

Anti-inflammatory flavonoids found in medicinal plants of acanthaceae family

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Plants of the Acanthaceae family are a broad range of small flowering herbs extensively found in India and other Asian countries. They are known for their potent anti-inflammatory activities, as evidenced by their traditional uses and different studies performed on animal models. This review aims to compile all the anti-inflammatory plants of different species belonging to different genera of the family Acanthaceae, their traditional uses, their potent anti-inflammatory flavonoids and the mechanism of action targeting specific receptors or signalling pathways present in the pathophysiology of inflammation. Literature was explored to obtain detailed information about different plants of the Acanthaceae family and the different bioactive flavonoids present in them. About 40 plants were found distributed all over India, encompassing different flavonoids, mainly from the classes Flavonols and Flavones. Their mechanism of action was elaborately discussed, associated with the normal pathophysiology of inflammation. These anti-inflammatory flavonoids can be isolated and further investigated for therapeutic efficacies and toxicities in various *in-vivo* models, thus providing an informative reference for more detailed targeted therapy for modern medicines.

Keywords: Acanthaceae, Anti-inflammatory, Apigenin, Flavonoids, *Justicia*, Quercetin

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Introduction

Inflammation is a critical and complex process mediated by the defensive mechanism of the host against any foreign pathogen or any trauma to the host. Inflammation in the presence of any pathogens, termed "Infectious Inflammation", is hallmarked by the activation of oxidative stress in the body. On the other hand, inflammation in the absence of pathogens, termed "Sterile Inflammation", generally occurs due to obesity, poor nutrition and poor lifestyle habits. Sterile inflammation is characterized by senescence, where the tissue cells undergo DNA damage and finally lead to Apoptosis^{1,2}.

Inflammation can occur due to various medical conditions. One of the most prevalent conditions is Ischemia Reperfusion Injury (IRI), where the blood flow to an organ is abruptly stopped and then reoccurs. This brief occurrence of Hypoxia with the reoxygenation of the supplied blood causes tissue damage to the organ. Instances of Inflammation occurring in Acute Myocardial infarction, Cerebral infarctions and Kidney tissue damage are results of IRI³. Other occurrences of inflammation include

deposition of crystals within joints resulting in Arthritis, Acute atherosclerosis conditions where acute atherosclerotic plaque can rupture, interrupting the flow of blood to the heart, Toxins such as Cobra poison, occurrences of drug misuse like Acetaminophen can also lead to muscle and hepatic inflammations. Trauma or injuries like crushing or internal haemorrhages lead to immediate inflammatory responses. Lung inflammations can also occur in case of prolonged exposure to particles like Silica and Asbestos⁴.

In most scenarios, Acute inflammation is a highly specific and self-orchestrated process designed for the host's cells to defend against foreign pathogens, fight infections and aid in the healing process. However, with ageing, the defensive capabilities of the cells are lost, leading to increased susceptibility towards infections. Chronic inflammations occur in the body, which is characterized by low-grade, continuous inflammations when compared to acute inflammation, which finally leads to tissue degeneration⁵. Many reasons have been hypothesized for the possible mechanism of chronic inflammation. The continuous destruction of pathogens by the leukocytes results in the production of high concentrations of reactive molecules, which thereby damages the cellular

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elements of the tissues. A high concentration of cytokines is being produced by the damaged immune cells, which increases the inflammatory responses and finally alters the normal functioning of the non-immune cells⁶.

Inflammation has been evident to be involved in different stages of several diseases like Asthma, Cardiovascular diseases, Diabetes, Neurogenerative diseases and Cancer as well. Poor diet is one of the main causes of chronic inflammation; a diet consisting of saturated fats, ultra-processed food, processed meat, and alcohol is directly involved with pro-inflammatory processes⁷. Plants are considered to be an excellent source of medicinal value against different diseases with fewer disease-related complications. According to the World Health Organization, about 25% of the drugs are plant-derived, with more than 21,000 plants being used as therapeutic approaches for different diseases. Acanthaceae family of plants is one such family of plants with a high enrichment of different phytochemicals like Flavonoids, Carotenoids, Vitamins, Minerals and fibres. Scientific studies have been conducted to prove that plant flavonoids can play a great therapeutic role in inhibiting complications of inflammatory diseases. This review aims to summarize the different flavonoids present in the plants of the Acanthaceae family, along with their potential health benefits and mechanism of action on different inflammatory diseases⁸.

Methodology

This review is based upon concepts and fundamentals derived from primary literature sources like peer-reviewed research and review articles. Comprehensive insights about the Acanthaceae family of plants, the inflammatory pathophysiology, the bioactive flavonoids present in Acanthaceae plants, and therapeutic targets of anti-inflammatory flavonoids were enquired from various online databases like Web of Science, PubMed, Willey, ScienceDirect, and Google Scholar.

Pathophysiology and resolution

The process of inflammation is quite complex and requires the participation of several immune triggers, receptors, signalling pathways, pro-inflammatory mediators and phagocytic cells⁹. The process starts with the stimulation of the innate immune cells, which have phagocytic properties. This stimulation is caused by the activation of various immune triggers. The

innate immune cells undergo the recruitment of lymphocytes, which further participate in the adaptive immune response. During the process of inflammatory response, different reactive species like Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and cell proteases are produced. These species cause fibrosis, tissue damage and proliferation of cancerous cells, leading to further chronic complexity of inflammation¹⁰. To understand the overall mechanism more clearly, we need to keep in mind that there are mainly three significant factors that govern the process of inflammation. These are immune triggers, receptors and signalling pathways.

Immune triggers

Immune triggers are activated during both acute and chronic inflammations. They are usually present in dormant stages, being hidden away during normal physiology. These triggers are generally activated during conditions like IRI, trauma, and the presence of foreign particles, crystals or toxins in the body. Immune triggers can be both intracellular or extracellular, originating from the external matrix. Intracellular immune triggers are nuclear proteins like High Mobility Group Box-1 (HMGB1), Mitochondrial peptides, uric acid molecules and other cellular components like Heat Shock proteins. Extracellular immune triggers is Hyaluronan, which is a glycosaminoglycan synthesized by mesenchymal cells. It mainly causes the recruitment of the macrophages via the Toll Like Receptors (TLRs) like TLR-2 and TLR-4¹¹.

Receptors for the immune trigger recognition

Once the immune triggers are activated, they need to be recognized. These specialized receptors are present within the physiology of the body. TLRs is one such receptor responsible for the recognition of immune triggers. TLR-2 and TLR-4 are the receptors responsible for the recognition of hyaluronan in the case of IRI. TLR-9, an endosomal receptor, recognizes hepatic inflammatory triggers caused by misuse of Acetaminophen. TLR-3 is another receptor responsible for the recognition of any foreign viral RNA. Another important recognition receptor is NOD-like Receptors (NLRs), which are primarily responsible for activating caspase-1 and IL-1 β ¹². Thus, the immune triggers are being recognized, and different pro-inflammatory mediators like cytokines and interleukins are recruited via different signalling pathways.

Signaling pathways involved in inflammation

Recognition receptors like TLRs mainly mediate the recruitment of pro-inflammatory factors through the signalling pathway of myeloid differentiation, which is the primary response of protein 88 (MyD88). NOD-LRR and Pyrin domain-containing 3 (NLRP3) is one such important signaling pathway via which the NLRs receptor transverse their information¹³. A self-signalling receptor that recognizes the immune trigger HMGB1 is known as a receptor for advanced glycation end-products (RAGE). These receptors are primarily expressed in low concentrations in vascular endothelial cells, immunogenic cells and cardiac cells. Another receptor which self-signals its own recognition is Interleukin-1 Receptor (IL-1R), which recognizes the IL-1 α from the necrotic cells and signals for the increased production of neutrophils recruiting chemokines¹³. The overall pathophysiology of inflammation is depicted in Fig. 1.

Resolution of inflammation

Neutrophils are the predominant cells that immediately migrate towards the site of an injury or trauma. They form clusters there and initiate the initial phase of inflammation. Now, an effective resolution of inflammation would be the clearing of these neutrophils after they have undergone apoptosis of necrosis. The recruitment of more neutrophils to

the site of inflammation should also need to be inhibited to obtain an effective resolution of inflammation¹⁴. Neutrophils usually secrete a specialized mediator known as Annexin A1, which impairs the further recruitment of neutrophils. Further, they also secrete Sphingosine-1-phosphate, which stimulates the migration of Macrophages to the site. Macrophages secrete VEGF, which promotes angiogenesis to the site of inflammation by restoring oxygen to the hypoxic tissues and immunosuppressive cells, thus assisting in the resolution of inflammation¹⁵. Finally, proresolution mediators like Lipoxins are also secreted by macrophages, offering better resolution to inflammation¹⁶. Another proresolution mediator, IL-4 secreted by eosinophil, also helps in resolving acute muscle inflammation¹⁷.

Acanthaceae family medicinal plants

The Acanthaceae family of plants consists of about 4300 species, belonging to 346 genera, making it one of the most diverse plant families in the world. They are usually flowering herbs of dicotyledonous nature, along with shrubs and twinning vines. The taxonomical classification is represented as Plantae (Kingdom); Angiospermae (Division); Dicotyledonae (Class); Gamopetalae (Subclass); Bicarpellatae (Series); Personales (Order); Acanthaceae (Family).

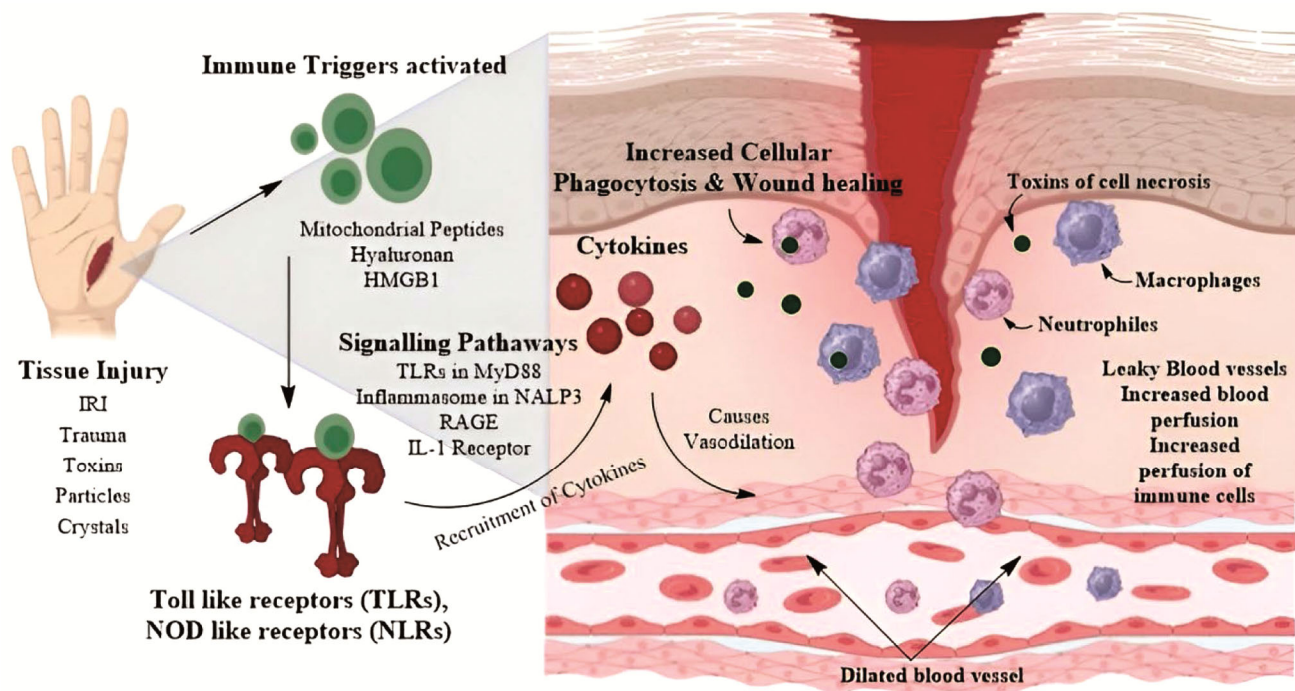


Fig. 1 — Patho-physiology of inflammation.

Among several genera, major genera consisting of medicinal plants are *Acanthus*, *Andrographis*, *Barleria*, *Blepharis*, *Hygrophila*, *Justicia*, *Lepidagathis*, *Ruellia*, *Strobilanthes* and *Thunbergia*, with *Justicia* being the largest genus¹⁸.

The distribution regions are mainly in the tropical, subtropical, and temperate regions of the world. They are mainly found in countries of Asia like India, Malaysia, and Indonesia, along with regions of Africa and Central and South America. In India, these plants are mainly found in mountainous regions of central, Southeast and West India, along with regions having shady and moist environment¹⁸.

Leaves of such herbs are usually simple with opposite exstipulate parts. The flowers are bisexual, arranged in the form of Raceme, and terminally placed in the form of axillary spikes. Calyx are usually present in two pairs of lobes with 5 limbed Corolla attached to it. The ovary is diloculed and superior in nature¹⁹. Leaves, roots and other parts are evident to contain rich amounts of bioactive phytochemicals like Glycosides, Flavonoids, terpenoids, alkaloids and fatty acids. Indigenously, extracts of these plants are being used for their Anti-inflammatory, Anti-pyretic, Antidiabetic, Anti-spasmodic, and Analgesic activities against numerous medical conditions and symptoms¹⁹.

Medicinal plants of the Acanthaceae family are widespread all over the globe, with many of their traditional uses prevalent in several tribes worldwide. Some of the well-known tribes of Malaysia, like "Proto Malay" tribe use pounded leaves of *Justicia gendarussa* to relieve joint pains and are also treated with lime for deworming and stomach aches, "Semang" tribes incorporate the crushed leaves of *Barleria lupulina*, which are applied over inflamed tissues, the "Senoi" tribes mix crushed leaves of *Thunbergia atroplicifolia* with kerosene which are further applied to alleviate the symptoms of Shingles²⁰. Indigenous tribes of Polynesian islands also use plants of *Thunbergia* species for their diuretic and digestive benefits. Aboriginal tribes native to Australia incorporate plants of *Ruellia* species to treat wounds and skin infections. Moreover, indigenous tribes from South Africa and Sub-Saharan regions are known to use pounded leaves of *Lepidagathis incurva*, which are termed "Swartoognooi" in the vernacular Zulu language. This formulation is used as an antiseptic wash for the treatment of sores and swellings. Ethnic groups in East Africa like "Kikuyu"

and "Masai" utilize plants of *Acanthus montanus*, also known as "Zebra Bush", for its wound healing and antipyretic properties. The "Totonac" tribes of Mexico, Papantla, Veracruz and the adjacent regions are also well-known for their traditional practice of formulating different decoctions and herbal infusions with aerial parts of the plants belonging to the Acanthaceae family. The famous Amazonian tribe known as the "Yanomami tribe" of South America thrives on *Justicia pectoralis* leaves commonly termed by them as "Piri-piri" for their potent anti-inflammatory and analgesic properties²¹.

As plants of the Acanthaceae family are mostly prevalent in India and other countries of Asia, their quantity is huge in number, ranging almost over 68 genera, including 250-300 species. These plants are wild flowering plants that are invasive in nature. The geographical location varies from mangrove forests to marshlands and hot and humid grasslands to cool hilly regions. Therefore, the major genera of the Acanthaceae family, with some of the important species having bioactive anti-inflammatory roles along with their native geographical distribution, are gathered from the Indian Medicinal Plant Database (IMPD) and are listed in Table 1.

Anti-inflammatory effects of acanthaceae family plants

Plants of the Acanthaceae family belonging to different genera have been shown to have anti-inflammatory activity, as evidenced by different experimental studies. A study conducted with methanolic extracts of *Acanthus illicifolius* in the bodies of pylorus-ligated rats revealed that the methanolic extract of the herbs has been shown to reduce inflammations of the gastrointestinal tract, thus protecting the tract from ulcerative lesions. The herbal extract has proved to be effective against Indomethacin and Acetyl salicylic acid induced inflammations in rats³².

Inflammations caused by increased concentration of Histamine, Adrenaline and Dimethyl benzene were greatly reduced by methanolic extracts of *Andrographis paniculata*. The extract reduced the inflammations considerably due to increased synthesis of adrenocorticotrophic hormone, an endogenous anti-inflammatory agent, and increased vascular permeability leading to increased perfusion of blood and phagocytic cells or by suppressing the COX-2 expression³³.

Table 1 — Ethnomedicinal uses of important medicinal plants of Acanthaceae family

S. No.	Scientific name	Common Name	Parts Used	Geographical Distribution	Traditional uses
<i>Acanthus</i>					
1	<i>Acanthus illicifolius</i> L.	Harkuchkanta (Bengali)	Leaves	Indigenous to Sundarbans, mangrove regions of West Bengal, the coastal regions of the Southern Peninsula and coasts of Andaman & Nicobar Islands	Infusions and herbal teas are consumed for antidiabetic, anti-inflammatory properties used to treat respiratory disorders, skin diseases, urogenital infections ²²
2	<i>Acanthus mollis</i> L.	Bear's Breeches (English)	Leaves		
3	<i>Acanthus montanus</i> (Nees) T. Anderson	Mountain thistle (English)	Leaves		
<i>Andrographis</i>					
4	<i>Andrographis echinoides</i> (L.) Nees	Kalukariyatun (Marathi)	Whole plant	Indigenous to Odisha, also found in West Bengal, Tamil Nadu and Karnataka	Herbal teas and decoctions are preferred for anti-pyretic, anti-inflammatory, anti-arthritic, antidiabetic, hepatoprotective, analgesic and relieves symptoms of IBD ²³
5	<i>Andrographis alata</i> (Vahl) Nees	Peria Nangai (Tamil)	Leaves		
6	<i>Andrographis paniculata</i> (Burm.) Wall. ex Nees	Kalmegh (Bengali)	Leaves		
<i>Barleria</i>					
7	<i>Barleria buxifolia</i> L.	Rose mullippoindu (Tamil)	Leaves and roots	Native to Uttar Pradesh and are most prevalent in hilly regions of Northern and Southern India	Topical pastes are prepared for their potent blood clotting and wound healing effects, other pharmacological activities include anti-viral, anti-bacterial, anti-fungal, anti-inflammatory, antioxidant, and analgesic properties ²⁴
8	<i>Barleria courtallica</i> Nees	Karimkurunni (Tamil)	Leaves and roots		
9	<i>Barleria cristata</i> L.	Janti (Bengali)	Leaves and roots		
10	<i>Barleria dichotoma</i> Roxb	White Barleria (English)	Whole plant		
11	<i>Barleria lupulina</i> Lindl.	Bishalyakarani (Bengali)	Leaves		
12	<i>Barleria longiflora</i> L.f.	Ekakantaka (Sanskrit)	Leaves and roots		
13	<i>Barleria prionitis</i> L.	Bajradanti (Hindi)	Leaves		
14	<i>Barleria strigosa</i> Willd.	Nili Koranti (Marathi)	Leaves and roots		
<i>Blepharis</i>					
15	<i>Blepharis edulis</i> Pers.	Chaupatia (Hindi)	Leaves	Native to Gujrat and Maharashtra, also found in states of Karnataka, Andhra Pradesh and West Bengal.	Topical poultice formulated to treat snake bites and fractures for the anti-inflammatory, wound healing properties also used to treat oedema, gout and rheumatism ²⁵
16	<i>Blepharis indica</i> Stocks ex T. Anderson	Bhongri (Hindi)	Leaves		
<i>Hygrophila</i>					
17	<i>Hygrophila auriculata</i> (K. Schum.) Heine	Kulekhara (Bengali)	Leaves, seeds	Wet and marshy regions around river Ganga and swamps of Eastern and Western ghats of India.	“Rasa” or the extracted juice is prepared and incorporated for treating diarrhea, urogenital infections, other therapeutic applications are its anti-cancer, anti-inflammatory, antidiabetic, anti-pyretic, antioxidant properties ²⁶
18	<i>Hygrophila phlomoides</i> Nees	Swampweeds (English)	Roots, Seeds		
19	<i>Hygrophila salicifolia</i> (Vahl) Nees	Ikata (Sanskrit)	Leaves		
<i>Justicia</i>					
20	<i>Justicia adhatoda</i> L.	Basak (Bengali)	Whole plant	Native to the state of Bihar and Jharkhand, thrives well in other states like West Bengal, Tamil Nadu and Kerala	Herbal decoction is preferred in many regions for its potent anti-inflammatory properties against respiratory tract infections like cold, rhinitis, bronchitis and asthma; also incorporated in diet as salads to treat diarrhea, dysentery; other pharmacological attributes are antimicrobial, antidiabetic, antioxidant, anti-inflammatory, anti-spasmodic properties ²⁷
21	<i>Justicia bicalyculata</i> Vahl	Atrilal (Hindi)	Whole plant		
22	<i>Justicia gendarussa</i> Burm.f.	Jagatmadan (Bengali)	Leaves		
23	<i>Justicia nasuta</i> L.	Juipana (Bengali)	Leaves		
24	<i>Justicia procumbens</i> L.	Kalmashi (Marathi)	Whole plant		
25	<i>Justicia repens</i> Deless. ex Nees	Kharmar (Hindi)	Whole plant		
26	<i>Justicia betonica</i> L.	Mokander (Hindi)	Whole plant		

(Contd.)

Table 1 — Ethnomedicinal uses of important medicinal plants of Acanthaceae family (Contd.)

S. No.	Scientific name	Common Name	Parts Used	Geographical Distribution	Traditional uses
<i>Lepidagathis</i>					
27	<i>Lepidagathis cristata</i> Willd.	Bukhar Jadi (Hindi)	Whole plant	Native to Southern parts of India like	Herbal ointments are prepared for Antiseptic, wound healing properties, also possess
28	<i>Lepidagathis hamiltoniana</i> Wall.	Agnikhair (Hindi)	Whole plant	Tamil Nadu, Karnataka and Kerala	anti-microbial, anti-inflammatory, anti-emetic, antidiabetic, immunosuppressive properties ²⁸
29	<i>Lepidagathis incurve</i> Buch. -Ham. ex D. Don	Vangvattur (Mizo)	Leaves		
30	<i>Lepidagathis trinervis</i> Nees	Harancharo (Gujrathi)	Whole plant		
<i>Ruellia</i>					
31	<i>Ruellia prostrata</i> Poir.	Kali Dhraman (Gujrati)	Whole plant	Prevalent in stream beds in regions of	“Kadha” or herbal decoction are formulated of anti-pyretic,
32	<i>Ruellia suffruticosa</i> Roxb	Desert Petunia (English)	Whole plant	Andhra Pradesh, Kerala, Karnataka and Odisha	anti-inflammatory, antidiabetic, anti-microbial,
33	<i>Ruellia tuberosa</i> L.	Minnie Root (English)	Roots		anti-hypercholesteremia
34	<i>Ruellia strepens</i> L.	Limestone Ruellia (English)	Leaves		and diuretic properties ²⁹
<i>Strobilanthes</i>					
35	<i>Strobilanthes callosus</i> Nees	Maruadana (Marathi)	Leaves	Native to the moist conditions of the	Herbal or medicated pills are prepared as they aid in effective
36	<i>Strobilanthes cusia</i> (Nees.) Kuntze	Assamese Indigo (English)	Leaves	western ghats forest, also found in regions of	digestive functioning and also possess
37	<i>Strobilanthes lupulinus</i> Nees	Karun Kurinji (Tamil)	Flowers	Kerala, Tamil Nadu and Karnataka.	anti-inflammatory, anti-cancer, antioxidant, anti-microbial, diuretic and laxative properties ³⁰
<i>Thunbergia</i>					
38	<i>Thunbergia alata</i> Bojer ex Sims	Black Eyed Susan (English)	Leaves	Native to Northern parts of India, states like	Herbal teas for potent anxiolytic, anti-inflammatory, antioxidant,
39	<i>Thunbergia laurifolia</i> Lindl.	Blue trumpet vine (English)	Leaves	Himachal Pradesh and Delhi	antidiabetic, anti-microbial, anti-proliferative and sedative
40	<i>Thunbergia grandiflora</i> (Roxb. ex Rottl.) Roxb.	Neel lata (Bengali)	Leaves		properties ³¹

Alcoholic extract of *Blepharis indica* showed significant results on carrageenan-induced oedema at a dose of 75 mg/kg measured using serotonin-induced assay techniques³⁴.

Extracts of ethanol and distilled water of *Hygrophila auriculata* were shown to have significant anti-inflammatory activity at a dose of 400 mg/kg body weight against carrageenan-induced inflammations in rats and mice when compared with the standard drugs of diclofenac sodium and metamizole³⁵.

Several bioactive compounds isolated from the extract of the plant *Justicia adhatoda* showed anti-inflammatory activity on gel application to oedema as well as moderate injuries. The study was done on rats with injury caused by a free falling weight of 300 g from a height of 30 cm to the calf of the rats³⁶. Another experiment was done with alcoholic extracts of *Justicia gendarussa*, which showed significant anti-inflammatory activity due to the inhibition of the TLR-4 receptors and also suppression of the TLR-NF- κ -B signalling pathway when compared with the standard drug diclofenac sodium³⁷.

Ethanol extracts of *Strobilanthes lupulinus*³⁸ and *Thunbergia grandiflora*³⁹ have been shown to exhibit a potent anti-inflammatory activity against serotonin-induced, carrageenan-induced inflammations in animal models.

Flavonoids

Flavonoids are a group of important secondary metabolites mainly found in green leafy vegetables, fruits, medicinal herbs, green stems, roots, flowers and seeds of different plants. Secondary metabolites are small organic molecules which are not directly involved in the growth and development of the plant, and unlike primary metabolites, the absence of such metabolites does not cause the immediate death of the plant, but rather leads to long-term harm to the plant's resistive and defensive mechanisms. Approximately about 10,000 flavonoids have been identified and isolated; many of them have rich therapeutic values like anti-inflammatory, antioxidant, antipyretic, and analgesic effects. Because of such pharmacological values, plant flavonoids have been

used indigenously for the treatment of various diseases and ailments. Even in modern times, experimental studies are performed to isolate the different bioactive flavonoids and formulate them as modern dosage forms⁴⁰.

Flavonoids are mainly synthesized through the phenylpropanoid pathway. It is the pathway which is successive to the Shikimate pathway, while it is the precursor of the Acetate pathway. The former generates the p-Coumaroyl -coA, and the latter generates the C₂-chain elongation⁴⁰. Chemically, flavonoids consist of 15 carbons, organized in 3 different rings, namely Rings A, C and B. The carbons are arranged in the skeleton of C₆-C₃-C₆⁴¹. Secondary metabolites like flavonoids are mainly responsible for the resistive and defensive mechanisms of the plant against different stress factors. The stress factors can be classified into abiotic stress, such as cold, drought, high salinity, ultraviolet radiation, heavy metals, and biotic stress, including herbivores and microbes like bacteria and fungi⁴². In plantae, flavonoids are mainly present in the vacuoles in the form of O-glycosides or C-glycosides. The flavonoids are mainly classified owing to their structural moieties, Unsaturation and Oxidation states of the carbon ring⁴³. Based on these, they are mainly classified into Flavones^{44,45}, Flavonols^{46,47}, Flavanones^{48,49}, Isoflavonoids^{50,51}, Flavanols^{52,53} and Anthocyanins^{54,55}. The role of these flavonoids in different inflammatory conditions is represented in Fig. 2. The overall classifications of flavonoids, along with the important compounds, their structures and molecular substitutions, are represented in Fig. 3.

Anti-inflammatory flavonoids present in acanthaceae family plants

Different flavonoids possessing potent anti-inflammatory activities are being isolated from the listed medicinal plants. The extracts of the plants were formulated usually in polar solvents like ethanol and methanol or sometimes less polar solvents like chloroform or petroleum ether. The techniques for extraction were cold macerations, digestion, or using heat, such as the exhalation technique. The different compounds were isolated using chromatographic techniques like High performance thin layer chromatography (HPTLC) or High-performance liquid chromatography (HPLC), and later the isolated compounds were identified using techniques like Nuclear magnetic resonance (NMR) or Mass spectroscopy (MS). Different flavonoids responsible for anti-inflammatory action have been isolated as well as their quantification via analytical techniques like Ultra-Performance Liquid Chromatography (UPLC), Liquid Chromatography-Mass Spectroscopy (LC-MS), High Performance Thin Layer Chromatography (HPTLC) or Capillary Electrophoresis (CE) have been estimated which are being listed in Table 2. For better understanding the nature of these bioactive flavonoids, the chemical structure of the above flavonoids is being listed according to their respective genera and the following is being represented in Figs. 4-6.

Mechanism of anti-inflammatory action of flavonoids present in acanthaceae family plants

The plants of the Acanthaceae family are thus evident to possess potent anti-inflammatory effects,

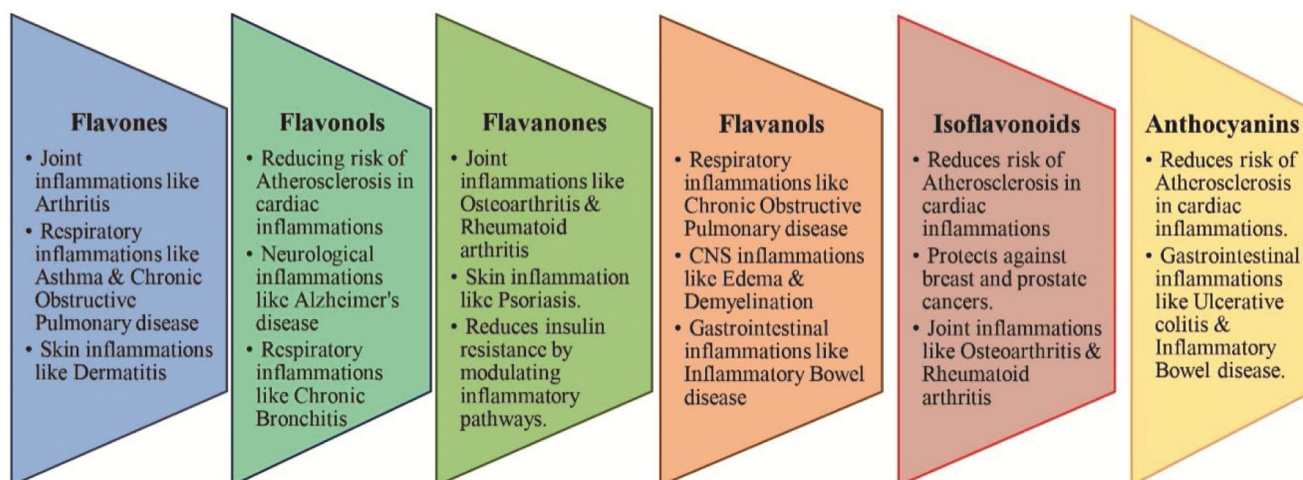


Fig. 2 — Role of classes of flavonoids in different inflammatory conditions.

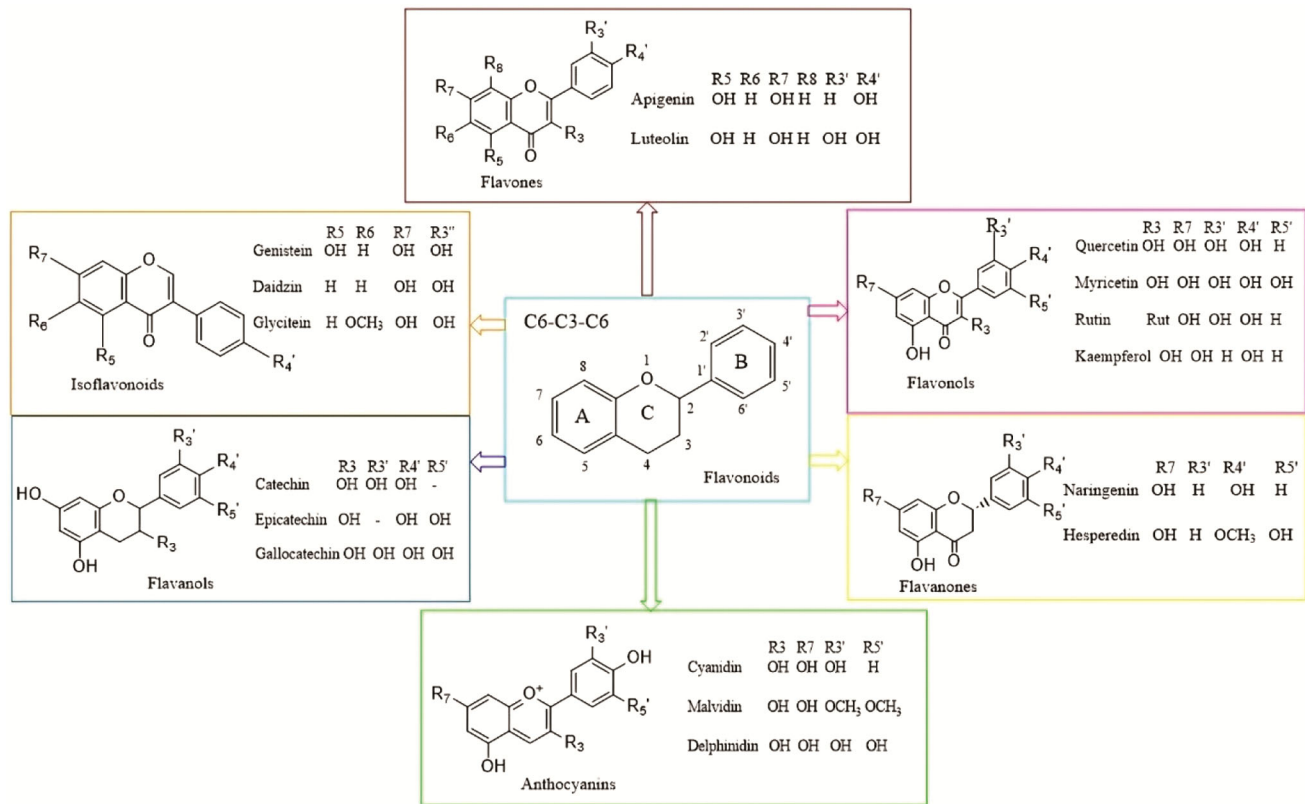


Fig. 3 — Classification of different flavonoids with their examples.

Table 2 — Anti-inflammatory flavonoids present in the Acanthaceae family of plants

S. No	Genus	Anti-inflammatory flavonoids Present	Quantification (µg/mg)	Ref.
1	<i>Acanthus</i>	Quercetin	1.22±0.14	56-58
		Quercetin-3-O-β-D-glucopyranoside	0.07±0.04	
		Myricetin	0.72±0.80	
		Isorhamnetin	ND	
		Linarin	ND	
		Vitexin	ND	
		2	<i>Andrographis</i>	
Apigenin	0.61±1.21			
Luteolin	1.03±0.82			
7,8-Dimethoxy-2'-hydroxy-5-O-β-D glucopyranosyloxy flavone	ND			
5,4'-Dihydroxy-7-methoxy-8-O-β-D glucopyranosyloxy flavone	ND			
5,7,8-trimethoxy dihydroflavone	ND			
3	<i>Barleria</i>	Quercetin	1.68±0.17	62,63
		3-O-methyl quercetin	ND	
		6-O-α-L-rhamnopyranoside-3,7,3'-O-trimethylated-8-hydroxy quercetin	ND	
		Quercetagenin	ND	
		Luteolin	1.37±0.96	
		7-O-methyl luteolin	0.38±0.74	
4	<i>Blepharis</i>	Apigenin	0.72±0.31	64-66
		Apigenin-7-O-(6''-E-P-coumaroyl)-β-D-glucopyranoside	ND	
		Naringenin-7-O-(3''-E-P-coumaroyl)-β-D-glucopyranoside	ND	
		Rutin	1.77±0.64	
		Genistein	ND	

(Contd.)

Table 2 — Anti-inflammatory flavonoids present in the Acanthaceae family of plants (*Contd.*)

Sl. No	Genus	Anti-inflammatory flavonoids Present	Quantification ($\mu\text{g}/\text{mg}$)	Ref.
5	<i>Hygrophila</i>	Quercetin	0.33 \pm 0.65	67-69
		Luteolin	0.0007 \pm 0.02	
		Luteolin-7-O-rutinosides	ND	
		Apigenin-7-O-glucuronide	ND	
		Apigenin-7-O-glucoside	ND	
		Ellagic acid	0.29 \pm 0.05	
6	<i>Justicia</i>	Quercetin	3.42 \pm 0.85	70-72
		Apigenin	0.21 \pm 0.72	
		Naringenin	0.06 \pm 0.008	
		Kaempferitrin	1.32 \pm 0.28	
		Vitexin	ND	
		3',4'-dihydroxy flavonol Apigenin-7-O-(6''-E-P-coumaroyl)- β -D-glucopyranoside	ND	
7	<i>Lepidagathis</i>	Apigenin	1.57 \pm 0.08	73,74
		Luteolin	2.03 \pm 0.54	
		6-hydroxy luteolin	ND	
		6-hydroxy luteolin-7-apioside	ND	
8	<i>Ruellia</i>	Apigenin	0.77 \pm 0.61	75,76
		Apigenin-7-O-glucuronide	ND	
		Apigenin-7-O-glucoside	0.04 \pm 0.21	
		Apigenin-7-O-rutinoside	ND	
		Luteolin	1.22 \pm 0.89	
		Luteolin-7-O-glucoside	1.03 \pm 0.26	
9	<i>Strobilanthes</i>	Quercetin	0.82 \pm 0.96	77,78
		8-p-hydroxybenzyl quercetin	ND	
		Quercetin-3-(6''-methyl glucuronide)	ND	
		Catechin	0.42 \pm 0.61	
		Epicatechin	0.18 \pm 0.11	
		Naringenin	0.74 \pm 0.90	
		Kaempferol	0.08 \pm 0.004	
10	<i>Thunbergia</i>	Apigenin	0.47 \pm 0.29	79,80
		Apigenin-7-O- β -D-glucopyranoside	ND	
		Apigenin-7-glucuronide	0.06 \pm 0.003	
		6,8-di-C-glucopyranosyl apigenin	ND	
		Luteolin	0.23 \pm 0.04	
		4'-hydroxy-5,6,7-trimethoxy flavone	ND	

*ND = Not Determined yet

which is attributed to their traditional uses as well as the significant results shown in different animal models. The anti-inflammatory activity is mainly due to the enrichment of different bioactive constituents present in them, primarily due to the presence of rich bioactive flavonoids. The anti-inflammatory activity is mainly attributed to the planar cyclic structure with the unsaturation at C2-C3 and the positions of the hydroxyl groups. A study revealed that the presence of hydroxyl groups at positions 3' and 4' of the B ring is very essential for imparting the anti-inflammatory activity⁸¹. Different anti-inflammatory flavonoids, as represented in Table 2, exhibit anti-inflammatory activity through different pathways.

Compounds Apigenin and Luteolin and their respective derivatives belong to the class of Flavones, the largest class of bioactive flavonoids. Apigenin, an important flavone, exhibits anti-inflammatory activity by suppressing the levels of mRNA levels induced by TNF- α by which it inhibits the different adhesion molecules like intercellular adhesion molecules-1 (ICAM-1), E-selectin and vascular cells adhesion molecules-1 (VCAM-1) thereby lowering the recruitment of leukocytes and other immune cells to the site of inflammation. It also inhibits TNF- α induced interleukins like IL-1 β and IL-6 and prostaglandin -E2 synthesis⁸². Another study revealed that the inhibition of the cellular recognition of TLR-4

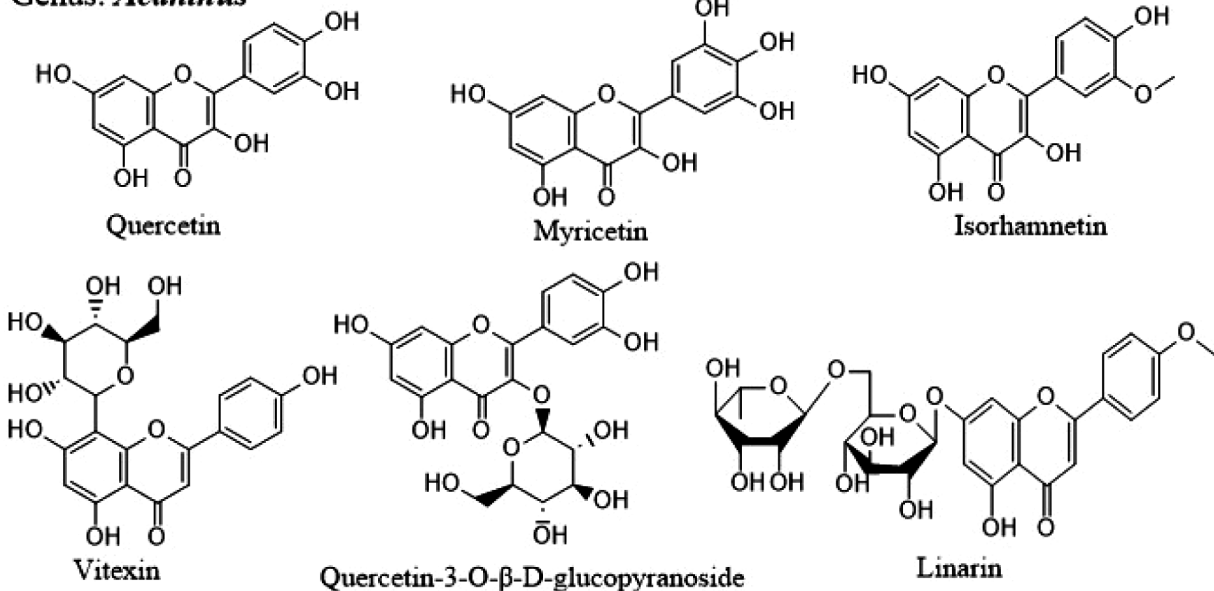
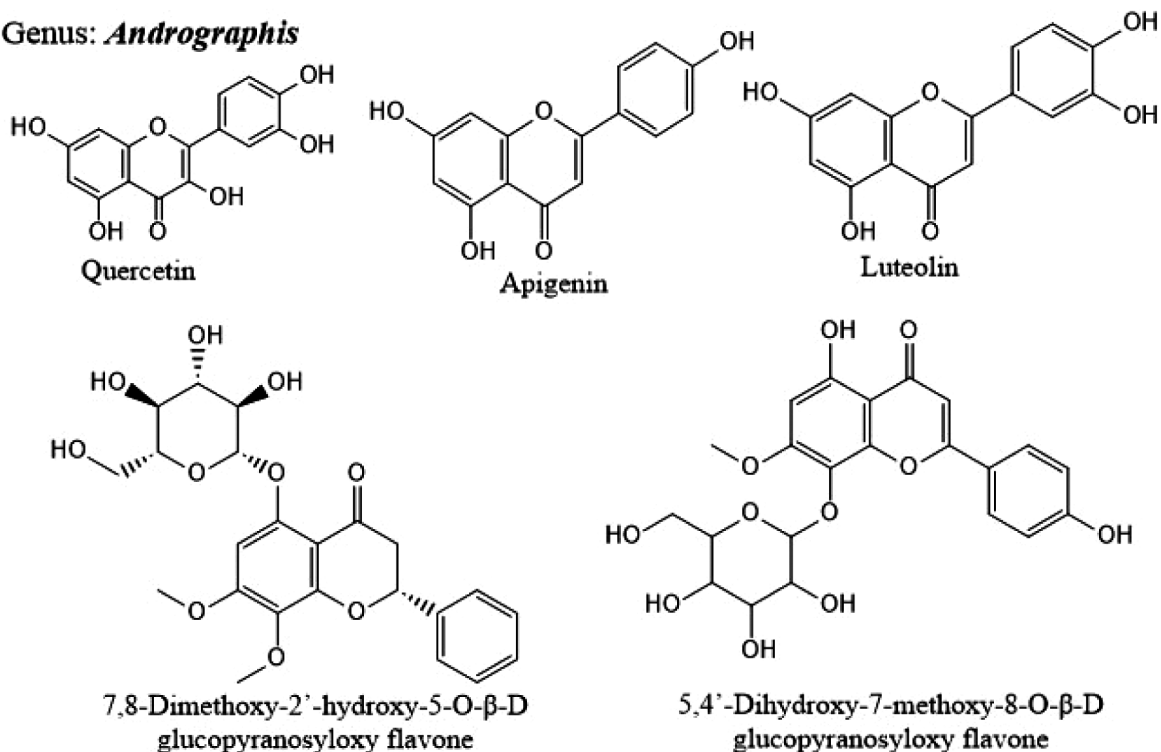
Genus: *Acanthus***Genus: *Andrographis***

Fig. 4 — Anti-inflammatory flavonoids of *Acanthus* and *Andrographis* genera.

receptor and the pathway of MyD88 leads to potent anti-inflammatory activity⁸³. Luteolin, another important flavone, induces the inhibition of NF- κ B and AP-1 pathways and also suppresses the TNF- α induced IL-6 expression for the potent anti-inflammatory activity⁸⁴.

The second and most important class of flavonoids, flavonols, consists of compounds like Quercetin, Rutin, Myricetin, Isorhamnetin and Kaempferol. Quercetin, the important bioactive flavonol, exhibits its anti-inflammatory activity in several ways. Firstly, it inhibits the induction of Heat Shock protein (HSP),

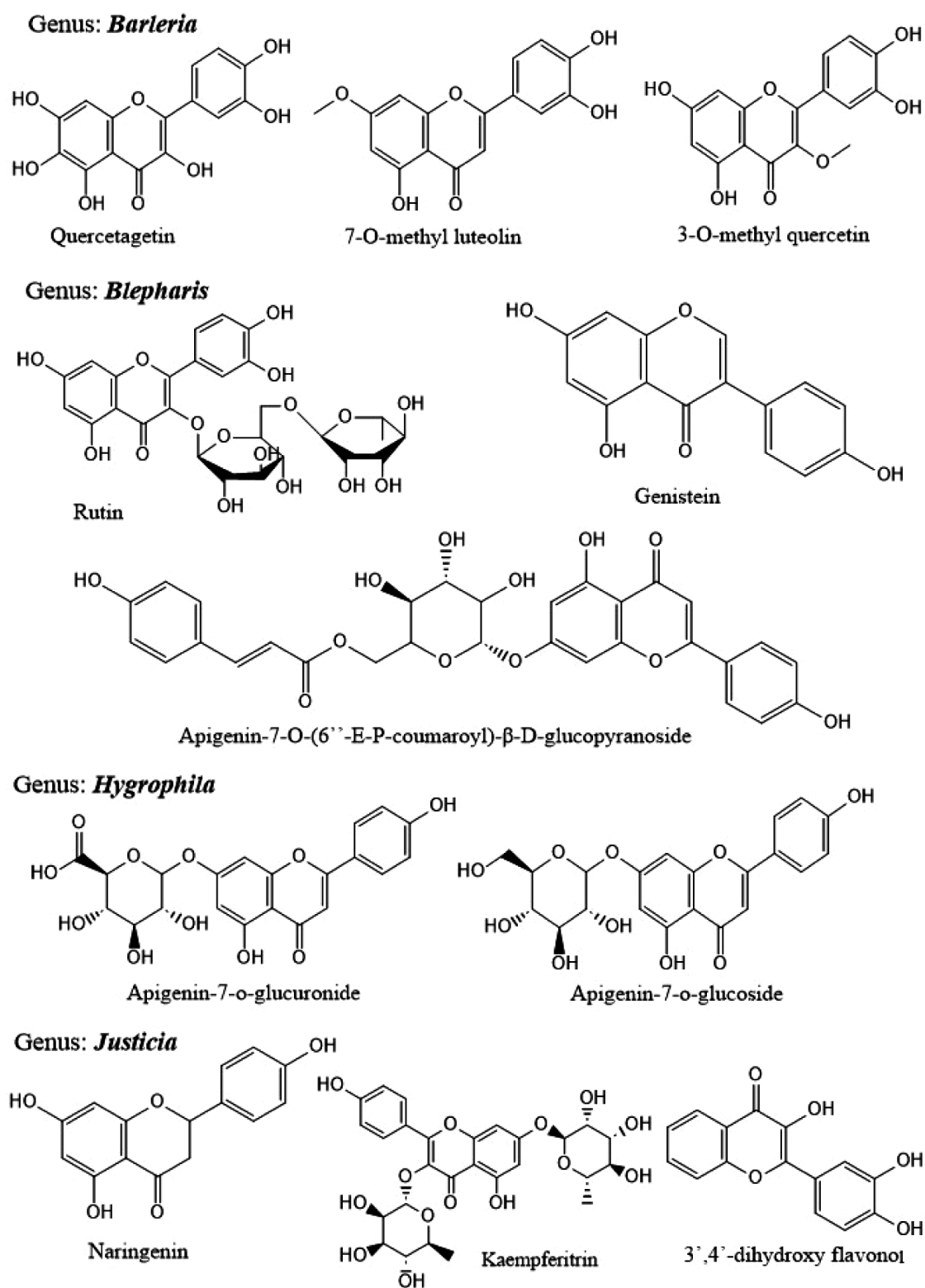
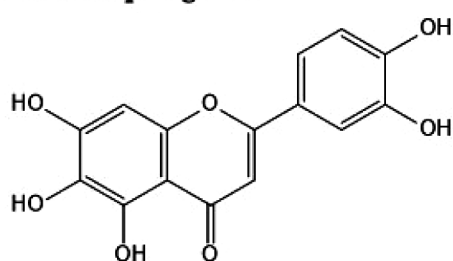
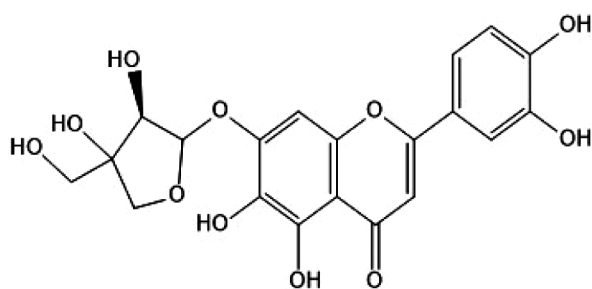


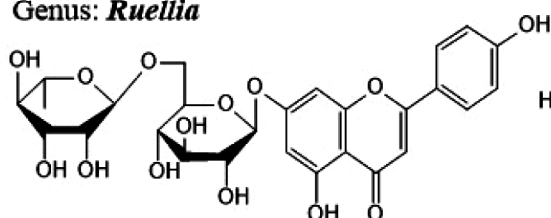
Fig. 5 — Anti-inflammatory flavonoids of genera *Barleria*, *Blepharis*, *Hygrophila* and *Justicia*.

Genus: *Lepidagathis*

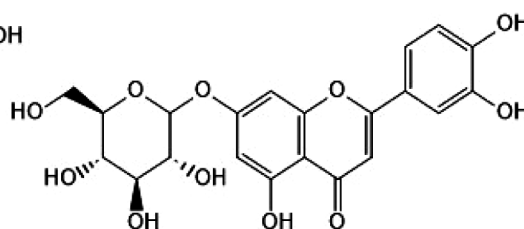
6-hydroxy luteolin



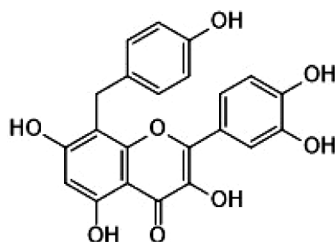
6-hydroxy luteolin-7-apioside

Genus: *Ruellia*

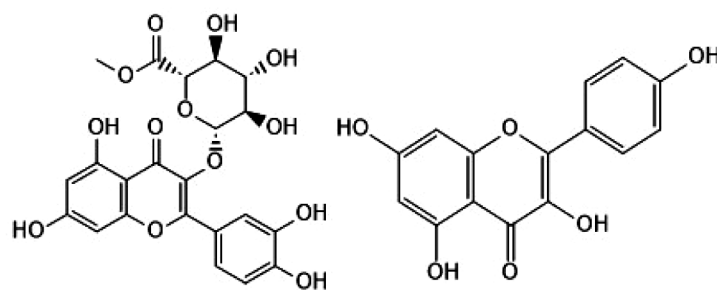
Apigenin-7-O-rutinoside



Luteolin-7-O-glucoside

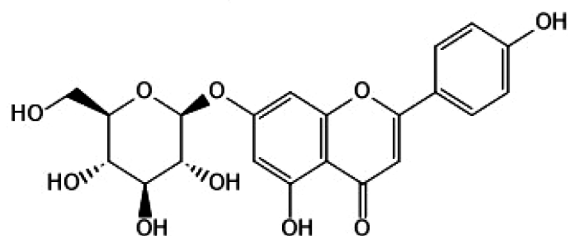
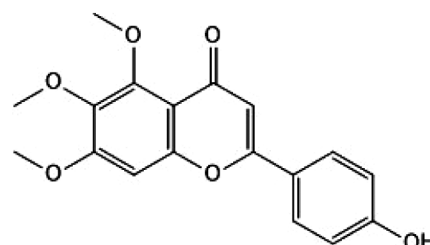
Genus: *Strobilanthus*

8-p-hydroxybenzyl quercetin



Quercetin-3-(6''-methyl glucuronide)

Kaempferol

Genus: *Thunbergia*Apigenin-7-O- β -D-glucopyranoside

4'-hydroxy-5,6,7-trimethoxy flavone

Fig. 6 — Anti-inflammatory flavonoids of genera *Lepidagathis*, *Ruellia*, *Strobilanthus* and *Thunbergia*.

HSP70, which is induced by the Heat Shock factor (HSF). Thus, the heat-induced inflammations are reduced⁸⁵. Secondly, quercetin inhibits c-Jun N terminal kinase and extracellular signal-regulated kinase, which in turn blocks the MAPK, AP-1 and NF- κ B pathways. These reduce the stimulation and secretion of cytokines to the site of inflammation⁸⁶. Thirdly, quercetin also inhibits the cyclooxygenase,

lipoxygenase and Nitric oxide synthase (NOS) pathway, thus inhibiting the production of prostaglandins, leukotrienes and NO, which are the chief mediators of inflammations. The fourth way is the activation of c-GMP/ATP sensitive K⁺ channels, which causes the hyperpolarization of nociceptive neurons, resulting in pain reduction⁸⁷. Quercetin is also able to chelate the transition ions, resulting in the

inhibition of the reactive oxygen species generation. Finally, quercetin also suppresses the Glyoxalase-1 enzyme, resulting in a reduction of histamine release and preventing the degranulation of neutrophils. Rutin, another important flavonol activates Nuclear factor E2-related factor (Nrf2), thus inhibiting ICAM-1, VCAM-1 and E-selectin. It also inhibits the cyclooxygenase pathway, thereby reducing the prostaglandin synthesis. Myricetin exhibits anti-inflammatory activity owing to an inhibition of the Lipoxygenase pathway⁸⁸. The anti-inflammatory activity of Isorhamnetin is attributed to the inhibition of iNOS expression, thereby reducing the generation of NO and also the NF- κ B pathway⁸⁹. Kaempferol, like quercetin, inhibits the cyclooxygenase and NF- κ B pathways⁸⁶.

Naringenin, an important bioactive flavonoid belonging to the class of flavanones, also possess potent anti-inflammatory activity. The mechanism of the anti-inflammatory activity is attributed to the suppression of leukocyte recruitment and migration. Thus, there is reduction of expression of pro-inflammatory cytokines like IL-2, IL-4, IL-4, IL-5, IL-6, IL-8, IL-13, IL-17, IL-22 and TNF- α . It also blocks NaV1.8, a sodium channel which inhibits the sodium influx⁹⁰.

Flavanols like Catechin and Epicatechin inhibit the c-Jun N terminal Kinase and extracellular protein kinase-like quercetin and thus inhibit the MAPK, AP-1 and NF- κ B pathways for the anti-inflammatory mechanism⁸⁶.

Isoflavonoids like Genistein also possess anti-inflammatory activity, and their mechanism is mainly attributed to the inhibition of tyrosine kinase activity as well as inhibition of P56 lck, a T-cell protein kinase involved in the recruitment of IL-2 and IL-2 receptors⁹⁰.

Glycosylated flavones like Vitexin and Linarin also depicts the same mechanism of anti-inflammatory activity like quercetin. But unlike quercetin, they do not inhibit the c-Jun N terminal kinase; rather, they inhibit the receptor activator of nuclear factor kappa-B ligand (RANKL) and thereby suppress the MAPK and NF- κ B pathways⁸². The detailed mechanistic pathways of Quercetin, Naringenin, Luteolin, Kaempferol, Catechin and Apigenin, Rutin are represented in Fig. 7 and 8 respectively.

Discussion

The anti-inflammatory activity of the plants of the Acanthaceae family is mainly due to the presence of

different bioactive flavonoids, as is evident from the anti-inflammatory action on different animal models and their relative mechanism on the targets of normal pathophysiology of inflammation. However, the various *in-vivo* experiments have few limitations. Due to the small population of animals being tested, the result obtained may not justify the efficacy of the test sample. The result may also not be reproducible to the same extent when performed in a large group of animals sampled from different geographical regions. Furthermore, the samples were assayed against the standard compounds when the inflammatory conditions were being induced by some chemicals or incurring trauma to the animal. This can be referred to as "Infectious inflammation". But in the case of "Sterile inflammations", where it takes a longer time for the inflammations or ulcerations to occur. It is quite difficult to initiate and monitor the *in-vivo* studies in those cases.

The anti-inflammatory effects of the sample extracts are being compared with standard drug molecules. These extracts also constitute varying bioactive phytochemicals which can function synergistically with the flavonoids to boost the anti-inflammatory potential of the test compounds. Some specific compounds have also been detected in recent years like three labdane diterpenoids Andrographolide, Neoandrographolide and 14-Deoxyandrographolide present in *Andrographis paniculata* and from *Acanthus illicifolius* triterpenoids like oleanic acid and Ursolic acid have been identified; These terpenoidal compounds can inhibit the inflammatory conditions by restricting the signalling pathways like Nuclear Factor Kappa-B (NF- κ B) and Mitogen-Activated Protein Kinase pathway (MAPK). These thereby reduce the concentration of pro-inflammatory cytokines like TNF- α , IL-6 and IL-1 β production in the body. Alkaloids like Asteracanthine and Asteracanthicine have been detected in *Hygrophila auriculata* while Vasicine and Vasicinone have been found in *Justicia adhatoda*. These nitrogen-containing compounds exhibit their activity by inhibiting the Cyclo-oxygenase-2 pathway, thereby suppressing the amount of prostaglandins and oxidative nitrous oxide produced in the body. Two Iridoid glucosides, like Grandifloride and Grandifloric acid, have been successfully isolated from *Thunbergia grandiflora*, promoting anti-inflammatory activity through inhibition of Leukocyte adhesion and migration

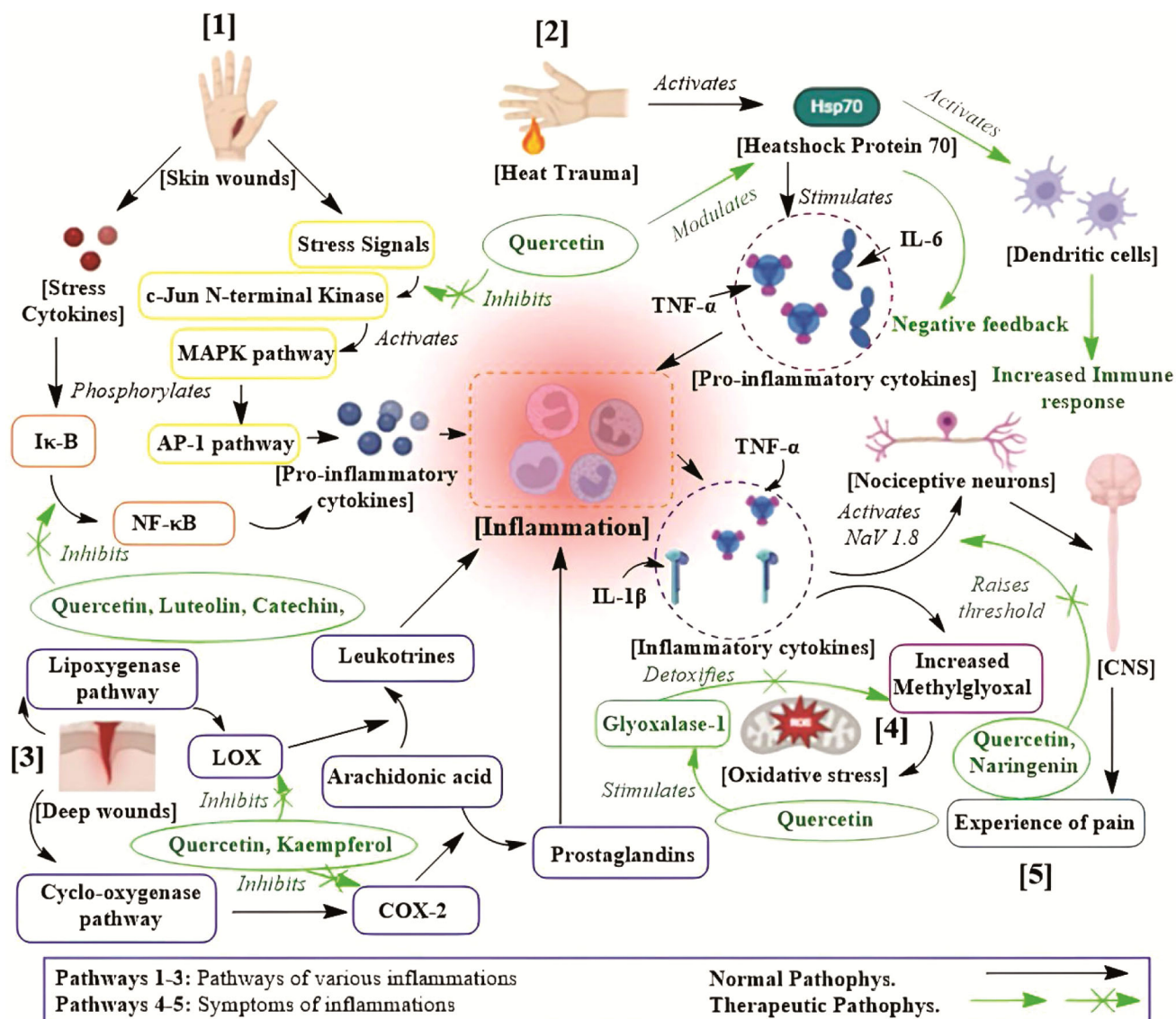


Fig. 7 — Anti-inflammatory action of Quercetin, Luteolin, Kaempferol and Catechin.

activity. Nevertheless, flavonoids are crucial molecules in modulating and stimulating the anti-inflammatory pathways in the body.

The main flavonoids responsible for the action are Quercetin, Apigenin, Naringenin, Kaempferol and their derivatives. Quercetin exhibits anti-inflammatory activity by inhibiting the heat shock proteins activated by heat trauma; inhibits the signalling pathways of MAPK, AP-1 and NF- κ B; it also suppresses the production of Prostaglandins and Leukotrienes by inhibiting the COX-2 and LOX pathways. The effects of inflammation in the body, like oxidative stress and experience of pain, are significantly reduced by the action of Quercetin. Apigenin inhibits inflammation by suppressing the

expression of endothelial adhesion molecules like E-selectin, ICAM and VCAM. Naringenin and kaempferol also exhibits similar mechanism of anti-inflammatory action. It has been found that different genera of medicinal plants consist of a singular class of flavonoids and their derivatives; however, in genus *Justicia*, the major classes of flavonoids responsible for the anti-inflammatory activity are present. The major flavonoids present are Quercetin, Apigenin and its derivative Apigenin-7-O-(6''-E-P-coumaroyl)- β -D-glucopyranoside, Naringenin, Kaempferitrin and Vitexin. These flavonoids exhibit anti-inflammatory activity through multiple pathways of pathophysiology, as elaborated in the context above. If the different genera are to be

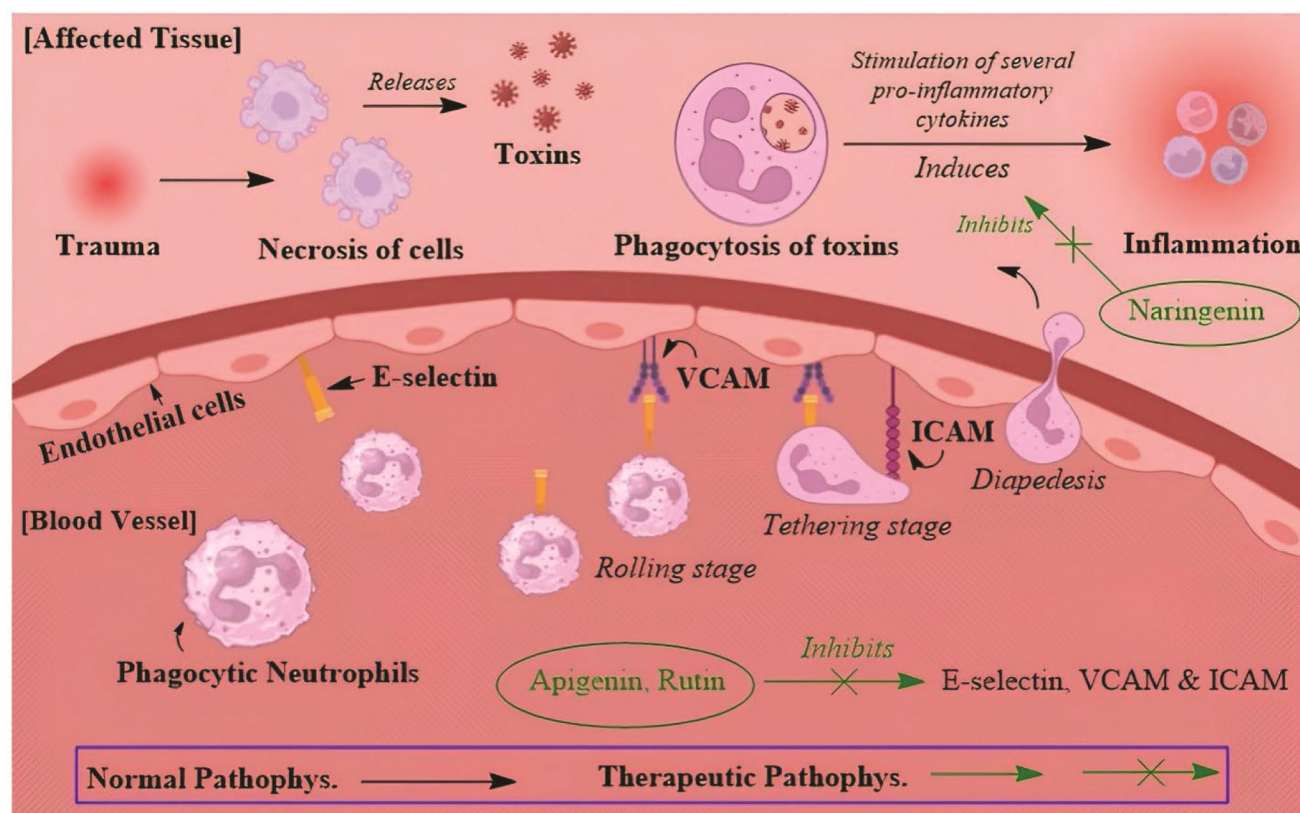


Fig. 8 — Anti-inflammatory action of apigenin, rutin and naringenin.

compared against each other, then *Justicia* is considered to be the most crucial and most therapeutic genus, having the major anti-inflammatory flavonoids and offering multiple physiological routes of anti-inflammatory action, followed by *Andrographis* being the second most important genus; succeeded by *Barleria* and *Hygrophila*. Several bioactive flavonoids along with their glycosylated derivatives have still not yet been quantified. These flavonoids can be isolated and estimated, and their anti-inflammatory activity with other phytoconstituents can be further investigated for formulating modern therapeutic molecules.

Conclusion

Inflammations can be considered to be a double-edged sword, being the immediate and most important defensive mechanism of the body against foreign agents or trauma; it also has long-lasting or chronic complexities in the body. The pathophysiology of inflammation is immensely complex, and no synthetic drug can aim for all the targets of the physiology, thus giving rise to toxicities and side effects. Thus, therapeutic agents from natural origin are being

considered, as almost 80% of modern medicines originate from natural molecules. Acanthaceae family of plants is one such family, which possess potent anti-inflammatory activity owing to their rich phytoconstituents mainly the bioactive flavonoids. This review thus converges the main genera, their respective species, their bioactive flavonoids and their role in targeting the pathophysiology of inflammations, with the focus to make a contribution to the research of formulating modern medicines.

Conflict of interest

The authors declare that there is no conflict of interest.

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