

Plants and Plant Constituents with Analgesic and Anti-inflammatory Activities: A Systematic Review

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ABSTRACT: Medicinal plants with potential therapeutic activities are a tremendous resources of prospective drug candidates. NSAIDs, opiates, and other anti-inflammatory & analgesic agents exhibit several unwanted side-effects. Thus, the development of new active compounds with minimum adverse effects necessitates an emergence. This study aims to provide a comprehensive summary of plant species and reported phytoconstituents with analgesic and anti-inflammatory activities. Eighty-seven species from fifty-two plant families with reported constituents and activities have been included in this review. In-depth research in the area of screening novel analgesic and anti-inflammatory agents from natural sources followed by the investigation of their pharmacological properties and clinical applications may lead to the generation of new active agents with better therapeutic activity and selectivity in the future.

Key words: Phytoconstituent, Plant extracts, Analgesic activity, Anti-inflammatory activity, Medicinal plants.

INTRODUCTION

Pain and inflammation are associated with each other. Pain is considered as an undesirable sensation and emotional experience that links to potential damage of tissue, whether inflammation is directly associated with the tissue injuries caused by various factors like infections (due to outside invaders; *e.g.*, bacteria or virus), chemicals, thermal deregulations, and mechanical circumstances. Pain lets the body to respond and preclude further tissue injuries, where pain sensation signals pass to the brain *via* nerve fibers for interpretation. On the other hand, inflammation is a defense mechanism against diverse aggressive agents comprising of parasites, pathogenic microbes, noxious chemicals, and physical injury to the tissue, which is also connected to the progression of enduring diseases like rheumatoid arthritis, cancer, Alzheimer's disease, asthma, etc. (Figure 1), where

heat, redness on the skin, swelling of tissues, pain, and loss of organ functions are considered as the cardinal signs of inflammation.^{1,2}

Various mediators like prostaglandins, cytokines, histamine, serotonin, substance P, and capsaicin can cause pain and inflammation. However, chemicals like prostaglandins specify and control tissue and cellular responses involving inflammation to protect the body from unidentified intruders. As a part of body's defense mechanism, the rush of endogenous mediators to the inflamed area can cause increased blood flow to the injured and/or infected area, resulting in skin blush, warmth, and swelling. These mediators, even in little quantities can trigger nerves and elicit a pain response. Higher quantities of these mediators produce joint irritation, swelling of the joint lining, and loss of cartilage over time. It has been reported that several degenerative syndromes like rheumatoid arthritis, polymyalgia rheumatism, along with cardiovascular diseases, asthma, malignancy, and inflammatory bowel diseases, are similarly associated with the physiological inflammatory progressions and concomitant ache.³

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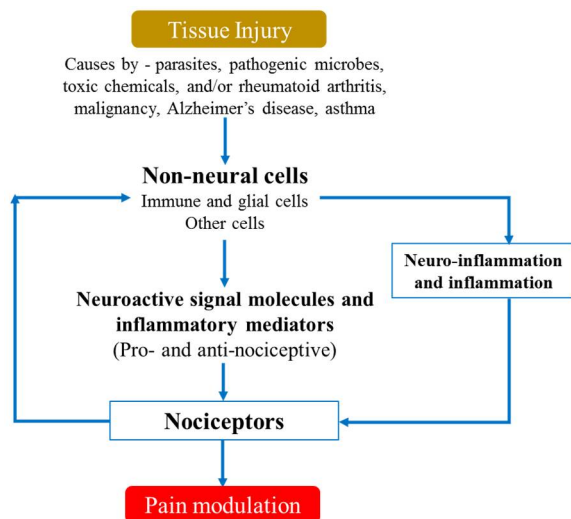


Figure 1. Interfaces between non-neuronal cells, neurons, and inflammation/neuroinflammation in diverse pain conditions after tissue injuries caused by various factors.

Pain is classified into two types - rapid and slow pain. Rapid pain can be sensed within a few seconds once the stimulant strikes the neural part of the brain, and the severity increases gradually in the following several seconds or even minutes. Conversely, the slow pain is accompanied by tissue damage leading to an intolerable condition. Such pain can be sensed both in skin and tissue or in superficial and deep organs.²

Inflammation can either be acute or chronic (*i.e.*, long-lasting). Typically, acute inflammation arises for a short duration yet often severe and resolves away within hours or days. However, chronic inflammation is a slower process and can last for months or years, which is thought to be linked to autoimmune disorders and prolonged stress.¹

Marketed analgesic and anti-inflammatory drugs mainly reveal their function by suppressing cyclooxygenase (COX) pathways of arachidonic acid metabolism responsible for the prostaglandin synthesis. Since mostly available analgesic and antiphlogistic agents have diverse adversarial consequences like gastric lesions, peptic ulcer links to NSAIDs, untoward thrombotic effects for selective COX-2 inhibitors, and opiates induce tolerance and addiction, the current drugs worsen the overall scenario and make these agents less effective. In this

case, prospective plant constituents with strong anti-inflammatory and analgesic activity are warranted to explore efficient and competent therapeutic agents.²

The core concept of this review is to summarize information on phytochemicals and plant extracts that have been tested and found effective against pain and inflammation, which are available on online databases, namely, Chemical Abstract Service (CAS) database, PubMed, Science Direct, Google Scholar, etc. This review compiles information on eighty-seven plant species belonging to fifty-two families that have been reported within 1992-2020 with analgesic and anti-inflammatory efficacy. Some of the reported structures for isolated phytochemicals are illustrated in Figures 2-6. This review will guide future researchers to explore further and isolate active phytochemicals aiming to the treatment of pain and inflammation.

Phytoconstituents reported from plants

Medicinal plants with pharmacological activities have long been used conventionally to treat diseases or fight against sickness. Phytotherapeutic agents, or herbal medicinal products with minimum or lower side effects are being used as medicament since the prehistoric era. This review article contains a summary of coherent and evidence-based research information on the usage of phytotherapeutic agents in preclinical animal models for pain and inflammation study.

***Acacia hydasypica* R parker (Leguminosae).** The ethyl acetate fraction, obtained from the methanolic crude extract of aerial parts of *A. hydasypica*, affords 7-O-galloyl catechin (**2.1**, Figure 2), catechin (**2.2**, Figure 2) and methyl gallate (**2.3**, Figure 2). The isolated compounds show significant antipyretic, analgesic, and anti-inflammatory properties.⁴

***Acacia modesta* (Fabaceae).** Bukhari *et al.* described that the methanolic extract of *Acacia modesta* leaves causes substantial inhibition of the writhing effect in mice induced by acetic acid and repressed the licking response induced by formalin in animals, after intraperitoneal administration (*i.p.*), at

doses of 50 and 100 mg/kg. Additionally, the extract, at doses of 50-200 mg/kg i.p., produced a remarkable antiphlogistic effect in carrageenan-induced rat paw edema compared to that of the standard drug, diclofenac. These results suggested the prominent pain-relieving and anti-inflammatory properties of the plant.⁵

***Agrimonia eupatoria* L. (Rosaceae).** Polyphenolic compounds, isolated from the ethyl acetate fraction achieved from the aqueous extract of the aerial parts of *Agrimonia eupatoria*, have been

found to have antioxidant, anti-inflammatory, and peripheral analgesic properties.⁶

***Alchornea cordifolia* (Euphorbiaceae).** Several phytoconstituents like diisopentenyl guanidine (**2.4**), triisopentenyl guanidine (**2.5**), β -sitosterol (**2.6**), and daucosterol (**2.7**), illustrated in Figure 2, were isolated and identified from the hexane portion of the methanolic hot extract of *A. cordifolia*. These compounds were reported to have prominent anti-inflammatory properties.⁷

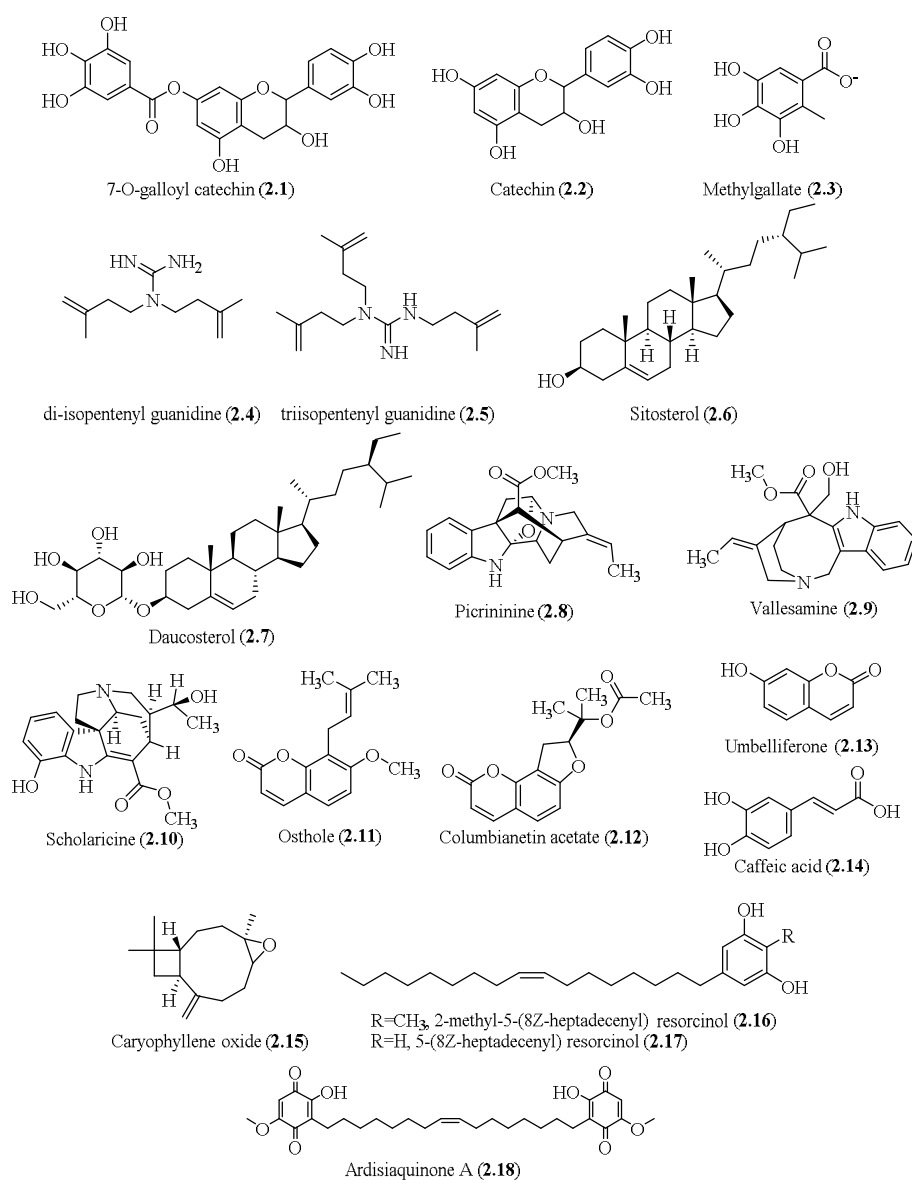


Figure 2. Some naturally occurring plant constituents and their structures having analgesic and anti-inflammatory properties.

***Alstonia scholaris* (Apocynaceae).** Picrinine (2.8), vallesamine (2.9), and scholaricine (2.10), illustrated in Figure 2, are the main alkaloids that have been found from the ethanolic extract of *Alstonia scholaris* leaves and contained significant analgesic and anti-inflammatory effects.⁸

***Angelica pubescens* (Apiaceae).** The chloroform and ethyl acetate extracts, attained from the methanolic crude root-extract of *A. pubescens*, indicated analgesic and anti-inflammatory activities. Sixteen compounds were isolated through further chromatographic technique from these extracts, and out of the isolated phytoconstituents, osthole (2.11), columbianetin acetate (2.12), umbelliferone (2.13), caffeic acid (2.14), illustrated in Figure 2, revealed substantial anti-inflammatory and analgesic activities.⁹

***Annona squamosa* L. (Annonaceae).** Caryophyllene oxide (2.15, Figure 2) was isolated, purified and characterized from the unsaponified pet ether extract of *Annona squamosa* bark. This compound exhibited noticeable central and peripheral analgesic effects along with antiphlogistic efficiency.¹⁰

***Apium graveolens* (Apiaceae).** The methanolic leaves-extract of *A. graveolens* displayed noteworthy antiphlogistic activity in rats at a dose of 300 mg/kg body weight. The authors have postulated that the existence of flavonoids and saponins in the methanolic extract is accountable for the bioactivity.¹¹

***Ardisia sieboldii* (Primulaceae).** Three phyto-compounds, 2-methyl-5-(8Z-heptadecenyl) resorcinol (2.16, Figure 2), 5-(8Z-heptadecenyl) resorcinol (2.17, Figure 2), and ardisiaquinone A (2.18, Figure 2), were identified from the methanolic extract of *A. sieboldii*, which demonstrated cytotoxic and antiphlogistic properties through inhibiting protein denaturation, nitrite development, and COX-2 inhibition.¹²

***Astragalus arbusculinus* (Fabaceae).** Shojaii and co-workers confirmed that the aqueous extract of *A. arbusculinus* gum could dose-dependently exhibit

acute and chronic anti-inflammatory properties in formalin-induced inflammation tests and analgesic effects in the hot-plate test.¹³

***Avicennia officinalis* (Acanthaceae).** Ethanolic extract of *A. officinalis* leaves exhibited 18.75% and 51.88% writhing inhibition in Swiss-albino mice at the doses of 250 and 500 mg/kg body weight, respectively, which proved the analgesic potential of the extract.¹⁴

***Bacopa monnieri* Linn. (Plantaginaceae).** The ethanolic extract of *B. monnieri* exhibited anti-inflammatory activity. According to Chana *et al.*, the antiphlogistic activity of *B. monnieri* was believed to be attributed to the isolated triterpene, betulinic acid (3.1, Figure 3).¹⁵

***Bauhinia purpurea* Linn. (Fabaceae).** It was reported that the ethanol extract of *Bauhinia purpurea* bark possesses the good analgesic activity and causes a substantial decline of 5-HT induced edema in rats, which evidenced its anti-inflammatory property.¹⁶

***Boerhavia procumbens* (Nyctaginaceae).** Out of methanolic crude extract of *B. procumbens* and varied fractions, for example, hexane, ethyl acetate, and *n*-butanol, prepared from the methanolic crude extract of *B. procumbens*, only methanol crude extract and *n*-butanol fraction showed anti-inflammatory activity.¹⁷

***Bougainvillea glabra* (Nyctaginaceae).** The essential oil, extracted from *B. glabra*, can block the nociceptive responses (*i.e.*, the course of stalling the recognition of painful or injurious spur by sensory neurons) and can show antiphlogistic activity. The antiphlogistic activity occurred through the suppression of both prostaglandins and the histamines in rats at doses of 100 mg/kg and 200 mg/kg body weight.¹⁸

***Bryophyllum pinnatum* (Crassulaceae).** The aqueous leaves-extract of *B. pinnatum* and a steroidal compound, stigmast-4, 20(21), 23-trien-3-one (3.2, Figure 3), isolated from *B. pinnatum*, exhibited prominent analgesic and anti-inflammatory activities.¹⁹

***Cassia siamea* (Fabaceae).** Among the petroleum, chloroform, ethanol, and aqueous extractives of the stem-bark of *Cassia siamea*, ethanolic and aqueous portions showed substantial and dose-dependent pain-relieving and antiphlogistic effects in rats at doses of 100, 200, and 400 mg/kg of body weight.²⁰

***Castanospermum australe* A. (Fabaceae).** The ethanolic leaves extract of *C. australe* showed potential analgesic property ($p < 0.001$) at a dose of 400 mg/kg in both hot plate (5.85 s) and acetic acid-persuaded writhing experiment (57%). Moreover, the extract showed anti-inflammatory property at a dose of 400 mg/kg in carrageenan-induced paw edema. The extract was found to be safe and devoid of toxicity, even at a larger dose of 2000 mg/Kg.²¹

***Citrullus colocynthis* (Cucurbitaceae).** The aqueous extracts of roots, stem, fruits, and seeds of *C. colocynthis* were assessed to weigh the analgesic and antiphlogistic properties without inducing critical toxicities. The stem and root extracts had presented to hold insignificant inhibitory activity against pain and inflammation models but were documented to inhibit rat paw edema at varying doses.²²

***Cleome scaposa* DC. (Cleomaceae).** The methanolic extract of *Cleome scaposa* leaves was evaluated for its painkilling and antiphlogistic efficacy by using analgesia meter test (intraperitoneally) in rats and carrageenan-induced rat paw edema (orally), respectively. The outcomes exhibited that the extract could substantially block the algesic responses and inflammatory consequences in tested animals.²³

***Cnestis ferruginea* (Connaraceae).** Varied oral doses (100, 200, and 400 mg/kg) of the methanolic root-extract of *C. ferruginea* were found to have significant analgesic property established through acetic acid and formalin-induced-writhing experiment. The nociceptive reaction potential was also noticeable in both tail clip and hot plate studies. The methanolic extract demonstrated substantial antiphlogistic property in inflammation experiments through dose-dependent inhibition of edema

development in the carrageenan-, formaldehyde-, egg albumin- and xylene-induced animal models.²⁴

***Combretum fragrans* F. Hoffm (Combretaceae).** Mbiancha *et al.* reported combretin A (3.3, Figure 3) and combretin B (3.4, Figure 3), identified in the ethyl acetate fraction of the methanolic crude extract of *C. fragrans* leaves, with significant antinociceptive and anti-inflammatory properties.²⁵

***Crataeva tapia* (Capparaceae).** Lectin was isolated from *Crataeva tapia* bark that exhibited anti-inflammatory and antinociceptive potential along with its significant anti-tumour property.²⁶

***Cyathula prostrata* Linn. Blume (Amaranthaceae).** The carrageenan, arachidonic acid, and xylene-induced experiments were conducted to assess the antiphlogistic properties of the methanolic extract of *C. prostrata*, and it was reported that the extract has substantial anti-inflammatory efficacy. The extract also demonstrated significant inhibition of the acetic acid-induced analgesia dose-dependently ($p < 0.05$) as well as in the hot plate analgesic experiments ($p < 0.001$).²⁷

***Cymbopogon citratus* (Poaceae).** Phytochemical evaluation on the methanolic extract of *Cymbopogon citratus* leaves revealed the presence of several classes of phytoconstituents like alkaloids, steroids, flavonoids, tannins, saponins, and carbohydrates, which possess moderate analgesic activity.²⁸

***Dracaena ombet* (Dracaenaceae).** It was reported that *Dracaena ombet* leaf contains two saponins, (25R)-5 β -spirostan-3- β -ol-3-O- β -D-galactopyranosyl-(1"→4")-O- β -D-galactopyranosyl-(1"→3')-O- β -D-glucopyranoside (3.5, Figure 3), and (25R)-5 β -spirostan-3- β -ol-3-O- β -D-galactopyranosyl-(1'"→4")-O- β -D-glucopyranosyl-(1"→3')-O- β -D-glucopyranoside (3.6, Figure 3), with noteworthy analgesic and antiphlogistic properties at the dose of 30 mg/kg body weight.²⁹

***Erigeron floribundus* (Asteraceae).** Asongalem *et al.* described that the aqueous extract of *Erigeron floribundus* has the ability to decrease the writhings effects in abdominal contractions caused by the induction of acetic acid and lickings of formalin-

induced ache and also expressively reduce the rat paw edema volume, which has suggested that the extract has palliative and anti-inflammatory properties.³⁰

***Erythrina senegalensis* (Fabaceae).** The aqueous stem-bark-extract of *E. senegalensis* was

proven to have strong analgesic properties along with potent acute anti-inflammatory activity, which were evaluated through acetic acid (0.75% v/v)-induced abdominal contraction and egg-albumin persuaded paw oedema in the rat model, respectively.³¹

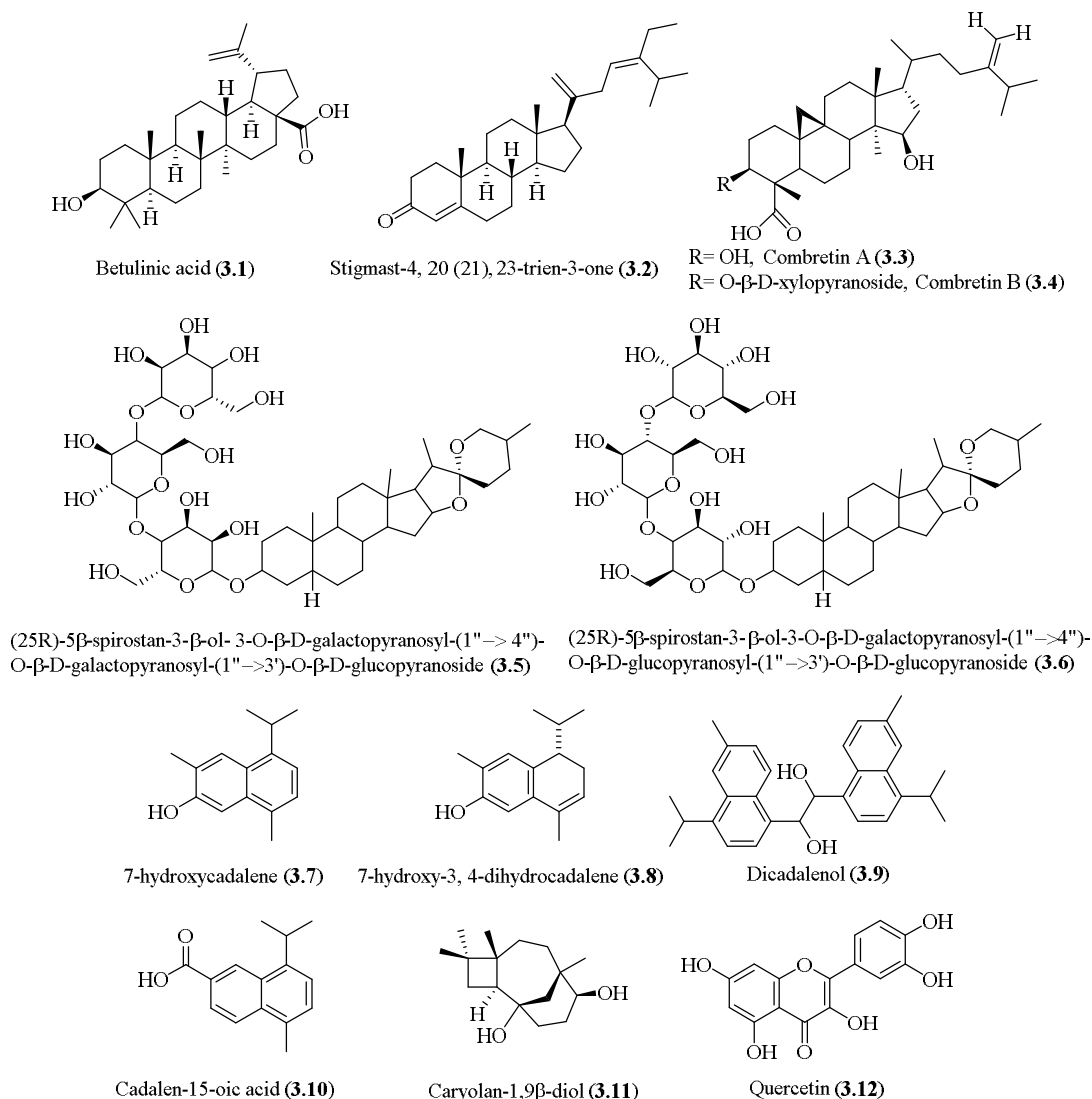


Figure 3. Some reported naturally occurring pain-relieving and antiphlogistic compounds with their structures.

***Eucalyptus* (Myrtaceae).** Silva and co-workers confirmed that the essential oil, extracted from three species of *Eucalyptus*, *E. citriodora*, *E. tereticornis* and *E. globulus*, possess central and peripheral analgesic properties since they evaluated the efficacy by measuring writhing effects on the acetic acid-

induced mice and through hot-plate thermal stimulation in rats. Besides, the oil extracts provided antiphlogistic effects, as shown in inhibition of carrageenan- and dextran-induced rat paw edema.³²

***Eugenia uniflora* Linn (Myrtaceae).** The crude acetone: water (7:3, v/v) extract and semi-purified

fractions of *Eugenia uniflora* leaf showed analgesic potential on the mice abdominal writhing model in a study conducted by Falcão and co-workers.³³

***Ficus iteophylla* (Moraceae).** It was reported that the ethanol leaf extract of *F. iteophylla* could reduce the acetic acid-induced abdominal constriction as an indicative test to evaluate the analgesic property. Additionally, the ethanolic extract has the ability to reduce carrageenan-induced paw edema in rats which confirm its antiphlogistic property.³⁴

***Globimetular braunii* Van Tieghem (Loranthaceae).** The painkilling property and antiphlogistic activity of ethanolic leaf-extract of *G. braunii* were confirmed through the hot-plate experiment and acetic acid-induced writhing method in mice, and by using the carrageenan-induced paw edema in rats, correspondingly. The extract showed positive responses noticeably in both events expressively exerting the analgesic and antiphlogistic activities of *G. braunii*.³⁵

***Haplophyllum tuberculatum* (Rutaceae).** Hamdi and co-workers screened three extracts, viz. pet-ether, ethyl acetate and butanolic extracts, to evaluate the antiphlogistic and pain-relieving properties of *H. tuberculatum* and it was reported that all the extracts of *H. tuberculatum* leaves could potentially reduce the inflammatory manifestations and analgesia.³⁶

***Heterotheca inuloides* Cass (Asteraceae).** Rodríguez-Chávez and co-workers reported the presence of 7-hydroxycadalene (**3.7**), 7-hydroxy-3,4-dihydrocadalene (**3.8**), dicadalenol (**3.9**), cadalen-15-oic acid (**3.10**), caryolan-1,9 β -diol (**3.11**), quercetin (**3.12**), illustrated in Figure 3, in the butanol fractions of *H. inuloides* extract. It has been reported that compounds **3.8-3.13** and a semisynthetic compound, 7-benzoxycadalene, have possessed antiphlogistic properties, and dicadalenol (**3.9**) exhibited *in-vivo* anti-inflammatory efficacy greater than indomethacin. Conversely, 7-hydroxy-3,4-dihydrocadalene (**3.8**) demonstrated a substantial antinociceptive action, similar to diclofenac.³⁷

***Hypericum perforatum* (Hypericaceae).** In 2005, Abdel-Salam reported that *H. perforatum*

extract has both antiphlogistic and antinociceptive potentials. Subcutaneous administration of *H. perforatum* (50-300 mg/kg) resulted in a dose-dependent inhibition of edema forming response towards the carrageenan-induced inflammation. To evaluate the nociception potential, *H. perforatum* was administered orally, and the extract exhibited antinociceptive responses in the tail-immersion and hot plate experiment. However, the writhing responses in acetic acid-induced (0.6%, i.p.) animal model was not noticeably observed.³⁸

***Ilex pubescens* Hook et Arn. (Aquifoliaceae).** Two new saponins, pubescenosides C (**4.1**, Figure 4) and D (**4.2**, Figure 4), structurally elucidated as (20 β)-3-O-[[β -D-glucopyranosyl-(1 \rightarrow 2)- β -D-xylopyranosyl]ursa-12,18-dien-28-oic acid 28-O- β -D-glucopyranosyl ester and (20 β)-3-O-[[β -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-glucopyranosyl-(1 \rightarrow 2)- β -D-xylopyranosyl]ursa-12,18-dien-28-oic acid 28-O- β -D-glucopyranosyl ester, were isolated from ethanolic root extracts of *Ilex pubescens*, which exerted effective anti-inflammatory property on carrageenan-induced paw edema in mice models.³⁹

***Jasminum sambac* (Oleaceae).** It was reported by Sengar and co-workers that the ethanolic root extract of *J. sambac* could reduce the writhing count up to 49.21% at an oral dose of 400mg/kg. However, in the tail-flick experiment, the extract increased the latency in the flicking tail dose-dependently, indicating its pain-relieving potential. The ethanolic extract, at the oral dose of 400 mg/kg, also showed substantial antiphlogistic activity at the 2nd, 3rd, 4th, and 6th hour of treatment in carrageenan-induced edema.⁴⁰

***Jatropha curcas* (Euphorbiaceae).** The painkilling effect and the anti-inflammatory property of the methanolic extract of *J. curcas* leaves were evaluated *via* writhing test on acetic acid-induced mice models and by using egg albumin-induced edema of the rat paw, respectively. The extract showed both the analgesic and antiphlogistic competency in the study reported by Uche *et al.*⁴¹

***Lactuca sativa* (Asteraceae).** Two triterpene lactones, namely 3,14-dihydroxy11,13-

dihydrocostunolide (**4.4**, Figure 4) and 8-tigloyl-15-deoxyl-actucin (**4.5**, Figure 4) were identified in the leaf extract of lettuce (*i.e.*, *Lactuca sativa*). Both compounds demonstrated dose-dependent anti-inflammatory action in a carrageenan model of inflammation.⁴²

Lactuca scariola (Asteraceae). The methanolic seed-extract of *L. scariola* was prepared through the cold extraction method, which was later found to have significant analgesic activity on intact mice through tail-flick latency period estimation during the tail immersion assay method.⁴³

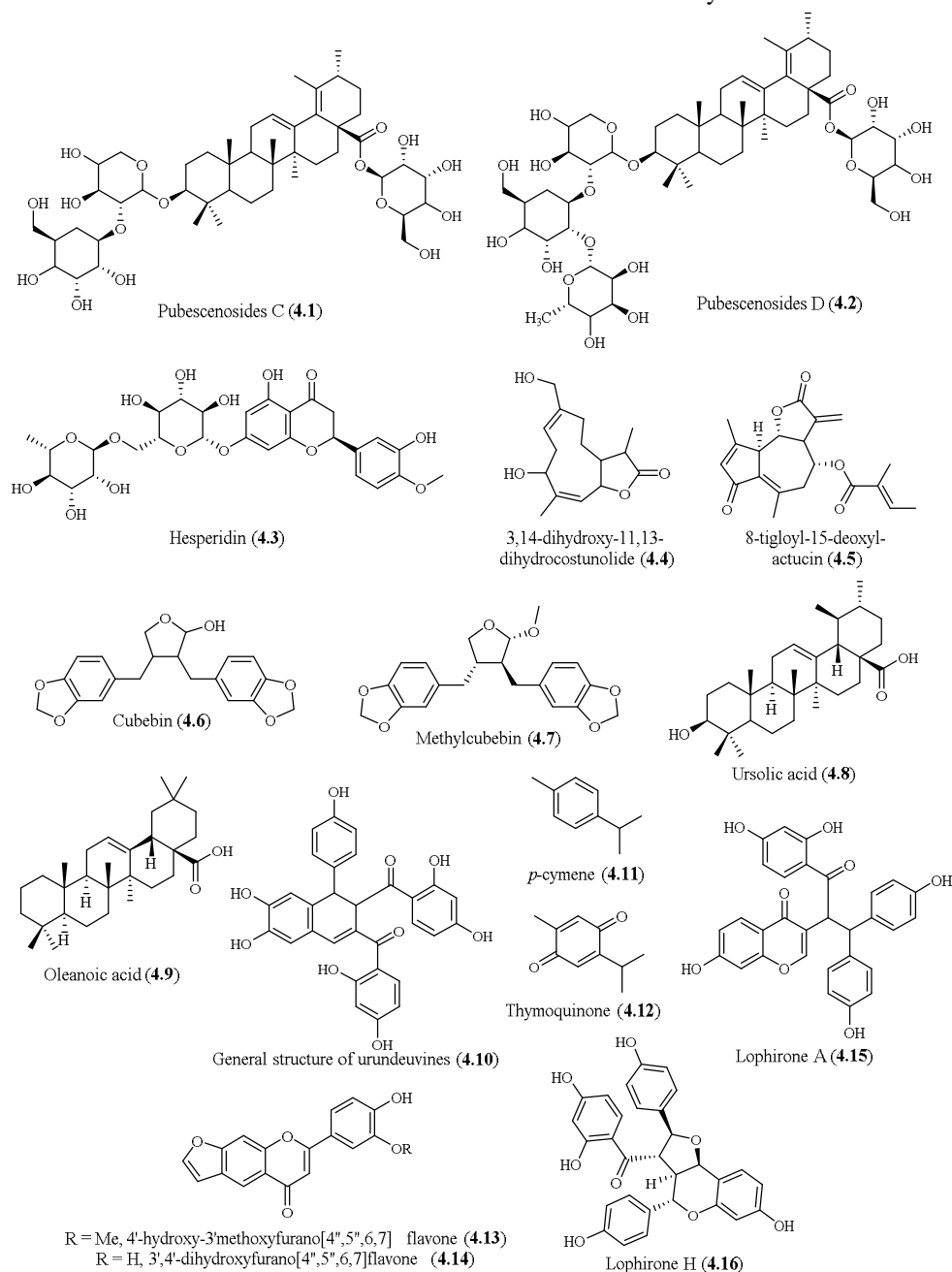


Figure 4. Few other reported phytoconstituents with analgesic and anti-inflammatory potentials.

***Lavandula angustifolia* (Lamiaceae).** Hydroalcoholic extract and the polyphenolic fraction of *Lavandula angustifolia* leaves showed potent analgesic and anti-inflammatory activities.⁴⁴

***Lychnophora ericoides* (Asteraceae).** The dichloromethane extract of *L. ericoides* roots yielded ten lignans, and cubebin (**4.6**) was reported as the most bioactive phytochemical. Cubebin (**4.6**) and methylcubebin (**4.7**), illustrated in Figure 4, possessed substantial analgesic activity in the writhing experiment on acetic acid-induced mice model, however, failed to show obvious antiphlogistic efficacy.⁴⁵

***Madhuca indica* (Sapotaceae).** Crude methanolic extract of the aerial parts of *M. indica* demonstrated similar anti-inflammatory, analgesic, and antipyretic properties compared to the standard NSAIDs like paracetamol and phenylbutazone. The presence of natural flavonoids, steroids and/or triterpenes in the extract are believed to be accountable for such anti-inflammatory and analgesic actions.⁴⁶

***Mahonia oiwakensis* (Berberidaceae).** Chao and co-workers have identified and reported that the ethanolic root extract of *M. oiwakensis* can reduce the writhing responses in acetic acid-induced animal model and licking times of the second phase in the formalin test in mice and also can lessen the carrageenan-induced mice paw edema, which suggested that the extract has analgesic and anti-inflammatory potential.⁴⁷

***Mallotus repandus* (Euphorbiaceae).** The methanolic extract of the *Mallotus repandus* stem exhibited remarkable analgesic responses in the writhing test induced by acetic acid, tail immersion assay, hot-plate test, and formalin-induced hind paw licking inhibition experiment. The extract also showed effective antiphlogistic action in carrageenan-induced edema in the paw, xylene-induced edema in the ear, and cotton pellet-induced granuloma studies.⁴⁸

***Mangifera indica* (Anacardiaceae).** The aqueous extract of the bark of *Mangifera indica* L.

(Vimang[®]) was reported for its antinociceptive and anti-inflammatory properties. The analgesic activity was found to be greater than that of indomethacin. The aqueous extract gave comparable anti-inflammatory potential to the standard oral dosages of indomethacin and sodium naproxen. According to Garrido *et al.*, the presence of several polyphenols in aqueous extract (Vimang[®]) are accountable for the antinociceptive and anti-inflammatory actions of Vimang[®].⁴⁹

***Miconia albicans* (Melastomataceae).** Ursolic acid (**4.8**, Figure 4) and oleanolic acid (**4.9**, Figure 4) were isolated as an isomeric mixture from the crude dichloromethane extract of the aerial parts of *M. albicans*, which possess analgesic and anti-inflammatory potentials.⁵⁰

***Moringa oleifera* (Moringaceae).** Martínez-González and co-workers confirmed that the polar extracts of the *M. oleifera* leaves have persistent antinociceptive and anti-inflammatory properties. The non-polar extracts also exhibited effective responses against ache and inflammation.⁵¹

***Myracrodruon urundeuva* Allemão (Anacardiaceae).** Chalcone enriched fractions of the ethyl acetate extract of the *M. urundeuva* stem bark was reported to have three dimeric chalcones namely urundeuvin I, II, and III (**4.10**, the general structure of urundeuvine, Figure 4), which demonstrated peripheral and central analgesic activity and anti-inflammatory properties.⁵²

***Nelsonia canescens* (Acanthaceae).** Owoyele and co-workers reported that the ethanolic extract of dried leaves of *N. canescens* is orally active and comprises flavonoids and saponins as chief phytoconstituents, which were proven previously for their ability to inhibit pain sensitivity along with their inhibitory actions for acute and chronic inflammatory processes in rats.⁵³

***Nilgella sativa* L. (Ranunculaceae).** Traditionally, the seed of this plant is known as black cumin and the steam-distilled fraction of essential oil of *N. sativa* seed, containing para-cymene (**4.11**,

Figure 4) and thymoquinone (4.12, Figure 4), have analgesic and anti-inflammatory properties.⁵⁴

***Nyctanthes arbortristis* (Oleaceae).** β -sitosterol, obtained from the pet-ether extract of *N. arbortristis* leaves demonstrated both analgesic and antiphlogistic potential, and the possible mechanism is thought to be the suppressed formation of prostaglandins and bradykinins.⁵⁵

***Ochna squarrosa* (Ochnaceae).** Two new furanoflavonoids, 4'-hydroxy-3'-methoxyfuran [4'',5'',6,7] flavone (4.13) and 3', 4'-dihydroxyfuran[4'',5'',6,7]flavone (4.14), two new chalcone dimers, lophirone A (4.15) and lophirone H (4.16), illustrated in Figure 4, were obtained from the ethyl acetate fraction of the methanolic crude extract of *O. squarrosa* root-bark, which showed notable analgesic and anti-inflammatory properties.⁵⁶

***Parinari polyandra* (Chrysobalanaceae).** The antinociceptive effect of the methanolic extract of the *P. polyandra* stem-bark was confirmed at doses of 100 mg/kg and 200 mg/kg body weight. However, the responses were not found to follow the dose-dependent manner. Conversely, the antiphlogistic effects of the extract in rat hind-paw edema, induced by albumin, was found to work dose-dependently.⁵⁷

***Passiflora foetida* L. (Passifloraceae).** The ethanolic extract of *P. foetida* leaves was assessed for its pain-relieving properties via the writhing test with acetic acid-induced animal model and hot plate technique in Swiss Albino mice. The antiphlogistic property was evaluated for the same extract in acute paw edema in rats through inducing carrageenan and histamine. At a dose of 200 mg/kg body weight, the leaf extract gave the highest analgesic effect at 20 min in the hot-plate technique in the mice model. However, the ethanolic extract provided substantially significant anti-inflammatory action in rats at a dose of 100 mg/kg.⁵⁸

***Passiflora subpeltata* Ortega (Passifloraceae).** Saravanan and co-workers suggested that *P. subpeltata* extracts can be used as an alternative or supplement to the herbal remedy to treat analgesia, inflammatory responses and pyretic conditions based on the preliminary *in-vivo* experimental outcomes on

the acetone extract of the leaves of *P. subpeltata* in mice and rats.⁵⁹

***Phaseolus vulgaris* Linn (Fabaceae).** Pradeepkumar *et al.* suggested the possible presence of steroids and flavonoids in the pet-ether extract of the seeds of *P. vulgaris*, which exerted substantial analgesic and antiphlogistic actions in mice and rats, respectively.⁶⁰

***Phyllanthus reticulatus* (Euphorbiaceae).** Out of three extracts, *i.e.*, pet-ether, ethyl acetate, and methanolic extract of *Phyllanthus reticulatus*, the ethyl acetate extract gave 51.23% and 65.12% inhibition of writhing in the writhing test in mice model, induced by acetic acid, at doses of 150 and 300 mg/kg, respectively. The methanolic extract exhibited 40.03% inhibition of edema formation at the end of the 4th hour in a carrageenan-induced rat paw edema rat-model at the dose of 300 mg/kg. Thus, the results suggested that the extracts of *P. reticulatus* comprised substantial pain-relieving and antiphlogistic properties.⁶¹

***Piper betle* (Piperaceae).** The methanolic extract of *Piper betle* leaves, at doses of 100 and 200 mg/kg, produced a noteworthy ($p < 0.05$) upsurge in the onset of pain in the hot-plate experiment, whereas reduced acetic acid-induced writhing significantly ($p < 0.05$) and lessen the number of licks induced by formalin dose-dependently. The leaf extract, at the same doses, also inhibited the carrageenan-induced paw edema after 4 hours of dosing in a dose-dependent manner, suggesting the potential analgesic and anti-inflammatory properties of the plant.⁶²

***Pisonia aculeata* (Nyctagenaceae).** The methanolic extract of *Pisonia aculeata* leaves significantly ($p < 0.001$) inhibited rat paw edema after oral administration (200 μ g/mL), which was pronounced at 4th and 5th hour of carrageenan injection. The leaf extract produced 35.21% and 79.14% inhibition of acetic acid-induced writhing at 250 and 500 mg/kg doses, respectively, and inhibited 49.19% early and 73.14% late phase of formalin-induced hyper nociception at 500 mg/kg dose.⁶³

***Pistacia integerrima* (Anacardiaceae).** *Pistacia integerrima* demonstrated a substantial pain-relieving

effect against chemically induced-pain ($p < 0.001$), whereas the galls extracts had significant protection against thermally induced algesia ($p < 0.0001$) in a dose-dependent way. Orally given galls extracts showed significant ($p < 0.05$) analgesic activity in thermally-induced algesia at a dose of 200 mg/kg. Additionally, the extracts, at oral doses of 50-200 mg/kg, gave moderate efficacy in acute and chronic inflammations, induced by formalin, in rat hind paw ($p < 0.01$).⁶⁴

***Plinia edulis* (Myrtaceae).** A leaf infusion was made from *Plinia edulis*, which showed antinociceptive activity in the acetic acid-induced writhing test in mice model through the reduction of writhing conditions in mice, as well demonstrated positive indications in the mechanical nociceptive paw test in rats. The leaf infusion was also found to have anti-inflammatory effects since the extract could inhibit carrageenan-induced footpad edema and leukocyte conscription into the peritoneal cavity in rats. Azevedo and co-workers postulated that the leaf infusion is comprised of triterpenoids and flavonoids, which are responsible for such bioactivity.⁶⁵

***Pogostemon cablin* (Lamiaceae).** The methanolic extract of *P. cablin* was tested for its analgesic and anti-inflammatory activities. The analgesic action was examined through the acetic acid-induced writhing test and by measuring the formalin-induced hind paw licking responses. The anti-inflammatory effect was evaluated through measuring responses related to edema formation in λ -carrageenan-induced mice paw. The decrease in creeping responses and drop of licking time in the second stage of the formalin test has supported the analgesic potential of the methanol extract of *P. cablin*. Moreover, the reduction in paw edema inflammation indicated its anti-inflammatory property.⁶⁶

***Portulaca oleracea* L. (Portulacaceae).** Chan *et al.* reported that intraperitoneal and topical administration of 10% ethanolic extracts of the aerial parts of *P. oleracea* has significant pain-relieving and anti-inflammatory properties.⁶⁷

***Pothomorphe umbellata* L. (Piperaceae).** In 2005, Perazzo and co-workers claimed that the oral administration (at a dose of 550 mg/kg) of crude water-ethanolic extract (70%) of the aerial parts of *P. umbellata* (synonym: *Heckeria umbellata* (L.) Kunth, *Piper umbellatum* L.) has an ability to lessen the inflammatory processes by 48.7% in carrageenan-induced rat paw edema assay. Moreover, it was reported that the number of writhing induced by the intraperitoneal injection of 0.6% acetic acid solution was dropped by 22% ($p < 0.05$) in a group of mice that were given *P. umbellata* crude extract orally.⁶⁸

***Pterocephalus hookeri* (Caprifoliaceae).** The ethanolic and aqueous extracts of *Pterocephalus hookeri* leaves exhibited both central and peripheral pain-relieving and antiphlogistic properties in traditional analgesic and anti-inflammatory assay methods. Further phytochemical screening on *P. hookeri* extracts by Zhang *et al.* has confirmed the presence of iridoid monoterpenoid, loganin (**5.1**, Figure 5), and saponins, which are believed to be the bioactive phytoconstituents with an ability to inhibit inflammatory responses as well as pain sensations.⁶⁹

***Ramulus mori* L. (Moraceae).** The *cis*-mulberroside A (**5.2**, Figure 5) was isolated from *R. mori* and reported by Zhang *et al.* that the **5.2** can produce a dose-dependent inhibition of pain due to the induction of acetic acid and has an ability to lessen Evans blue leakage in mice. Additionally, this compound exerted substantial systemic antiphlogistic action both in carrageenan-induced mouse paw edema and formalin-induced test.⁷⁰

***Rhododendron aureum* (Ericaceae).** A glycosidic compound, rhododendrin (**5.3**, Figure 5), was isolated from the butanol fraction of the methanolic crude extract of *R. aureum* leaves. Oral administration of rhododendrin demonstrated a reduction in writhing responses by 38.7% and 44.1% in acetic acid and *p*-benzoquinone-induced writhing test, respectively, at a dose of 20 mg/kg. The compound also gave an inhibitory action in carrageenan-induced paw edema in mice at a similar dose, which suggested the analgesic and anti-inflammatory properties of the compound.⁷¹

***Rhus chirindensis* (Anacardiaceae).** The aqueous extract of *Rhus chirindensis* stem-bark demonstrated substantial analgesic, anti-inflammatory and hypoglycemic effects in mice and rats. The flavonoids, tannins, and triterpenoids, present in the extract, were hypothesized to be responsible for such bioactivities of the aqueous extract.⁷²

***Salvia divinorum* (Lamiaceae).** Salvinorin A (5.4, Figure 5), a strong κ -opioid receptor agonist and

an allosteric modulator of cannabinoid type 1 (CB1) receptors, was isolated from *S. divinorum*. It was reported that 5.4 and its analogs could reduce pain induced by neuropathy and inflammation.⁷³

***Salvia lachnostachys* (Lamiaceae).** A diterpene, fruticulin A (5.5, Figure 5), was found from the ethanolic extract of the leaves of *Salvia lachnostachys*, which exerted anti-hyperalgesic and anti-inflammatory properties in mice and rat models.⁷⁴

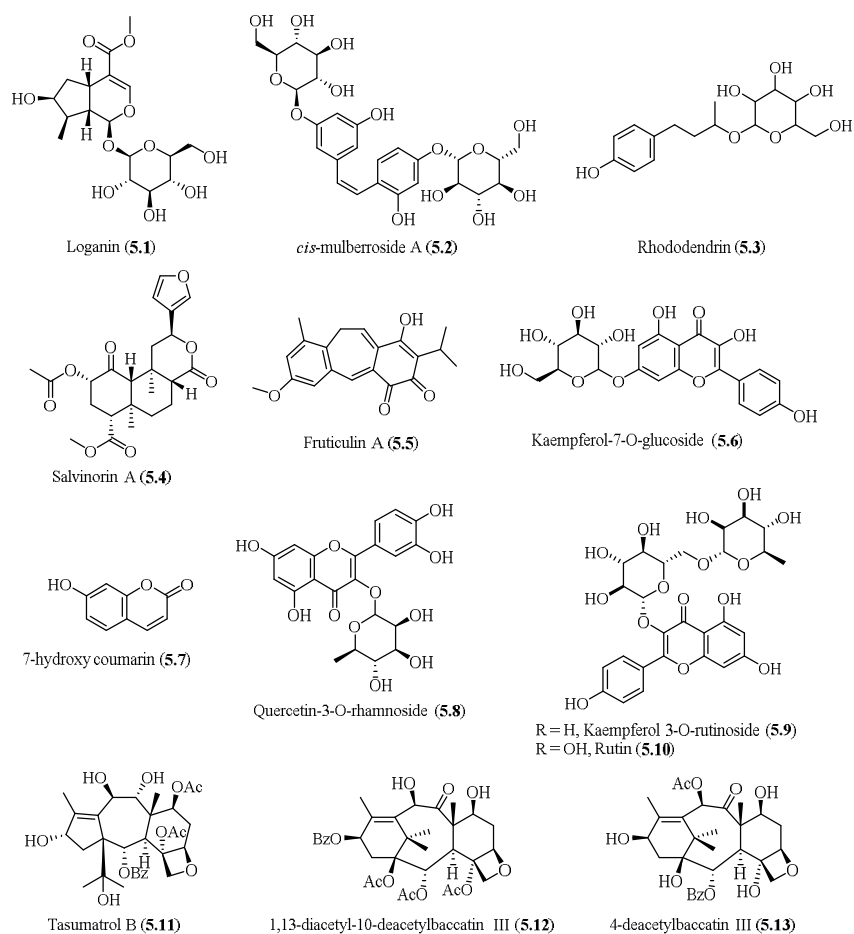


Figure 5. Bioactive phytochemicals isolated from plants with potent analgesic and anti-inflammatory properties.

***Securinega virosa* (Phyllanthaceae).** Acetic acid-induced writhing assay in mice model and formalin-induced pain test in rats were utilized to evaluate the analgesic effects of methanolic extract of *S. virosa* (synonym: *Flueggea virosa*) leaves. The responses of the leaves extract on acute inflammation was further studied on carrageenan-induced rat paw

edema. The extract was found to have substantial inhibitory properties ($p < 0.01$) of the acetic acid-induced writhing in mice. Besides, the extract could attenuate the neurogenic stage of the formalin-induced pain in rats significantly ($p < 0.05$). The methanolic extract showed a moderate anti-inflammatory activity as well.⁷⁵

***Sterculia tragacantha* (Sterculiaceae).** Hexane, chloroform, ethyl acetate and methanol extracts of *Sterculia tragacantha* leaves were assessed to evaluate the pain-relieving and anti-inflammatory properties of *S. tragacantha*. According to Mogbojuri *et al.*, all extracts exerted both analgesic and anti-inflammatory activities without causing any mortality in test animals at a larger dose of 3000 mg/kg, which indicated its safer therapeutic uses.⁷⁶

***Strychnos nux-vomica* L. (Loganiaceae).** The phytochemical works on the aqueous-methanolic crude extract of the leaves of *S. nux-vomica* yielded five compounds, namely kaempferol-7-O-glucoside (5.6), 7-hydroxy coumarin (5.7), quercetin-3-O-rhamnoside (5.8), kaempferol 3-O-rutinoside (5.9), and rutin (5.10), illustrated in Figure 5. It is speculated that the presence of these bioactive compounds is attributable to the probable strong pain-relieving and antiphlogistic actions.⁷⁷

***Syzygium aromaticum* (Myrtaceae).** Batiha and co-workers reported that GC-MS analysis of clove (*S. aromaticum* L.) essential oil had confirmed the presence of approximately 36 known phytoconstituents, majorly includes eugenol, caryophyllene, eugenylacetate, ethyl hexanoate, 2-heptanone, humulene, calacorene, and humulenol, all of which possess both antiphlogistic and analgesic activities.⁷⁸

***Tabernaemontana catharinensis* (Apocynaceae).** In 2018, Marques and co-workers conducted the phytochemical analysis of *T. catharinensis* by HPLC-HRESI-MS. Further bioassays were also carried out on the hydroethanolic leaf extract of *T. catharinensis* and its sub-fractions (*i.e.*, ethyl acetate and *n*-butanol) of *T. catharinensis*. The antiphlogistic potential was assessed through carrageenan-induced rat paw edema model, where both extract and the sub-fractions gave anti-edematogenic activity by decreasing myeloperoxidase production.⁷⁹

***Taxus wallichiana* Zucc. (Taxaceae).** Tasumatrol B (5.11), 1,13-diacetyl-10-deacetylbaaccatin III (10-DAD) (5.12) and 4-deacetylbaaccatin III (4-DAB) (5.13), illustrated in Figure 5, were obtained from the bark extract of *T. wallichiana* and reported as promising new lead bioactive phyto-compounds with analgesic and anti-inflammatory properties in drug discovery research.⁸⁰

***Terminalia arjuna* (Combretaceae).** Methanolic extract, obtained from *Terminalia arjuna* leaves, exhibited remarkable analgesic and acute anti-inflammatory activity.⁸¹

***Thespesia populnea* (Malvaceae).** The ethanolic extract of *Thespesia populnea* bark could inhibit - induced mice-paw edema, induced with carrageenan, histamine, and serotonin, and expressively reduced the wriggling responses induced by acetic acid in mice models at the doses of 200 mg/kg and 400 mg/kg. No mortality of the test animal was observed in the acute toxicity study.⁸²

***Tridax procumbens* L. (Asteraceae).** Prabhu and co-workers reported that the aqueous and ethanolic extracts of *T. procumbens* leaves exhibit remarkable effects against central, peripheral and inflammatory pain models and this could be attributable to the existence of flavonoid and sterols in the extract.⁸³

***Veratrum taliense* (Melanthiaceae).** Veratraline A (6.1), B (6.2) and C (6.3), illustrated in Figure 6, the three new jervine-type steroidal alkaloids and their five known analogs were isolated from the roots and rhizomes extracts of *V. taliense*. These phytoconstituents gave effective analgesic activity and showed prominent anti-inflammatory responses in mice paw edema, induced by carrageenan.⁸⁴

***Vernonia amygdalina* Delile (Asteraceae).** Ethanolic extract of both young leaves and old leaves of *V. amygdalina* exhibited substantial antiphlogistic, antipyretic and antinociceptive properties. However, extracts from young leaves exerted more potent pharmacological responses compared to old leaves.⁸⁵

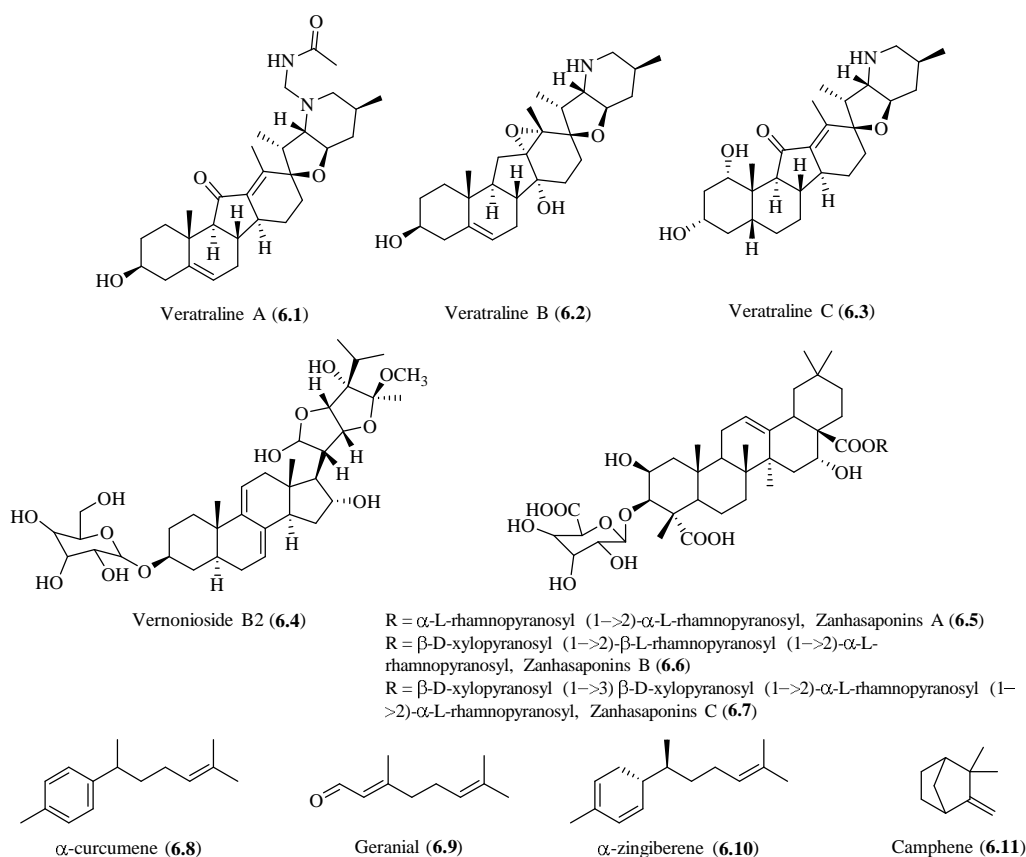


Figure 6. Some isolated phytochemicals having analgesic and anti-inflammatory activity reported in various published articles.

Vernonia condensata (Asteraceae).

Vernonioides B2 (6.4) shown in figure 6 was isolated from the methanolic extract of the Brazilian herb, *Vernonia condensata*, and assessed for its analgesic and anti-inflammatory properties. Valverde *et al.* reported that 6.4 has noticeable efficacy in reducing both pain and inflammation.⁸⁶

Viola betonicifolia Sm. (Violaceae).

Muhammad and co-workers reported that the methanolic extract of the whole plant of *V. betonicifolia* can antagonize both carrageenan and histamine-induced inflammation, by 66.30% and 60.80%, respectively, at a dose of 300 mg/kg. Additionally, the extract exhibited dose-dependent analgesia, having 78.90%, 69.96%, and 68.58% protection in acetic acid, hot plate and tail immersion pain model, respectively, at a similar dose.⁸⁷

Withania somnifera (L.) Dunal (Solanaceae).

Various extracts of the root of *W. somnifera* demonstrated the presence of various bioactive phytoconstituents including flavonoids, alkaloids, phenols, steroids, glycosides, tannins, saponins, terpenoids as well as reducing sugars, which are thought to be responsible for diverse therapeutic potentials of *W. somnifera* like analgesic, anti-inflammatory, neuroprotective, anti-spasmodic and diuretic effects.⁸⁸

Zanha africana (Radlk.) Exell (Sapindaceae).

Three new saponins namely zanhasaponins A (6.5), B (6.6), and C (6.7), illustrated in Figure 6, were obtained from the methanolic extract of *Zanha africana* root-bark Cuéllar and co-workers claimed that these zanhasaponins confirmed their efficacy topically against superficial inflammation induced by phorbol ester.⁸⁹

***Zingiber officinale* Roscoe (Zingiberaceae).**

The extracted essential oil of *Zingiber officinale* contains α -curcumene (6.8), geranial (6.9), α -zingiberene (6.10), camphenes (6.11), illustrated in Figure 6, and it was reported by Munda *et al.* that these phytochemicals have potent anti-inflammatory, anticancer, analgesic, anti-arthritic, antitussive and antimicrobial properties.⁹⁰

CONCLUSION

Long-term administration of NSAIDs and opiates may lead to serious complications like peptic ulcers, bleeding, renal disorders, etc. Therefore, new anti-inflammatory and analgesic drugs without any adverse effects are being searched all over the world as alternatives to NSAIDs and opiates. Medicinal plants represent a large natural source of useful chemical substances with potential therapeutic effects. The core chemical classes of anti-inflammatory and analgesic agents mentioned in this review have been usually reported to engage a vast range of compounds such as flavonoids, triterpenoids, tannins, alkaloids, anthraquinones, polysaccharides, saponins, glycosides, etc. The introduction of reported chemical scaffolds with possible folkloric use to relieve pain and inflammation will provide further information to identify specific drug candidate with pharmacological activities. This article will help future researchers to find a lead compound with ease for analgesic and anti-inflammatory drug discovery.

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