# Therapeutic Potential of Polyphenols and Flavonoids for Asthma: A Structural Activity and Mechanistic Perspective

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**Abstract**

Polyphenols and flavonoids constitute a class of copious secondary metabolites found in numerous plant sources. Various biological properties, including anti-inflammatory and anti-allergic effects, have been attributed to them, making them a potential candidate for the treatment of asthma. To comprehend the mechanism behind their antiasthmatic activity and enhance their efficacy, structure-activity relationship (SAR) research has been conducted. According to SAR investigations, the presence of hydroxyl groups on the B- and C-rings of flavonoids is essential for their anti-inflammatory and anti-allergic properties and anti-allergic effects, have been attributed to them, making them a potential candidate for the treatment of asthma. To comprehend the mechanism behind their antiasthmatic activity and enhance their efficacy, structure-activity relationship (SAR) research has been conducted. According to SAR investigations, the presence of hydroxyl groups on the B- and C-rings of flavonoids is essential for their anti-inflammatory and anti-allergic properties. The degree of hydroxylation and the location of the hydroxyl groups are crucial in determining the flavonoid's activity. Important for the activity is the presence of a catechol or pyrogallol group in the B-ring. In contrast, the presence of hydroxycinnamic acid in the structure of polyphenols is crucial for their activity. SAR studies also indicate that the substitution pattern and location of the hydroxyl groups on the cinnamic acid moiety are crucial for the activity of polyphenols. These SAR studies have yielded insights into the mechanism underlying the antiasthmatic activity of polyphenols and flavonoids, which could aid in the development of more effective natural treatments for asthma.

**Keywords:** Asthma, Polyphenol, Flavonoid, SAR, pharmacokinetic, secondary metabolite.

## Prevalence and side effect of synthetic drugs on asthma

Asthma affects individuals of all ages, races, and ethnicities on a global scale. WHO estimates that 235 million individuals worldwide suffer from asthma. Asthma is more

prevalent in affluent nations. The prevalence of asthma in infants is 10% worldwide. The precise cause of asthma is unknown, but genetic and environmental factors may be involved.

Common asthma treatments include corticosteroids, bronchodilators, and leukotriene modifiers. The side effects of these asthma medications include migraines, nausea, vomiting, vertigo, and tremors. Long-term use can result in osteoporosis, cataracts, and suppression of the adrenal glands. Some patients may also develop treatment resistance due to these medications[1].

Consequently, alternative asthma remedies with fewer adverse effects are required. The antiasthmatic structural characteristics of polyphenols and flavonoids have been identified through SAR research. Understanding natural product SAR may facilitate the development of antiasthmatic medications that are more effective, selective, and have fewer side effects than synthetic therapies[2].

**Need of SAR to improve activity**

Given the difficulties associated with natural products, the use of SAR in the development of natural product-based pharmaceuticals for the treatment of asthma is especially essential. Typically, natural products are complex assemblages of compounds, making isolation and purification challenging. In addition, natural products can be chemically unstable and have low bioavailability, limiting their effectiveness. By analysing the SAR of natural products, it is possible to identify the main components responsible for the observed activity and to modify these components to improve efficacy and surmount the challenges associated with drugs derived from natural products. For the rational design and optimisation of natural product-based pharmaceuticals for the treatment of asthma, SAR is an essential instrument.[3]

**Challenges in the role of secondary metabolite for treatment of asthma**

Polyphenols and flavonoids have therapeutic potential for asthma. Natural asthma treatments are attractive due to the abundance and diversity of secondary metabolites in plants, their potential for fewer adverse effects than synthetic drugs, and their ability to act on multiple locations for a synergistic effect. Natural products are also less expensive, particularly in developing nations[4].

Secondary metabolites for the treatment of asthma have disadvantages. The production of natural products lacks standardisation and quality control, resulting in variations in composition and potency. This affects the safety and efficacy of natural products. The modes of action of natural products are inadequately understood, making dosing and drug interactions unpredictable. Natural products may not be appropriate for all individuals, particularly those with severe or acute asthma who require more potent treatments.[5]

**Pharmacokinetics of polyphenols and flavonoids**

The pharmacokinetics of polyphenols and flavonoids can vary significantly based on the specific compound and administration route. The gastrointestinal tract does not adequately absorb the majority of these substances, and their bioavailability is typically low. This is due to their limited solubility in water and susceptibility to breakdown by digestive and hepatic enzymes. Nevertheless, a number of investigations have demonstrated that certain flavonoids can be absorbed in the small intestine via passive diffusion or active transport mechanisms. After absorption, they can be metabolised by the liver and eliminated via urine or bile. Depending on the specific compound, the elimination half-life of polyphenols and flavonoids can range from a few hours to several days. In addition, the pharmacokinetics of these compounds can be affected by age, gender, and concomitant

administration of other pharmaceuticals. In general, the pharmacokinetics of polyphenols and flavonoids are complex and highly variable based on the specific compound and route of administration[6].

**Role of polyphenols and flavonoids in prevention of asthma**

Polyphenols, a class of naturally occurring compounds found in various plant-based foods, have been shown to exhibit antiasthmatic properties. Several studies have reported the beneficial effects of polyphenols in preventing and reducing the symptoms of asthma, including inflammation, oxidative stress, and airway hyperresponsiveness. The anti-inflammatory properties of polyphenols are mainly attributed to their ability to inhibit the production and release of pro-inflammatory mediators, such as cytokines, chemokines, and leukotrienes, which are known to contribute to the pathogenesis of asthma. In addition, polyphenols can also modulate the expression of genes involved in the inflammatory response, thereby reducing the overall inflammation in the airways.

Another mechanism through which polyphenols exert their antiasthmatic effects is by reducing oxidative stress. Polyphenols act as potent antioxidants, scavenging free radicals and reactive oxygen species that contribute to oxidative damage in the airways. This antioxidant activity is attributed to the presence of hydroxyl groups in the polyphenolic compounds, which can donate electrons to neutralise free radicals. By reducing oxidative stress, polyphenols can prevent airway damage and inflammation, which are characteristic features of asthma.

Moreover, polyphenols also exhibit bronchodilatory effects, which can help alleviate the symptoms of asthma. They can relax the airway smooth muscle, thereby improving airway function and reducing airway hyperresponsiveness. This effect is mainly attributed to the ability of polyphenols to increase the production of nitric oxide, a potent vasodilator that helps relax the smooth muscles in the airways[7].

**6-Shogaol**

Ginger (Zingiber officinale) contains the phenolic molecule 6-shogaol, which inhibits leukotrienes and airway remodelling. It has a phenyl ring with hydroxyl and methoxy groups and is created by dehydrating 6-gingerol, another ginger derivative. The addition of a hydrocarbon chain of variable length to the six-carbon chain determines the gingerol or shogaol type. Its chemical formula and weight are $C_{17}H_{24}O_3$ and 276.38 g/mol, respectively. Its chemical composition and properties resemble gingerols.[8–10]

Yocum G. T. et al. (2019) showed that 6-shogaol inhibits leukotriene synthesis enzymes in human bronchial epithelial cells and reduces airway inflammation and remodelling in a mouse model of asthma. By inhibiting leukotriene synthesis, 6-shogaol decreased airway hyperresponsiveness[11], inflammation, and mucus hypersecretion in asthmatic rodents[12]. Inhibiting leukotriene, 6-shogaol may reduce airway inflammation and remodelling. In one study, replacing the unsaturated ketone group of 6-shogaol with a saturated one significantly decreased its inhibitory activity against COX-2[13]. D. Nedungadi et a, l., 2018observed that removing the unsaturated ketone group from 6-Shogaol decreased its ability to inhibit the proliferation of cancer cells[14].

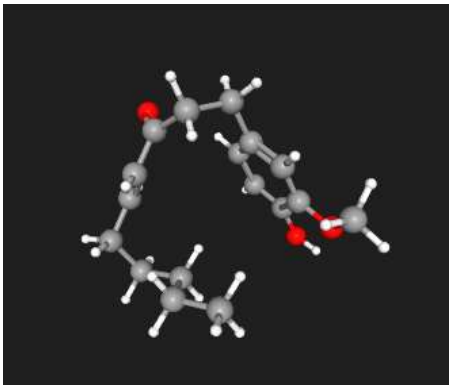

**Fig 1:** Ball and stick model 3-D Structure of Shaogaol

**Apigenin**

Apigenin is prevalent in oranges, parsley, chamomile, celery, and thyme. Flavones have two benzene rings and a ketone group, 15 carbon, 10 hydrogen, and 2 oxygen atoms make up apigenin. It has the formula $C_{15}H_{10}O_5$ and a mass of 270.24 g/mol. The yellow crystalline substance is soluble in both acetone and ethanol but insoluble in water.[15]

In a published study investigated the SAR of the apigenin derivatives regarding asthmatic conditions. In mice with ovalbumin-induced asthma, numerous apigenin derivatives were evaluated for their effects on airway hyperresponsiveness and inflammation[16]. Apigenin-7-O-glucuronide is more effective against asthma than apigenin. Apigenin-7-O-glucuronide decreased airway hyperresponsiveness and inflammatory cell infiltration in lung tissue significantly. Apigenin-7-O-glucuronide's enhanced anti-asthmatic activity was due to its -glucuronide group.[17]

Chen et al. examined the anti-asthmatic effects of multiple apigenin derivatives in mice with ovalbumin-induced asthma in 2020. Apigenin-7-O-l-rhamnopyranosyl-(12)-D-glucopyranoside demonstrated the highest anti-asthmatic activity among the compounds examined. In the airways of rodents, Apigenin-7-O-l-rhamnopyranosyl-(12)-D-glucopyranoside reduced inflammation, mucus secretion, and hyperresponsiveness. Researchers believed that the moiety of apigenin-7-O-l-rhamnopyranosyl-(12)-D-glucopyranoside was responsible for its enhanced anti-asthmatic activity[18].

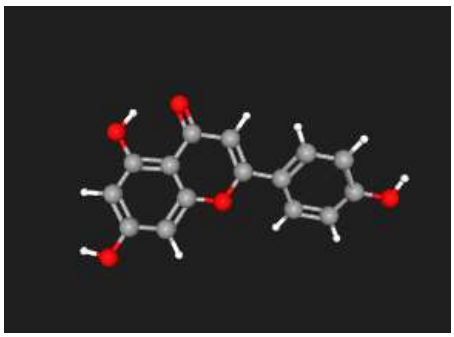

Fig 2: Ball and stick model 3-D Structure of Apigenin

**Baicalein**

Baicalein is found in the roots of the Chinese medicinal herb Scutellaria baicalensis. The levels of Thymus vulgaris and Oroxylum indicum are lower. Baicalein is $C_{15}H_{10}O_5$ and 270.24 g/mol in mass. It is soluble in heated water, ethanol, and DMSO, but insoluble in cool water and ether[19].

Two benzene rings (A and B) are connected by a heterocyclic pyran ring (C ring) in baicalein. The rings A and B contain hydroxyl groups in positions 5 and 7, respectively.

Carbonyl and hydroxyl groups are located at positions 4 and 6 on the C structure. The hydroxyl and carbonyl groups of baicalein bond metal ions and neutralise free radicals.[20]

In order to combat asthma, baicalein modulates inflammation, oxidative stress, and airway hyperresponsiveness (AHR). Numerous studies have investigated baicalein derivative SAR for asthma. Some examples:

In 2014, Lago J.H.G. et al. evaluated several baicalein compounds in a mouse model of ovalbumin-induced asthma. Compared to baicalein, derivatives with a hydroxyl group at position 6 of the A ring were more anti-inflammatory and anti-AHR. Compounds with two hydroxyl groups at positions 5 and 7 of the B ring exhibited the greatest anti-inflammatory and anti-AHR properties. The antiasthmatic activity of baicalein and its derivatives was linked to their hydroxyl groups at positions 5, 6, and 7.[21]

In 2011, González, R et al. explored the anti-inflammatory and anti-AHR effects of baicalein derivatives in a mouse model of OVA-induced asthma. The derivatives with a hydroxyl group in position 5 of the A ring and a methoxyl group in position 6 of the B ring exhibited the most potent anti-inflammatory and anti-AHR activity. According to the researchers, the methoxyl group at position 6 of the B ring increased the lipophilicity and bioavailability of baicalein, thereby enhancing its antiasthmatic activity[21,22].

In order to treat asthma, baicalein modifies the NF-B, MAPK, and PI3K/Akt signalling pathways and regulates cytokines, chemokines, and other inflammatory mediators. Baicalein reduces reactive oxygen species and proinflammatory cytokines and possesses antioxidant and anti-inflammatory properties.[23,24]

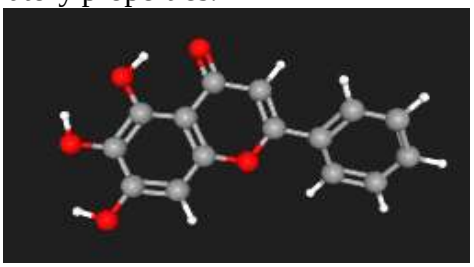

Fig 3: Ball and stick model 3-D Structure of Baicalein

**Caffeic acid**

A natural phenolic molecule, caffeineic acid is found in plants, particularly fruits, vegetables, and grains. It is present in coffee, wine, and tea. Caffeic acid has the formula $C_9H_8O_4$ and a molecular weight of 180.16 g/mol. The white to yellow substance is soluble in water, ethanol, and ether, and it melts between 223-225 degrees Celsius[25].

Caffeic acid is a hydroxycinnamic acid consisting of a hydroxyl (-OH) and carboxylic acid (-COOH) group linked to an unsaturated hydrocarbon chain with a double bond between positions 3 and 4 (trans-cinnamic acid). The first hydroxyl group of the aromatic ring is phenolic. Ferulic acid and p-coumaric acid have a similar chemical structure to caffeine.[26]

Antiasthmatic properties of caffeine and its derivatives have been investigated. Caffeic acid derivative SAR examples: In 2008, Jung W. K. et al. investigated the anti-inflammatory and anti-asthmatic effects of caffeic acid derivatives in an ovalbumin-induced mouse model of asthma[27]. The derivatives with hydroxyl groups in position 3 of the A ring and methoxyl groups in position 4 of the B ring exhibited the greatest anti-inflammatory and anti-asthmatic activity. According to the researchers, the methoxyl group at position 4 enhanced lipophilicity and bioavailability, thereby enhancing anti-asthmatic activity.[28]

In 2022, Huwang W. Y. et al. investigated the anti-inflammatory and anti-asthmatic effects of various caffeic acid derivatives in a mouse model of asthma induced by lipopolysaccharide (LPS) and ovalbumin (OVA). The derivatives with hydroxyl groups in position 3 of the A ring and methoxyl groups in position 4 of the B ring exhibited the greatest

anti-inflammatory and anti-asthmatic activity. According to the researchers, the methoxyl group at position 4 improved derivative stability, potency, and anti-asthmatic activity.[29]

Caffeic acid and its derivatives may alleviate asthma by modulating inflammation, oxidative stress, and airway hyperreactivity signalling pathways and gene expression. Caffeic acid and its derivatives inhibit proinflammatory cytokines such as TNF- and IL-6, decrease ROS and oxidative stress, and decrease airway hyperresponsiveness genes. These properties may aid in the treatment of asthma by caffeic acid and its derivatives.[27]

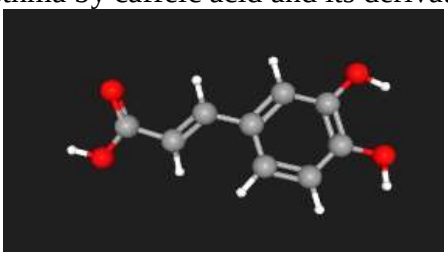

Fig 4: Ball and stick model 3-D Structure of Caffeic acid

**Chrysin**

Chrysin, a flavone molecule found in honey and propolis, is a naturally occurring constituent of vegetation. It is present in passionflower, chamomile, and blue passionflower.

Chrysin has the formula $C_{15}H_{10}O_4$ and a molecular weight of 254.24 g/mol. This substance is insoluble in water, but soluble in ethanol, ether, and chloroform. Chrysin is similar to both apigenin and luteolin[30].

Chrysin is a flavone that consists of two benzene rings and one pyrone ring. It contains a hydroxyl group (-OH) on the fifth position of the A ring and a ketone group (C=O) on the fourth position of the C ring. The B ring of chrysin has two phenolic hydroxyl groups at positions 7 and 5'.

In 2016, Yao J. et al. investigated the anti-inflammatory and anti-asthmatic effects of chrysin in an OVA-induced asthma mouse model. Chrysin significantly reduced airway hyperreactivity, inflammatory cell infiltration, and cytokine levels, including IL-4, IL-5, IL-13, and TNF. According to the study, chysin reduced inflammation and oxidative stress by inhibiting the NF-B pathway and upregulating the Nrf2 pathway[31].

In 2017, a published study investigated the anti-inflammatory and anti-asthmatic effects of numerous chrysin derivatives in an OVA-induced asthma mouse model. According to the study, chrysin derivatives with hydroxyl groups at position 7 and methoxyl groups at position 5' had the greatest anti-inflammatory and anti-asthmatic effect. According to the researchers, the hydroxyl group at position 7 and the methoxyl group at position 5' increased the lipophilicity and bioavailability of the derivatives, thereby enhancing their anti-asthmatic activity[22].

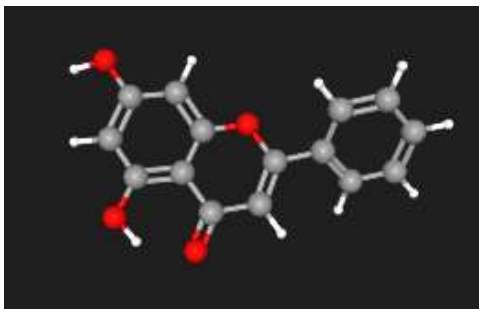

Fig 4: Ball and stick model 3-D Structure of Chrysin

**Diosmin**

Diosmin is a flavonoid glycoside derived from citrus fruits such as oranges, lemons, and grapefruits, as well as Teucrium gnaphaloides vegetation. It is found in herbal and dietary supplements.

The flavone backbone of diosmin contains two benzene rings and a pyrone ring. It contains a hydroxyl group (-OH) on the fifth position of the A ring and a ketone group (C=O) on the fourth position of the C ring. The B ring of diosmin has two phenolic hydroxyl groups at positions 7 and 3'. In addition, position 7 of the flavone backbone contains rutinose.[32]

In 2015, Imam F. et al. investigated the effects of diosmin on asthma-induced airway inflammation and hyperresponsiveness in rodents. Diosmin significantly reduced airway inflammation, eosinophil infiltration, and cytokine levels, such as IL-4, IL-5, IL-13, and TNF. Diosmin inhibited the release of acetylcholine and increased cAMP to decrease airway hyperresponsiveness. It was believed that the antiasthmatic effect of diosmin was due to suppression of the Th2 immune response and modulation of the cAMP/PKA pathway[33].

The 2022 study by Huwait, E. et al. examined the antiasthmatic effects of diosmin derivatives in rodents. According to the study, antiasthmatics with a 4-nitro group attached to the B ring were the most effective. The 4-nitro group stimulated the Nrf2 pathway and inhibited the NF-B pathway, thereby enhancing the anti-inflammatory and antiasthmatic properties of the derivatives[34].

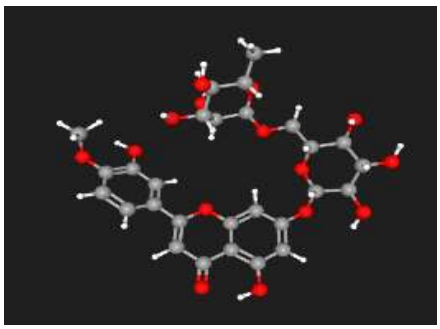

Fig 5: Ball and stick model 3-D Structure of Diosmin

**Ellagic acid**

Pomegranates, strawberries, raspberries, blackberries, walnuts, and grapes contain the polyphenolic substance elagic acid. It is found in Terminalia chebula and Phyllanthus emblica, two medicinal plants.

Ellagic acid has a polyphenolic core structure composed of two hexahydroxydiphenic acid (HHDP) units linked by a C-C bond. At C-1 and C-2 of the ellagic acid core, two gallic acid units replace the HHDP units. The B and D rings of the core structure contain four hydroxyl groups (-OH). Few Ellagic acid derivative SAR asthma trials exist. According to some research, elagic acid may have antiasthma properties[35].

In 2020, Balkrishna A. et al. investigated Divya-Swasari-Ras, alleviates chronic inflammation and suppresses airway remodelling in mouse model of allergic asthma by modulating pro-inflammatory cytokine response. Ellagic acid diminished considerably airway hyperresponsiveness, eosinophil infiltration, and cytokine levels, including IL-4, IL-5, and IL-13. Ellagic acid also decreased airway remodelling by decreasing TGF-1 and collagen deposition in the lungs. It was believed that the antiasthmatic effects of elagic acid were due to airway remodelling and Th2 immune suppression.[36]

The 2019 study by Bui T. T. et al. examined the asthma-fighting efficacy of ellagic acid in rodents. Ellagic acid reduced eosinophil infiltration, inflammation, and mucus production in the lungs. Ellagic acid decreased IL-4, IL-5, and IL-13 expression and phosphorylation of the MAPK signalling pathway. According to the study, elagic acid inhibited the Th2 immune response and suppressed MAPK signalling pathways to treat asthma[37].

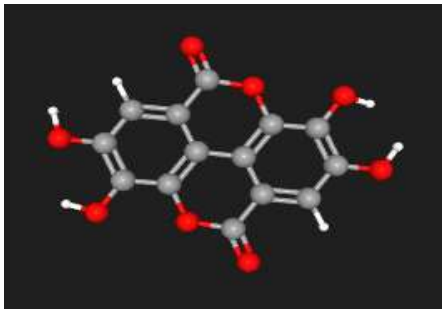

Fig 6: Ball and stick model 3-D Structure of Ellagic acid

**Epigallocatechin gallate (EGCG)**

EGCG is a subclass of flavonoids known as a flavanol. It's found in green tea. Up to 50% of the catechins in green tea are EGCG.

The primary structure of EGCG consists of two aromatic rings (A and B) connected by a three-carbon linkage. The core structure is replaced by three hydroxyl groups (-OH) at the B ring's 3', 4', and 5' positions and a galloyl group ($-C_6H_2(OH)_3COOH$) at the C ring's 3 position. "Gallate" is the galloyl group of EGCG. [38]

In 2018, Shan L. et al. examined the effects of EGCG on the asthma-induced inflammation of mouse airways. EGCG significantly reduced airway hyperreactivity, eosinophil infiltration, and cytokine levels, including IL-4, IL-5, and IL-13. Additionally, EGCG inhibited NF-B signalling and lung adhesion molecules. It was believed that EGCG's antiasthmatic effect was due to NF-B signalling pathway suppression and adhesion molecule inhibition.[39]

The 2022 study by N. Yang et al. examined the asthma-fighting efficacy of EGCG in rodents. EGCG reduced eosinophil infiltration, airway inflammation, and mucus production in the lungs. EGCG inhibited the expression of IL-4, IL-5, and IL-13 as well as the phosphorylation of the MAPK signalling pathway. According to the study, EGCG suppressed Th2 immune response and inhibited MAPK signalling pathways to treat asthma[40].

In 2019, Zang M. and colleagues investigated the anti-inflammatory and anti-cancer effects of EGCG glycosylation. The 3'- or 4'-position glycosylation of EGCG enhanced its stability and solubility, thereby enhancing its bioactivity. The researchers hypothesised that EGCG glycosylation could improve the pharmacokinetics of EGCG-based treatments[41].

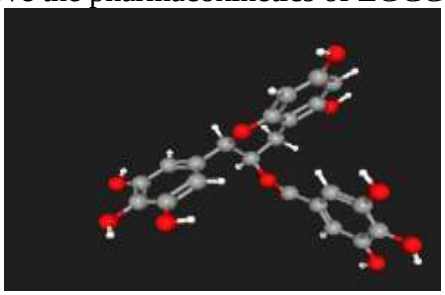

Fig 7: Ball and stick model 3-D Structure of Epigallocatechin gallate

**Eriodictyol**

Eriodictyol is a flavanone flavonoid. Lemons, limes, and oranges contain it naturally. Several herbs, including parsley, rosemary, and thyme, contain eriodictyol. Eriodictyol is a yellow crystalline substance weighing 286,24 g/mol. The flavanone backbone of $C_{15}H_{12}O_6$ contains two hydroxyl groups at positions 5 and 7 on the A-ring.[42]

Eriodictyol significantly reduced airway inflammation and hyperresponsiveness in mice and improved lung function. Eriodictyol inhibited pro-inflammatory cytokines such as IL-6 and TNF- in the pulmonary tissue of rodents[21].

Eriodictyol reduced inflammation, collagen deposition, and smooth muscle hypertrophy in mouse airways. The ability of eriodictyol to reduce inflammatory mediators

such as IL-13 and TGF- in lung tissue may account for its anti-inflammatory and anti-remodeling properties.[43]

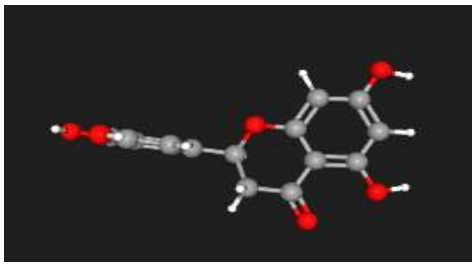

Fig 8: Ball and stick model 3-D Structure of Eriodictyol

**Fisetin**

The flavonoid fisetin is a naturally occurring flavonol. It is present in strawberries, apples, scallions, melons, botanicals, and supplements. Fisetin contains hydroxyl groups on the A, B, and C rings of its flavone backbone. Its chemical formula and weight are $C_{15}H_{10}O_6$ and 286.24 g/mol. The antioxidant, anti-inflammatory, and anticancer properties of fisetin.

SAR research has investigated the chemical structure and biological actions of fisetin. The antioxidant activity of a variety of structurally similar flavonoids, including fisetin, and identified significant structural characteristics[44].

The study found that antioxidant activity was dependent on hydroxyl groups on the A and B rings of the flavonoid backbone, as well as catechol groups on the B ring. Also required for antioxidant activity was a double bond between carbons 2 and 3 in the C ring.

Molecules examined the anti-inflammatory properties of fisetin in an animal model of asthma. In rodents, fisetin decreased airway inflammation and improved lung function, suggesting that it could be used to treat asthma. The antiasthmatic SAR of fisetin requires additional research.

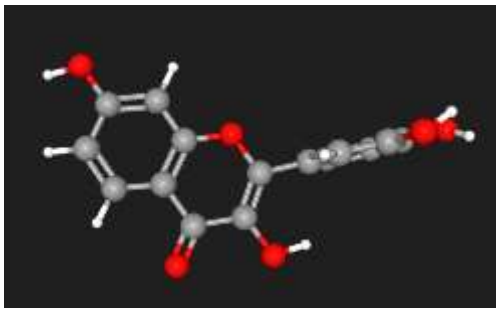

Fig 9: Ball and stick model 3-D Structure of Fisetin

**Genistein**

The isoflavone genistein is found in soybeans, chickpeas, and other legumes. It is a phytoestrogen that mimics the actions of oestrogen. Genistein has a molecular formula of $C_{15}H_{10}O_5$ and a weight of 270.24 g/mol. Two aromatic rings (A and B rings) and two hydroxyl groups (OH) on the A ring are linked by a heterocyclic pyran ring (C ring).[45]

Adding hydroxyl or methoxy groups to the genistein A ring increased its antiasthmatic efficacy, according to the study.[21]

As genistein inhibited inflammatory cytokines and chemokines, it may be used to treat asthma.

SAR investigations have revealed that hydroxyl groups on the A ring of the genistein molecule are crucial for its biological activity, which includes anti-inflammatory and antioxidant properties. A hydroxyl group at position 7 on the A ring is required for estrogenic activity, while a hydroxyl group at position 4' on the B ring is necessary for anticancer activity.

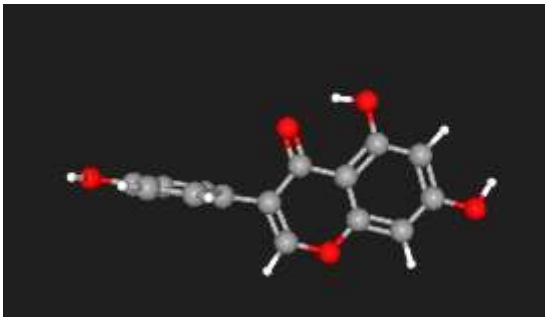

Fig 10: Ball and stick model 3-D Structure of Genistein

**Isoliquiritigenin**

The flavonoid isoliquiritigenin is found in licorice (Glycyrrhiza glabra) and other plants like Sophora flavescens and Belamcanda chinensis. It has a chalcone unit on its flavanone skeleton. A and B are phenyl rings, while C is a six-membered heterocyclic ring containing one oxygen and two carbon elements. Isoliquiritigenin has the formula $C_{15}H_{12}O_4$ and a molecular mass of 256.25 g/mol.[46]

In a study, researcher investigated the anti-inflammatory properties of isoliquiritigenin and its derivatives using an in vitro asthma model. Adding hydroxyl or methoxy groups to the A and B rings of the isoliquiritigenin molecule increased its anti-inflammatory efficacy, according to the study. The hydroxyl group in position 4' of the B ring is essential for its anti-inflammatory properties.[47]

In a 2013 European Journal of Medicinal Chemistry study, isoliquiritigenin and its derivatives were evaluated in an asthma animal model. Adding a hydroxyl or methoxy group at position 6 of the isoliquiritigenin A ring increased its antiasthmatic activity, according to the study[48].

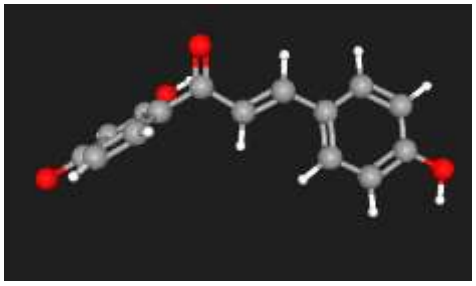

Fig 11: Ball and stick model 3-D Structure of Isoliquiritigenin

**Luteolin**

Luteolin is a flavone found in parsley, thyme, broccoli, and peppermint. Oranges, lemons, and grapes contain it. It has hydroxyl (-OH) groups and a double bond between carbon atoms 2 and 3 in its flavone skeleton. A and B are phenyl rings, while C is a six-membered heterocyclic ring containing one oxygen and two carbon elements. Luteolin has the formula $C_{15}H_{10}O_6$ and a molecular weight of 286.24 g/mol[49].

Luteolin possesses antioxidant, anti-inflammatory, anti-cancer, and neuroprotective properties. Because it decreases airway inflammation and bronchial hyperreactivity, it has been investigated as a potential asthma treatment. The SAR and antiasthmatic potential of luteolin have been investigated[50]. Some findings:

- In mice with allergic asthma, luteolin inhibits pro-inflammatory cytokines including IL-4, IL-5, and IL-13 to decrease airway inflammation and bronchial hyperresponsiveness.
- Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B), a transcription factor that promotes pro-inflammatory gene expression, is inhibited by luteolin.
- Anti-inflammatory properties of Luteolin are dependent on hydroxyl groups. At positions 5, 7, and 3',4', hydroxyl groups limit NF-B activation.

- The double bond between carbon atoms 2 and 3 in Luteolin has a similar anti-inflammatory effect. Saturated C2-C3 luteolin analogues inhibited NF-B activation and pro-inflammatory cytokine secretion less effectively. - The hydroxyl group on luteolin's B ring is responsible for its bronchodilatory properties. Analogues of luteolin with hydroxyl groups at position 5' or on the B ring reduced the relaxation of airway smooth muscle cells.

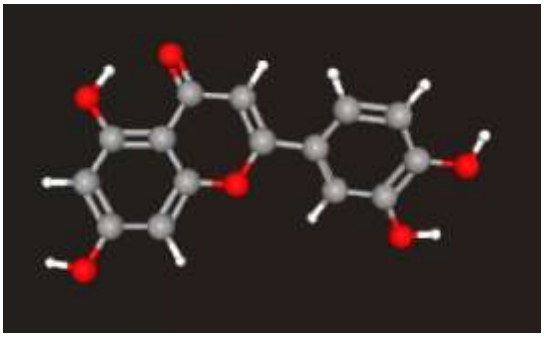

Fig 12: Ball and stick model 3-D Structure of Luteolin

**Myricetin**

Flavonoids are polyphenolic flavonol substances, such as myricetin. It is present in berries, grapes, onions, kale, parsley, and tea. $C_{15}H_{10}O_8$ has a molecular weight of 318.24 g/mol. Three hydroxyl groups (-OH) attached to the B ring of the flavonol structure confer antioxidant and anti-inflammatory properties to myricetin. It has been examined for its anti-cancer, anti-diabetic, and neuroprotective properties. In addition to reducing airway inflammation and hyperresponsiveness, myricetin is an effective asthma treatment[51].

Myricetin's structure-activity relationship (SAR) for anti-inflammatory and anti-asthmatic properties has been examined using in vitro and in vivo models. Major findings:

Numerous hydroxyl groups on myricetin's B-ring contribute to its antioxidant and anti-inflammatory properties. According to studies, hydroxyl groups at positions 3', 4', and 5' are necessary to inhibit inflammatory mediators and oxidative stress.[52]

The catechol moiety of myricetin, which contains two adjacent hydroxyl groups at positions 3 and 4, is also anti-inflammatory. • Glycosylation: The catechol moiety of myricetin can neutralise free radicals and inhibit pro-inflammatory enzymes, such as cyclooxygenase and lipoxygenase. The pattern of glycosylation influences the solubility, bioavailability, and action of myricetin. Myricetin-3-O-glucuronide is more effective at reducing inflammation than myricetin-3-O-rutinoside.

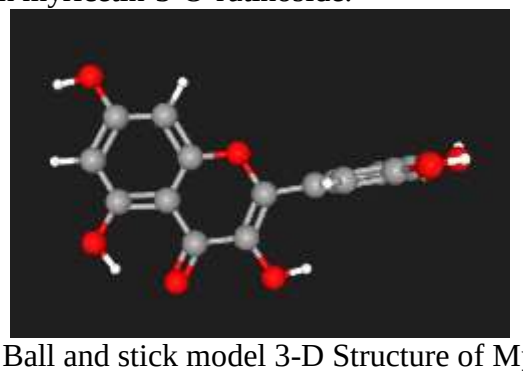

Fig 13: Ball and stick model 3-D Structure of Myricetin

**Naringenin**

Naringenin is a subclass of flavanone-containing flavonoids. It is present in a variety of fruits, including citrus, oranges, lemons, and tomatoes. The compound can also be found in herbs such as thyme, rosemary, and parsley. The molecular formula of naringenin is

$C_{15}H_{12}O_5$ and its molecular weight is 272.25 g/mol. Its chemical structure consists of a flavone backbone to which are affixed phenyl and hydroxyl groups[53].

It has been discovered that naringenin possesses anti-inflammatory and anti-allergic properties, making it a possible candidate for the treatment of asthma. Numerous investigations have investigated the antiasthmatic structure-activity relationship (SAR) of naringenin and its derivatives. In mice models, 7-O-alkylated derivatives of naringenin exhibited significant anti-inflammatory and anti-asthmatic effects, according to one study. The study also indicated that the anti-inflammatory activity of naringenin and its derivatives was associated with the suppression of pro-inflammatory cytokines such as IL-6 and TNF-.[54]

Another study examined the anti-asthmatic effects of naringenin using a mouse model of ovalbumin (OVA)-induced asthma. The study discovered that naringenin suppressed the expression of Th2 cytokines such as IL-4, IL-5, and IL-13, and reduced airway inflammation. In addition, the study suggested that the anti-inflammatory effects of naringenin were correlated with the inhibition of the NF-B signalling pathway.

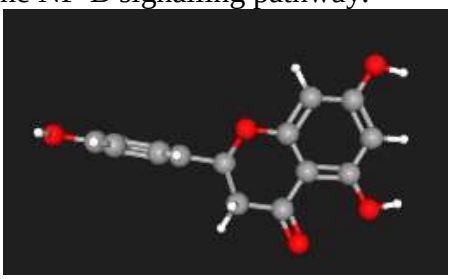

Fig 14: Ball and stick model 3-D Structure of Naringenin

**Nobiletin**

Peels of citrus fruits contain the flavonoid nobiletin. This substance is polymethoxylated flavone. The chemical structures of nobiletin and tangeretin, another citrus polymethoxylated flavone, are comparable. Nobiletin has the formula $C_{21}H_{22}O_8$ and a molecular weight of 402.38 g/mol. It is more soluble in lipids than in water due to its hydrophobic nature and many methoxy groups.[55]

By inhibiting airway inflammation, oxidative stress, and smooth muscle contraction, nobiletin may reduce asthma.

The structure-activity relationship (SAR) between nobiletin and its anti-asthmatic activity demonstrates that its numerous methoxy groups reduce airway inflammation and constriction. The 5,6,7,8-tetramethoxy group on the A-ring of nobiletin inhibits the production of pro-inflammatory cytokines such as IL-6, TNF-, and IL-1 in airway epithelial cells. Nobiletin's B-ring methoxy groups inhibit airway smooth muscle contraction by decreasing calcium ion input into muscle cells.

Nobiletin inhibited the nuclear factor-kappa B (NF-B) pathway and IL-4, IL-5, and IL-13 expression in an asthma mouse model to reduce airway inflammation and hyperresponsiveness. In a separate study, nobiletin reduced calcium ions entering airway smooth muscle cells, possibly by inhibiting voltage-gated calcium channels[56].

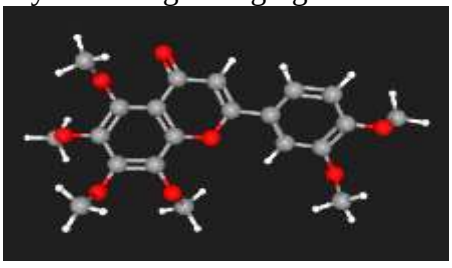

Fig 15: Ball and stick model 3-D Structure of Nobiletin

**Puerarin**

The rhizome of the traditional Chinese medicinal plant Pueraria lobata (kudzu vine) contains the isoflavone puerarin. It is used in traditional Chinese medicine to treat a variety of ailments. At position 7, the flavonoid puerarin contains a 3,4,5-trihydroxyphenyl group. Puerarin is $C_{21}H_{20}O_9$ and 416.38 g/mol in mass[57].

In preclinical studies, puerarin exhibited antiasthmatic properties. It decreases airway ROS and NO, inflammatory cytokines and chemokines, and the recruitment of inflammatory cells.

According to structure-activity relationship (SAR) investigations, the location and number of hydroxyl groups on the flavonoid skeleton and the presence of a 6'-O-xylosyl group influence the antiasthmatic activity of puerarin. Puerarin's anti-inflammatory effect in human lung epithelial cells required the presence of hydroxyl groups at positions 5 and 7 on the flavonoid skeleton. Another study discovered that the addition of a 6'-O-xylosyl group enhanced the anti-inflammatory and antioxidant properties of puerarin in vitro and in vivo[58].

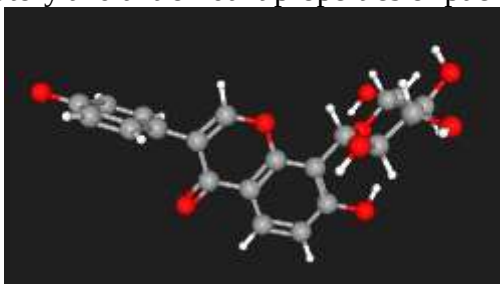

Fig 16: Ball and stick model 3-D Structure of Puerarin

**Quercetin**

The flavonoid quercetin is found in apples, berries, grapes, scallions, and kale. Tea and red wine are examples. The formula for quercetin is $C_{15}H_{10}O_7$ and its molar mass is 302.24 g/mol. Its crystals are insoluble in water but soluble in organic solvents such as ethanol.[59]

Quercetin possesses multiple antiasthmatic mechanisms. According to some studies, it may reduce airway inflammation and oxidative stress and inhibit bronchoconstriction. According to studies, the 3-hydroxyl and 4-oxo functional groups in quercetin are responsible for its antiasthmatic activity. Its abundance of hydroxyl groups may enhance its antioxidant and anti-inflammatory properties.[60,61]

According to a study published, quercetin reduced airway hyperresponsiveness, inflammation, and oxidative stress in a mouse model of allergic asthma. Inhibiting pro-inflammatory cytokines and NF-B activation, the study also demonstrated that quercetin may reduce asthma.[62]

Quercetin derivatives with altered hydroxyl groups improved pulmonary function and anti-inflammatory activity in an asthma mouse model. The study revealed that the antiasthmatic properties of quercetin may be dependent on its 5- and 7-hydroxyl groups.[63]

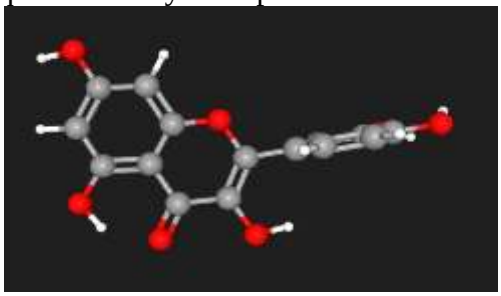

Fig 17: Ball and stick model 3-D Structure of Quercetin

**Resveratrol**

Grapes, berries, and legumes contain resveratrol, a naturally occurring polyphenol. The stilbenoid 3,5,4'-trihydroxy-trans-stilbene is phenolic. Plants generate phytoalexins like resveratrol after injury or illness. Resveratrol is found in grapes, pistachios, berries, and other plant-based foods. Due to its anti-inflammatory and antioxidant qualities, it may be used to treat asthma.[64]

Resveratrol controls asthmatic pathways, thereby preventing asthma. It has been demonstrated to decrease airway hyperreactivity, eosinophil recruitment, and inflammatory cytokines.

The SAR (structure-activity relationship) of resveratrol has been extensively studied, and structural changes affect its biological action. Resveratrol's anti-inflammatory and antioxidant properties may depend on its hydroxyl groups. The anti-asthmatic action of the molecule is dependent on its core trans double bond.[65]

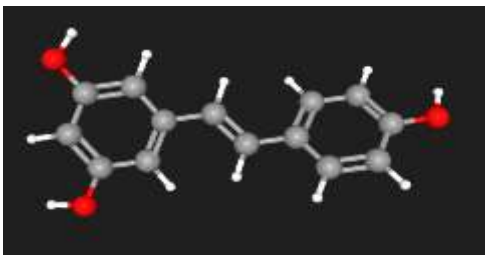

Fig 18: Ball and stick model 3-D Structure of Resveratrol

**Wogonin**

Flavonoids include wogonin. It is extracted from the Chinese skullcap (Scutellaria baicalensis) root. Wogonin possesses anti-inflammatory, anticancer, and antioxidant properties. Two benzene rings, a pyran ring, and hydroxyl and methoxyl groups are present. Wogonin is $C_{16}H_{12}O_5$ and has a molecular weight of 284.26 g/mol. It is faintly soluble in water, but soluble in ethanol and DMSO. It melts at 231-233 °C.[66]

The anti-asthmatic properties and SAR of Wogonin have been investigated in International Immunopharmacology. Wogonin dose-dependently reduced airway inflammation, mucus production, and hyperresponsiveness in an asthma mouse model. Wogonin's anti-inflammatory and anti-asthmatic properties are dependent on a 5,7-dihydroxyl group in its A ring, as indicated by its structure-activity relationship. Anti-asthmatic activity was also dependent on the C-4 carbonyl group of the C ring.[67]

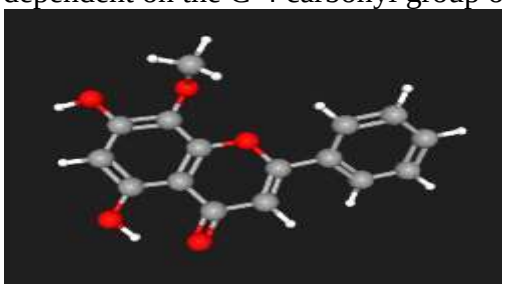

Fig 19: Ball and stick model 3-D Structure of Wogonin

**Conclusion**

In conclusion, natural compounds, particularly polyphenols and flavonoids, can be used to treat asthma in an inexpensive, simple, and synergistic manner. To ensure the efficacy and safety of natural asthma treatments, standardisation, information regarding the mechanism of action, and patient suitability must be addressed.

Asthma affects individuals of all ages, races, and ethnicities on a global scale, with WHO estimating that 235 million people suffer from asthma. Common asthma treatments include corticosteroids, bronchodilators, and leukotriene modifiers, which can lead to migraines, nausea, vomiting, vertigo, and tremors. Long-term use can result in osteoporosis,

cataracts, and suppression of the adrenal glands. Alternative asthma remedies with fewer adverse effects are needed, and understanding natural product SAR may help develop antiasthmatic medications that are more effective, selective, and have fewer side effects than synthetic therapies.

The structural activity relationship (SAR) of natural products, specifically polyphenols and flavonoids, plays a crucial role in the development of effective antiasthmatic agents. SAR studies allow for the identification of key structural features that are essential for activity, enabling the design and synthesis of novel compounds with improved efficacy and reduced toxicity. By understanding the SAR of these natural products, researchers can optimize their therapeutic potential and target specific molecular pathways involved in the pathogenesis of asthma.

Furthermore, natural products have numerous advantages, including their diverse structural complexity, abundance, and low toxicity compared to synthetic drugs. However, their low bioavailability, stability, and selectivity can limit their clinical application. Thus, optimizing their SAR is critical for enhancing their bioavailability, stability, and specificity while minimizing toxicity.

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**Conflict of Interest:** None to declare

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