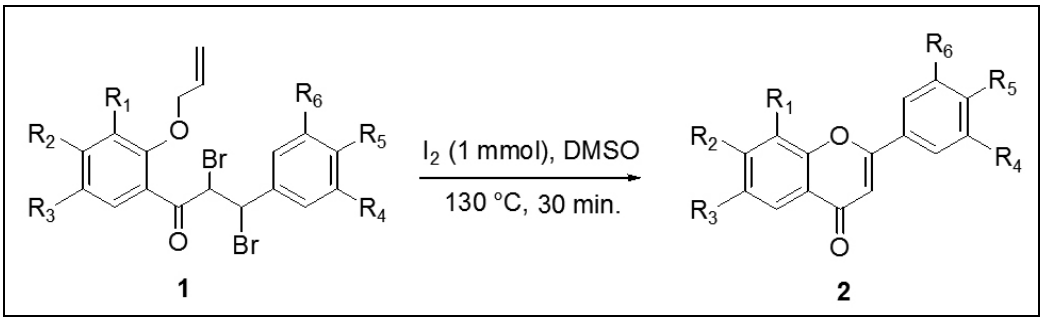

FIG. 9: CREATION OF FLAVONES THROUGH IODINATION OF 2'-ALLYLOXY-A,B-DIBROMOCHALCONES

According to the aforementioned findings, 3-bromoflavanones (4) that had undergone dehydrobromination in DMSO-I_2 reagent may be used as an intermediary to create flavones (2) from 2'-allyloxy-α, β-dibromochalcones (1) **Fig. 10**.

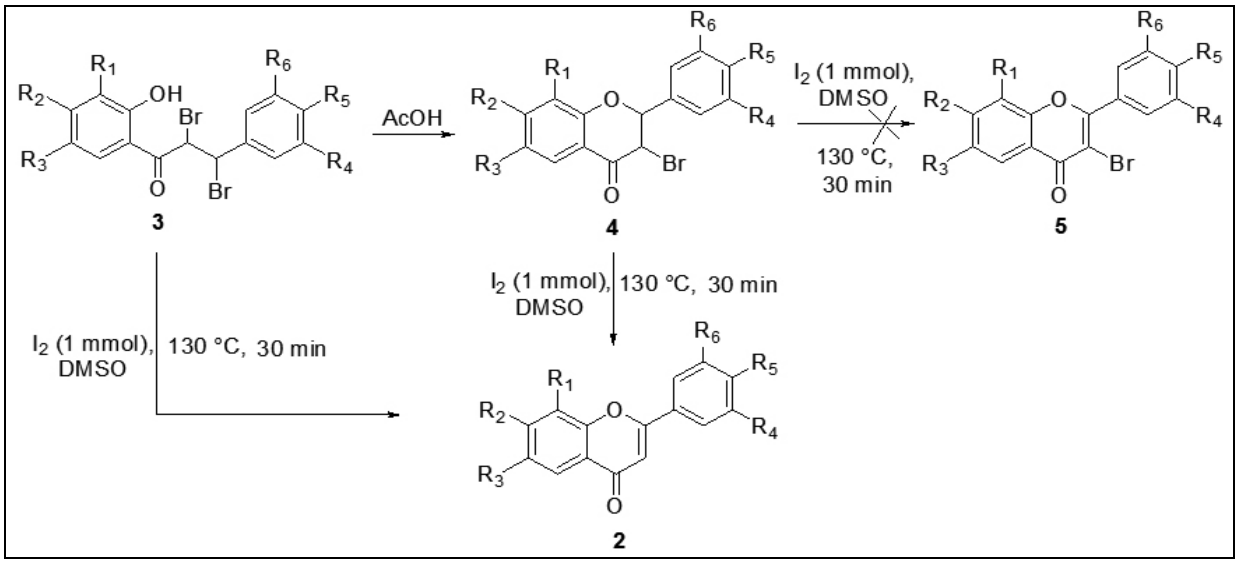

FIG. 10: DEVELOPMENT OF FLAVONES FROM 2'-ALLYLOXY-A, B-DIBROMOCHALCONES

Debromination of 2'-allyloxy-α, β-dibromo-chalcones, followed by deallylation, cyclization, and oxidation, is another potential reaction order. Iodine was reacted with α, β-dibromochalcones (6) in the dimethylsulfoxide reagent to explore these reactions **Fig. 11.** Chalcones (7) have been produced as a result of its debromination at 130°C.

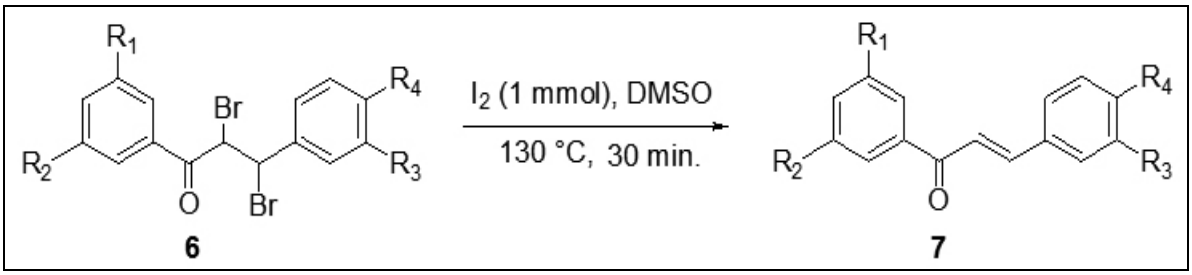

FIG. 11: DEBROMINATION REACTION OF CHALCONES

It is thought that deallylation produces oxyanion when iodine and 2'-allyloxy-α, β-dibromochalcones (1) are combined in dimethylsulfoxide. Cyclization aids debromination in the following step, producing 3-bromoflavanone (5). Finally, under the action of the iodide ion, dehydrobromination of 3-bromoflavanone (5) yields flavone (2) **Fig. 12.**

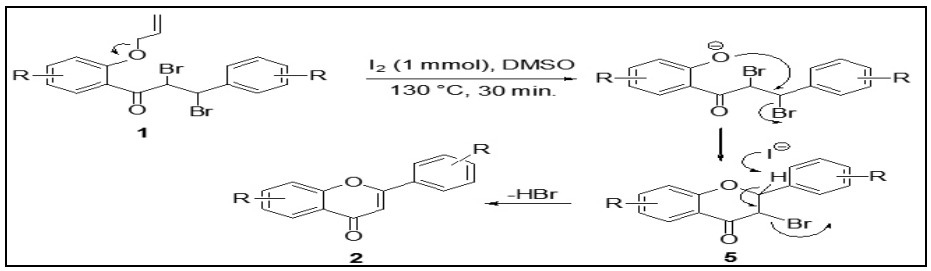

FIG. 12: SYNTHESIS OF FLAVONES *VIA* DEHYDROBROMINATION OF 3-BROMOFLAVANONE

Synthesis of Flavones Derivative from *N*-Amination Reaction: The required product was produced in 45% of the yield when commercially available 2,4,6-trihydroxyacetophenone was first methylated with MeI in dry DMF **Fig. 13**. When Me_2SO_4 was used as the methylation reagent in place of MeI, the synthetic process was modified, and only the desired product was produced with a 98% yield [30]. The mixture was then filtered, and vacuum distillation was used to remove the solvent to produce the pure product.

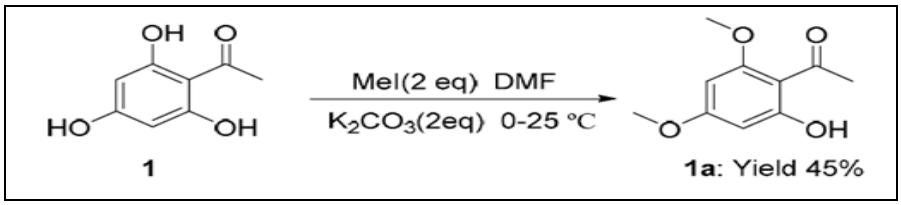

FIG. 13: SYNTHESIS OF 2,4,6-TRIHYDROXYACETOPHENONE

2b was quickly produced by using a technique similar to that mentioned in Reference [31, 32]. Aldol condensation between **1a** and **2b** at 40°C with NaOH (aq. 40%) as the base was used to produce the intermediate chalcone **3** [33,34]. The transition depended heavily on the temperature and NaOH content. Chalcone **3** was cyclized into compound 4 at 160°C in DMSO using I_2 as a catalyst [34].

Using a well-known procedure and Pd/C (10%) as the catalyst in MeOH, compound **5** was created [35]. Compound **6** might be created from compound **5** using extra K_2CO_3 as a basis [36, 37]. Palladium-catalyzed N-arylation processes were used to develop compounds from a variety of compounds [36] **Scheme 14**.

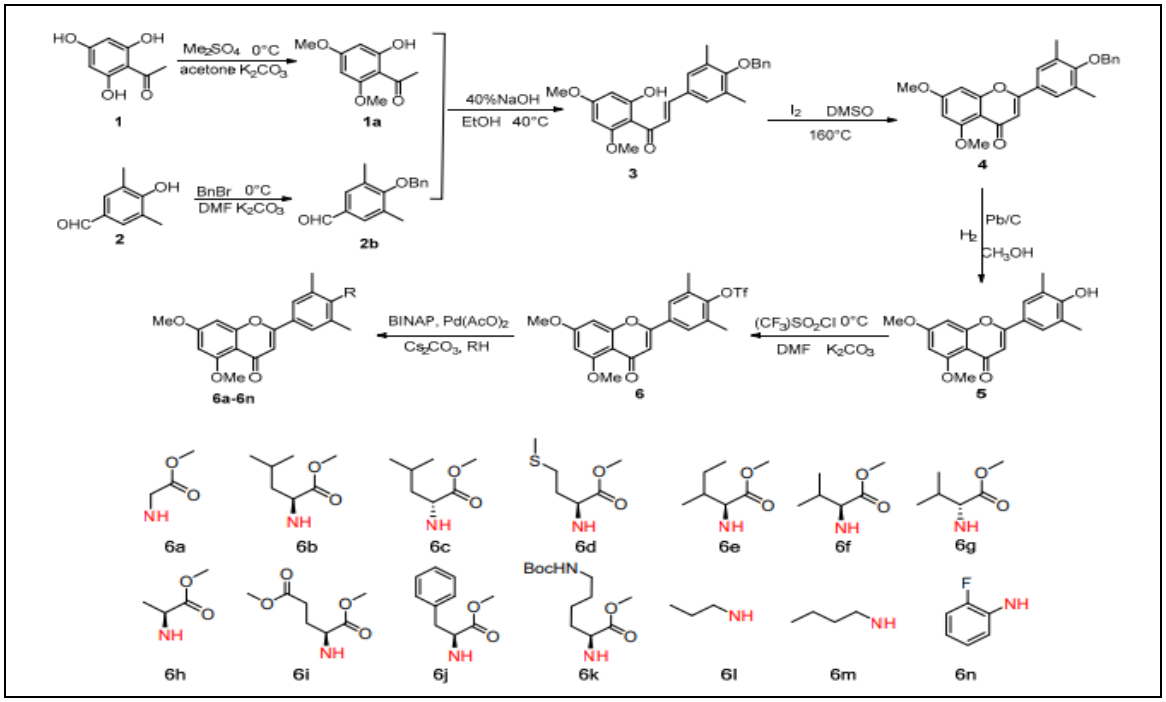

FIG. 14: SYNTHESIS OF FLAVONES DERIVATIVE

Emerging Pharmacological Perspectives:

Anti-cholinesterase Activity: One of the medications for the symptomatic alleviation of mild to moderate AD is the inhibition of the important enzyme acetylcholinesterase (AChE), which elevates brain acetylcholine levels [37]. Therefore, one of the main areas of interest for the development of drugs to treat AD is the inhibition of cholinesterases. Numerous flavones have been identified as having anti-cholinesterase properties. AChE and butyrylcholinsterase (BChE) can be inhibited by quercetin and macluraxanthone at varying concentrations, according to *in-vitro* inhibitory experiments done on flavones including quercetin, rutin, kaempferol 3-O-β-D-galactoside, and macluraxanthone [38].

Macluraxanthone, with 50% inhibitory concentration (IC_{50}) values of 8.47 μM and 29.8 μM, was discovered to be the most effective and selective inhibitor of both enzymes. According to enzyme kinetic tests, maclurax-anthone was non-competitive against AChE and competitive against BChE, whereas quercetin inhibited both enzymes in a competitive manner. These two compounds underwent molecular docking investigations at the active sites of both enzymes to get insight into the intermolecular interactions. The docking tests revealed that compared to quercetin, macluraxanthone binds to both enzymes significantly more firmly. When developing, synthesising, and evaluating flavonoid derivatives as effective AChE inhibitors, Sheng *et al.* [39] found that the majority of the derivatives exhibited AChE-inhibitory capabilities. The most effective inhibitor, isoflavone derivative, inhibits AChE with an IC_{50} of 4 nM and is superior to donepezil due to its high BChE: AChE inhibition ratio. In order to investigate the precise interaction with AChE, molecular docking experiments were also carried out.

Anti-inflammatory Activity: Arachidonic acid is converted from an endogenous enzyme, COX, into prostaglandins and thromboxanes [40]. COX-1 and COX-2 are the two isoforms of the enzyme. In contrast to COX-2, which is an inducible enzyme and only produced in response to an inflammatory stimulus, COX-1 is a constitutive enzyme and is in charge of producing the prostaglandins necessary to preserve the integrity of the stomach mucosa and ensure sufficient vascular homeostasis [41]. The purpose of COX-2 is to produce prostaglandins, which are used to cause pain and inflammation [42]. Some flavonols and flavones having a 2, 3-double bond may serve as preferred COX-2 inhibitors, according to research employing in silico approaches on the binding mechanisms of flavonoids with COX-2 [43]. For the classes of flavonol, flavone, and flavanone or isoflavone, these observations were made. This finding sparked the creation of selective COX-2 inhibitors, a class of drugs with potent anti-inflammatory properties and fewer gastrointestinal side effects. The COX-inhibitory action of a number of commercially available flavonoids, including silbinin, galangin, scopoletin, hesperitin, genistein, daidzein, esculatin, taxifolin, naringenin and celecoxib, was also examined [44]. When compared to the standard (8.30 kcal/mol; -34.73 kJ/mol), the chosen flavonoids had greater binding energies that ranged from 8.77 to 6.24 Kcal/mol (-36.69 to -26.11 kJ/mol). This resulted in the creation of powerful COX inhibitors for the treatment of inflammation.

Madeswaran *et al.* [45] used *in-silico* docking studies to assess the COX-inhibitory efficacy of flavonoids. They employed flavonoids such xanthotoxin, rutin, glaziovianin-A, gericudranin-B, and farobin-A in this context. Due to the structural characteristics of all the chosen flavonoids, their docking studies demonstrated that they all provided higher aldose reductase inhibitory action. Therefore, more extensive research might result in the creation of powerful aldose reductase inhibitors for the management of diabetes.

In-silico docking investigations of the lipoxygenase-inhibitory activity of commercially available flavonoids were also reported by Madeswaran *et al.* [46]. In this light, they chose flavonoids for examination, including aromadedrin, eriodictyol, fisetin, homoeriodictyol, pachypodol, rhamnetin, robinetin, tangeritin, and theaflavin. Because of their structural characteristics, it was found that all of the chosen flavonoids contributed to lipoxygenase-inhibitory action and the entire analysis may help in the future creation of effective medications for the treatment of inflammation. With the use of the molecular docking technique, Wu *et al.* research's on antiplatelet effects and preferential interaction of COX with flavonoids and

lignans. The flavonoids taken into account were ginkgetin, Taiwan-homo-flavone A, Taiwan-homo-flavone B and Taiwan-homo-flavone C, as well as eight well-known lignans from *Cephalotaxus wilsoniana* and Justicia species, including justicidin B, justicidin C, justicidin D, chinensinaphthol methyl ether, procumphthalide A, In terms of antiplatelet effects, ginkgetin, Taiwan-homo-flavone C, justicidin B and justicidin D were determined to be the most effective flavonoids [47].

Steroid-genesis Modulators: Three steroid-genesis pathway enzymes - 3-hydroxysteroid dehydrogenase (HSD), 17-hydroxysteroid dehydrogenase and aromatase can be inhibited by abyssinones and related flavonoids [48]. The virtual screening experiment found that flavonones had a stronger affinity than their corresponding chalcones. The flavonones are more effective steroidogenesis modulators in hormone-dependent malignancy and had consistent binding affinities to all three of the enzymes studied.

Xanthine Oxidase Modulators: Hypoxanthine is converted to xanthine by XO, which then catalyses the conversion of xanthine to uric acid. Hyperuricaemia, or a rise in uric acid levels in blood serum, can cause serious problems such gout and kidney stones [49, 50]. Alnajjar *et al.* [51] studied natural flavonoids in an effort to find a possible XO inhibitor. Licoisoflavone-A isolated from the roots of liquorice plant Glycyrrhiza glabra exhibited the strongest XO inhibitory action. Using *in-silico* docking experiments, Umamaheswari *et al.* [52] assessed the XO-inhibitory activity of flavonoids.

It was discovered that all of the flavonoids studied butein, fisetin, diosmetin, tricetin, genistein, tricin, vitexycarpin, herbacetin, biochanin, rhamnetin, isorhamnetin, robinetin, peonidin and okanin exerted inhibitory activity. Its XO-inhibitory action would have been enhanced by the presence of a benzopyran ring in its basic nucleus. For the prevention and treatment of gout and other associated inflammatory diseases, this molecular docking study may also result in the creation of strong XO inhibitors. Aldose Reductase inhibiting drugs are currently being developed and attempts are being made to evaluate them in preclinical and clinical settings. Polycystic kidney disease (PKD), known as the "silent killer," has not yet been adequately treated. A unique strategy emphasising the importance of natural products as a top solution has been investigated [53]. Cystic fibrosis transmembrane conductance regulator, the important protein that causes PKD and its altered three-dimensional structure were the topic of molecular docking and in silico toxicity tests using flavonoids derived from plants. The findings suggested that flavonoids derived from plant sources might be used as prospective, all-natural medicinal agents to treat PKD.

With varying xanthine concentrations, Lin *et al.* conducted *in-vitro* kinetic investigations on several flavonoids acting as inhibitors. Studies on the kinetics of various flavonoids and xanthine concentrations were conducted *in-vitro* [54]. Ninety-five percent ethanolic (v/v) gnaphalium affine extract contained four effective XO inhibitors. Comparing them to allopurinol, a well-known synthetic XO inhibitor, the flavone eupatilin had the best inhibitory impact on XO.

The inhibitory impact of gnaphalium affine extract on XO activity was additionally aided by apigenin, luteolin and 5-hydroxy-6, 7, 3′, 4′-tetramethoxyflavone. The traditional use of gnaphalium affine against gout is rationalised by this study. The aglycone hesperetin and its glycosylated derivatives (hesperidin and G-hesperidin), as well as their effects on the plasma lipid profile and the oxidative-antioxidative system have been studied *in-vitro* for XO-inhibitory action in rats [55]. Following oral administration of these substances, the concentrations of the principal conjugated metabolites in rat plasma were also established. Hesperetin has been discovered to have a greater XO-inhibitor action than the glycosylate derivatives, according to reports.

Countering Antibiotic Resistance: In order to combat the issue of antibiotic resistance, β-ketoacyl acyl carrier protein synthase III (KAS III), which starts fatty acid synthesis in bacteria, is a significant target enzyme. Flavonoids like naringenin (5,7,4′-trihydroxyflavanone) and eriodictyol (5,7,3′,4′-tetrahydroxyflavanone) are effective antimicrobial inhibitors of *Staphylococcus aureus* KAS III, according to Lee *et al.*'s [56] research on the known flavonoid inhibitors of KAS III against the methicillin-resistant bacteria.

In-silico modelling and docking investigations of the superbug enzyme New Delhi metallo lactamase-1 (NDM-1), which is present in *Escherichia coli*, were conducted by Ganugapati *et al.* [57]. According to reports, this enzyme is a member of the metallo-lactamases B1 subclass and is known to cause resistance to common intravenous antibiotics. Utilizing the method of *in-silico* molecular docking, similar investigations on the suppression of NDM-1 in superbugs by flavonoids were conducted [58]. Since, there are currently no effective antibiotics to combat the NDM-1-positive pathogen, this study offers hints for further research into the molecular causes of NDM-1's extensive antibiotic resistance. This will speed up the search for new antibiotics to combat the NDM-1-positive strain in clinical trials. It was discovered that the flavonoids quercetin and penta-O-ethylquercetin may inhibit NDM-1.

Disease-combating Activity: Green tea flavonoids were investigated as potential insulin mimics by Ganugapati *et al.* [59]. Diabetes mellitus is a metabolic condition in which a lack of insulin prevents the entry of glucose, the body's main energy source, into the cells. According to the study, epicatechin functions as an activator of the insulin receptor and lessens the negative consequences of diabetes.

To anticipate the binding modes of flavonoid derivatives with the 2009 haemagglutinin 1 neuraminidase (H1N1) influenza virus, Lu & Chong [60] used computational methods. They optimised the X-ray crystal structure of the 2009 H1N1 influenza neuraminidase using molecular dynamics modelling methods. The twenty flavonoid derivatives were all shown to be effective at binding to the virus and inhibiting its activity. These results might be used to build a flavonoid derivative medication that could be used to treat H1N1 influenza.

Apigenin is a dietary flavonoid that has been shown by Cardenas *et al.* [61] to exert immune-regulatory function through a research on mice. A reduction in lipopolysaccharide-induced lung apoptosis and infiltration of inflammation, which resulted in the restoration of normal lung architecture, were all seen in the research on NF-κB luciferase transgenic mice. These findings highlight the functions of flavonoids in immunological regulation. A diet high in flavonoids has been linked to a lower risk of cardiovascular disease (CVD), according to Kim *et al.* [62]. The effects of a total and individual flavonoid diet were the focus of the investigation. Improved CVD risk factors were discovered to be related to higher flavonoid consumption. Citrus flavonoids' capacity to influence lipid metabolism and other metabolic factors associated with the metabolic syndrome was the main focus of Mulvihill *et al.*'s study [63]. Citrus flavonoids have recently come under the spotlight as prospective therapeutic agents for the management of metabolic dysfunction.

Dietary flavonoids are linked to a lower incidence of hypertension and CVD, according to observational studies conducted by Hügel *et al.* [64]. An all-flavonoid-class-rich diet that includes herbs and drinks enhances vascular health and lowers the risk of illness. It has been noted that their ingestion is linked to an improvement in endothelial function through the activation of protein kinase B (Akt) and vascular endothelial nitric oxide synthase. Seventy patients with stage-I hypertension and pre-hypertension were examined to determine the impact of regular quercitin consumption on blood pressure. Both office and ambulatory blood pressure were assessed. In individuals with hypertension, the blood pressure was shown to be lower [65].

According to recent reports, pelingo apples are full of nutrients that can significantly reduce *in-vitro* carcinogenesis and the expansion of human breast cancer cells [66]. Pelingo juice was found to promote autophagy, an increase in lipidated microtubule-associated protein-1 light chain-3β (LC3B), suppression of extracellular signal-regulated kinases 1/2 (ERK1/2) activity, and cell accumulation in the G_2/M phase of the cell cycle.

Therefore, it may be employed as a source of bioactive substances that have the potential to have chemopreventive effects. Through the analysis of randomised controlled studies, it has been found that consuming anthocyanins in their pure and extract forms significantly lowers LDL cholesterol without having any negative side effects [67]. Fenugreek seeds were tested for their impact on alcoholics' renal pathology using a rat *in-vivo*

experimental model [68]. Transmission electron microscopy was used to examine the impact of the various seed concentrations. Results indicated that kidney shape and function had improved and that cell degradation had decreased. The pinho (*Araucaria angustifolia*) seed's tannin-rich extract was discovered to inhibit α-amylase [69]. The ability of the same extract to inhibit pancreatic lipase was also investigated. For pancreatic lipase, an effective amount of inhibition was seen as well. The levels of TAG in mice were significantly decreased by the extract as well. These findings suggest that tannin may be a useful anti-obesity molecule [70]. *In vitro* aggregation and oligomerization of β-amyloid have been discovered to be inhibited by an extract of mixed polyphenolic chemicals from grape seeds, and behavioural impairments in a mouse model of AD have also been found to be improved [71].

Flavonoids have been studied by Paris *et al.* [72] and have been shown to reduce the synthesis of Alzheimer's amyloid protein (Aβ) through an NF-κB-dependent mechanism. It is widely recognised that neurofibrillary tangles and the buildup of Aβ peptides in the brain are the causes of AD [73, 74]. It has been established that some flavonoids, including genistein, quercetin, taxifolin, kaemferol, luteolin, apigenin, daidzein, aminogeneistein, α- and β-napthoflavone, can influence the formation of Aβ, which is thought to play a significant role in AD. The active site cleavage enzyme-1 (BACE-1) is the rate-limiting enzyme responsible for the synthesis of Aβ peptides. It has recently been proposed that flavonoids' Aβ-lowering effects are achieved by a direct suppression of BACE-1 activity [72].

It has been noted that a substantial link exists between flavonoids' ability to reduce A and their ability to inhibit NF-κβ activation, indicating that flavonoids work through NF-κβ-related pathways to stop Aβ synthesis in entire cells. It has been determined that NF-κβ-lowering flavonoids decrease BACE-1 transcription in human neural cells since NF-κβ has been proven to influence BACE-1 production.

New pharmacophore characteristics of flavonoids were discovered by Shimmyo *et al.* [75] while researching structure-activity connections in cell-free, cell-based and *in-silico* modalities. Their findings helped specific natural flavonoids (myricetin, quercetin, kaempherol, morin and apigenin) produce novel BACE-1 inhibitors for the treatment of AD. In order to investigate the action of various natural and synthesised flavones and flavonols against radio ligand binding to human cloned muscarinic receptors, Swaminathan *et al.* The possibility of treating AD with muscarinic acetylcholine receptor-active substances has been discussed [76].

According to their research, a number of flavonoids compounds have competitive binding affinities that are equivalent to those of acetylcholine. According to research using molecular modelling, the chemicals mostly interact non-polar with the receptor's orthosteric site to bind there. Furthermore, it is noted that no appreciable energy differences were found for the binding of the active compounds compared to the inactive compounds due to limitations in the docking and scoring systems utilised. The possibility of using flavonoid compounds to treat AD is suggested by these findings [77].

Antioxidant Effect: Although flavonoids have a wide range of biochemical characteristics, their ability to function as antioxidants is the one that practically every category of flavonoids is most known for. The positioning of functional groups around the nuclear structure affects flavonoids' antioxidant action. Numerous aspects of antioxidant activity, including the capacity to scavenge free radicals and chelate metal ions, are significantly influenced by the structure, substitution, and total quantity of hydroxyl groups. Because it gives hydroxyl, peroxyl and peroxynitrite radicals hydrogen and an electron to stabilise them and create a rather stable flavonoid radical, the B ring hydroxyl configuration is the most important factor in scavenging ROS and RNS [78].

Antioxidant activity can be mediated by a number of different mechanisms, such as: (1) scavenging ROS; (2) upregulating or protecting antioxidant defences; and (3) suppression of ROS synthesis, either by inhibiting enzymes or by chelating trace elements involved in free radical creation. Most of the aforementioned processes have a role in flavonoid activity. Some of the effects they mediate

could be the consequence of a synergistic interplay between their radical scavenging capacity and interactions with enzyme activities. Microsomal monooxygenase, glutathione S-transferase, mitochondrial succinoxidase, NADH oxidase, and other ROS-producing enzymes are all inhibited by flavonoids [79].

Oxidative stress often leads to lipid peroxidation as a result. By using a number of ways, flavonoid defends lipids from oxidative degradation. By reducing hydrogen peroxide and producing the very reactive hydroxyl radical, free metal ions promote the production of reactive oxygen species (ROS). Flavonoids (Fl-OH) are able to diminish highly oxidising free radicals such superoxide, peroxyl, alkoxyl and hydroxyl radicals through hydrogen atom donation due to their lower redox potential.

Flavonoids have the ability to chelate metal ions (copper, iron, *etc*.), which helps to prevent the production of free radicals. Particularly quercetin is renowned for its abilities to stabilise and chelate iron. At particular locations on the various rings of flavonoid structures, trace metals bind [80].

Future Research and Development: Over the past ten years, flavones have attracted a lot of interest in the literature and a number of possible positive effects have been clarified. However, some investigations that were conducted included *in-vitro* and *in-silico* research. Therefore, more research is required to increase the value of flavones in the diet and promote human health. Because of the variety of the many molecular structures and the lack of information on bioavailability, studying flavones is difficult.

Additionally, it is difficult to evaluate objective end goals because there aren't enough tools available to assess oxidative damage *in-vivo*. To enable the gathering of additional information on absorption and excretion, analytical procedures must be improved. Particularly less information exists on the long-term effects of chronic flavone consumption. Numerous papers have emphasised the need for molecular docking studies to locate prospective flavone compounds for use in treating a range of illnesses in the human healthcare system. Future study should focus on how flavones interact with receptor molecules to treat both acute and chronic illnesses. To replace the usage of synthetic drugs that are damaging to the body, further study is required to find new flavones from the abundance of nature. Research and development initiatives incorporating *in-vivo* investigations are required in this position in order to provide a positive and secure prospective for the future. Though it is still too early to prescribe daily flavone intakes, it is now advised to consume fruit, vegetables, and drinks that contain flavones.

CONCLUSION: We tried to offer several flavone synthesis strategies in this review. Additionally, these findings offer fresh information on pharmacological activity resulting from flavones as well as upcoming research and development initiatives. Researchers in this discipline will determine the most effective strategy with the aid of this review. The results show that flavones may be readily synthesised and functionalized. The current review has demonstrated that a variety of flavone derivatives with academic and therapeutic value may be effectively synthesised using flavones. Compounds containing flavones can perform a variety of functions. As a result, utilising substituted flavones and an appropriate heterocycle as a basic moiety, synthetic scientists and chemists have a lot of freedom to construct novel compounds with a variety of substitutions. It is still possible to do research on this ring and examine the potential therapeutic benefits of the flavone moiety.

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