



Anti-inflammatory activity of plants

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Abstract

As a result of the inherent problems associated with the current anti-inflammatory agents, there is continuous search especially from natural sources for alternative agents. A good number of plants are employed in the treatment of inflammatory disorders by natural healers. Some of these plants include *Aloe vera*, *Consolida regalis*, *Chasmanthera dependens*, *Culcasia scandens*, *Crataeva religiosa*, *Tanacetum vulgare*, *Holmskioldia sanguinea*, *Mitracarpus scaber*, *Turner ulmifolia*, etc. Most of these plants have demonstrated varying activities in the various *in vivo* and *in vitro* inflammatory models. The potency of these plants is attributed to several active principles present in them, which may act at any of the multiple targets in the inflammatory response pathway. In addition to anti-inflammatory activity, some of these plants also possess beneficial properties such as antimicrobial, analgesic, antipyretic and antiulcer effects. These additional effects complement the inherent anti-inflammatory activity and may confer advantage on these plants. Some active anti-inflammatory principles of these plants have been identified, isolated and characterized. They include – lupeol, premnazole, (+) – usnic acid, (+) – pinitol, zanthaxaponins A and B, sasanquol, parthenolide etc. These compounds could provide drugs with comparative advantage over existing agents and may as well serve as leads for further development into more active drugs with lesser adverse effects. This review discusses some of these plants with putative anti-inflammatory properties.

Keywords: Inflammation, anti-inflammatory plants, natural products.

1. Introduction

Inflammation is the reactive state of hyperemia and exudation from blood vessels with consequent redness, heat, swelling and pain which a tissue manifests in response to physical or chemical injury or bacterial

invasion [1]. It is a tissue reaction by the body to injury and involves a complex array of enzyme activation, mediator release, extravasations of fluid, cell migration, tissue breakdown and repair [2].

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Three components of the inflammatory response have been distinguished [3, 4] and these may involve vasoactive substances [5] chemotactic factors [6, 7], degradative enzymes and superoxides [8] and the neuropeptide, Substance P [9].

Rheumatoid arthritis represents the commonest form of chronic inflammatory joint disease [10]. Arthritis is one of the most distressing and disabling syndromes encountered in medical practice [11]. An estimated 1-2% of adult population is affected [12]. In the United States, approximately 0.1% of the population experience rheumatoid arthritis in childhood [13]. Steroids e.g. betamethasone and the non-steroidal anti-inflammatory drugs (NSAIDs) e.g. acetylsalicylic acid are the mainstay in the treatment/management of inflammation and inflammatory disease conditions.

However, these agents are fraught with severe adverse effects such as adrenal suppression for steroids and gastric ulceration and perforation for NSAIDs. Most NSAIDs are known to exert potentially adverse effects on the gastrointestinal tract [14, 15]. These have seriously limited the employment of these agents in inflammation and inflammatory diseases therapy.

Several efforts have been made to reduce the adverse effects of NSAIDs. It is now accepted that cyclooxygenase (COX) enzyme exists in two isoforms – COX I (constitutive) and COX II (inducible). The therapeutic activities of NSAIDs are attributed to the inhibition of COX II.

Therefore, an ideal anti-inflammatory drug is expected to inhibit prostaglandin synthesis mediated by COX II while sparing COX I [16], inhibition of which is believed to mediate the side effects. Much as it would seem that the selective COX II inhibitors such as celecoxib and rofecoxib might be cost effective for patients at high risk of ulcer complications [17],

serious theoretical concerns exist due to the potential risk of thrombosis [18]. And so, though arthritis is one of the oldest known diseases, there is yet no drug leading to a permanent cure [11] and which is devoid of adverse effects.

Nature endows the world with medicinal plants to take care of health needs. The potentials of plants as sources of drugs have long been recognized. Several medicinal plants species are commonly used in traditional medicine as inflammatory remedies. Some of these plants are shown in Table 1.

There are representative anti-inflammatory herbs in almost each family in the plant kingdom. Many of these plants have proven oral and documented evidence of their use in the treatment of inflammatory disorders in traditional medicine. For some plants, inherent anti-inflammatory activity is inferred from other identified pharmacological activities related to modulation of the complex inflammatory response.

At present, there is mounting scientific evidence for the anti-inflammatory activity of many herbs. For some, the anti-inflammatory activity has been extensively studied while preliminary evidence has been established for others. A number of anti-inflammatory constituents have been isolated and characterized structurally and pharmacologically.

2. Plants with reported anti-inflammatory activity

2.1 Aegle marmelos Roxb. (Rutaceae)

A. marmelos, also known as Bilva, is a commonly growing deciduous tree with sharp axillary thorns. It has been reported that aqueous root and bark extracts significantly decreased the rat paw edema induced by carrageenan [25]. The activity was comparable to that of

Tabel 1.
Some common anti-inflammatory plants

Plant	Parts used	Reference
APIACEAE		
<i>Conium maculatum</i> L.	Aerial	23
<i>Heteromorpha trifoliata</i> (Wendl.) Eckl and Zeyh	Leaves	21
ASTERACEAE		
<i>Tenacetum vulgare</i>	Aerial	189
<i>Felicia muricata</i> (Thunb.) Nees	Stem bark	21
BERBERIDACEAE		
<i>Berberis vulgaris</i> L.	Root	23
BURSERACEAE		
<i>Commiphora molmol</i> Engl.	-	22
CAESALPINACEAE		
<i>Erythropheum lasianthum</i> Corbishley	Stem bark	21
CAPARIDACEAE		
<i>Crataeva religiosa</i> Forst. F	Stem bark	186
<i>Crataeva nurvala</i>	Stem bark	21
CHENOPODIACEAE		
<i>Beta vulgaris</i> L.	Root	22
<i>Chenopodium botrys</i> L.	Aerial	23
COMBRETACEAE		
<i>Combretum molle</i> Young	leaves	20
COMPOSITAE		
<i>Latuca sativa</i> L.	Seeds	22
EUPHOBIAEAE		
<i>Bridelia ferruginea</i>	Aerial	20
LABIATAE		
<i>Mentha piperita</i> L.	Leaves	22
LAMIACEAE		
<i>Marrubium peregrinum</i> L.	Aerial	23
<i>Scutellaria baicalensis</i> Georgi	Root bark	24
LAURACEAE		
<i>Cinnamomum zeylanicum</i> L.	Bark	22
MORINGACEAE		
<i>Moringa pterygosperm</i>	Root	19
MYRICACEAE		
<i>Myrtaceae serrata</i> Lam	Root bark	21
MYRTACEAE		
<i>Eucalyptus camaldulensis</i> Dehn	Leaves	22
OLEACEAE		
<i>Olea europea</i> L.	Leaves	21
<i>Jasminum officinale</i> L.	Flower	22
PAPAVERACEAE		
<i>Glaucium flavum</i> Crantz	Aerial	23
PINACEAE		
<i>Abies pindrow</i> Spach	Leaves	190, 101
RANUNCULACEAE		
<i>Consolida regalis</i> S. F. Grey	Aerial	23
<i>Coptis chinensis</i> Franch	Root	24
<i>Isopyrum thalictroides</i> L.	Root	23
<i>Thalictru minus</i> L.	Aerial	23

Plant	Parts used	Reference
ROCELLACEAE		
<i>Rocella montagnei</i> Bel	Whole plant	196, 201
RUTACEAE		
<i>Pholiodendron amurense</i> Rupr.	Root	24
<i>Ruta graveolens</i> L.	Leaves	22
<i>Zanthoxylum zanthoxyloides</i>	Root	185
SAPINDACEAE		
<i>Ptaeroxylon obliquum</i> (Thunb). Radlk.	Wood	21
THYMELAECEAE		
<i>Gridia anthylloides</i> (LE) Gilg.	Leaves	21
UMBELLIFERAE		
<i>Apium graveolens</i> L.	Seeds	22
VERBENACEAE		
<i>Gmelina arborae</i> Roxb	Leaves	195
<i>Premna integrifolia</i> Linn	Leaves	195
ZYGOPHYLLACEAE		
<i>Peganum harmala</i> L.	Aerial	23

ibuprofen. The extracts also significantly decreased granuloma weight and were thus found effective in both acute and chronic inflammation [25].

2.2 *Ageratum conyzoides* L. (Asteraceae)

A. conyzoides is a plant known in Brazil variously as “Mentrasto”, “Erva de So Joao” and used in traditional medicine for its anti-inflammatory, analgesic and anti-diarrhoeal properties [26]. In some African countries, *A. conyzoides* is used as an antienteralgic and antipyretic drug [27].

Experimentally, the leaf extract has been shown to be effective in the treatment of chronic pain in osteoarthritis [28] and in causing a fall in rectal temperature [29]. Reports showed that the essential oil exhibited significant anti-inflammatory effect [30] while the water-soluble fraction of the 70% ethanol leaf extract exhibited anti-inflammatory and analgesic properties [31].

Further experimental evidence suggest that the water-soluble fraction of the 70% ethanol leaf extract inhibited zymosan-induced neutrophil migration into the peritoneal cavity [32]. The fraction was however ineffective on zymosan

and dextran-induced edema [32], suggesting that the extract could act by inhibiting cyclooxygenase enzyme [32].

2.3 *Aloe vera* Linn Burm. f. (Liliaceae)

A. vera is a pineapple-like plant with rosettes of fleshy, sword-shaped toothed leaves found in rocky hills and near streams in swampy places [33].

The anti-inflammatory activity of the fresh juice has been reported [34]. The fresh juice obtained from leaves of the plant inhibited carrageenan-induced rat paw edema to a degree comparable to that of ibuprofen. However, in chronic inflammation model, the extract did not significantly reduce granuloma weight in treated animals. The fresh juice was effective in acute inflammation but exhibited no effect in chronic inflammation [34].

Atta and Alkofahi [22] have reported that the ethanolic extract significantly reduced the weight of xylene-induced ear edema in mice with a calculated inhibition of 71%. In separate investigations, Aloe gel has been reported effective in inflammation induced by kaolin,

carrageenan, albumin, gelatin, mustard and croton oil [35]. Aqueous or chloroform extracts of the gel have been reported to inhibit carrageenan-induced inflammation and migration of neutrophils [36].

2.4 *Ambrosia artemisiaefolia* L. (Compositae)

A. artemisiaefolia is also known as “Tamaris” in Mexican folk medicine. The leaves are used as topical anti-inflammatory remedy. The local population use the juice of the leaves administered externally and systemically to relieve different states of arthritis and rheumatism. [37]

The ethanolic leaf extract was reported to inhibit the development of granulomatous tissue produced by croton oil-induced inflammation in rats. The extract also significantly reduced carrageenan-induced inflammation in rats, and inhibited early stages of formaldehyde induced arthritis in rats. The extract was more active topically than orally and believed to be more suited for use in arthritis. [37]

2.5 *Anthurium cerrocampanense* Croat (Araceae)

A. cerrocampanense is a rarely epiphytic terrestrial and deeply rooted plant [38]. The anti-inflammatory activity of the aqueous, ethanolic and dichloromethane extract on topical inflammation of the mouse ear, and edema of the rat paw induced by carrageenan, dextran, arachidonic acid, zymosan and C₁₆-PAF was also reported [38]. The report indicated that all the extracts exhibited anti-inflammatory activity with the dichloromethane extract as the most active in both acute and topical inflammation.

Further investigation of the dichloromethane extract revealed that it inhibited dextran, carrageenan and zymosan-induced rat paw edema which is associated with histamine and serotonin release [39, 40, 41]. The extract was

however not active in arachidonic acid-induced inflammation of the rat paw suggesting the absence of involvement of the lipoygenase pathway. [38]

2.6 *Aspilia africana* CD Adams (Compositae)

A. africana formerly known as *Wedelia africana* Pers or *Aspilia latifolia* is a weed widespread in Africa [42]. The crushed leaves have been used for patients suffering from rheumatic pains [43]. Healing of wounds occurs when treated with the crushed leaves. [44]

The anti-inflammatory activity of isosaline and ethanolic leaf extracts based on their effects on heat and hypotonicity-induced lysis of bovine red blood cells has been reported [45]. Both extracts stabilized bovine red blood cell membrane against heat and hypotonicity-induced lysis, producing effects comparable to that of indomethacin, a standard anti-inflammatory drug [45].

2.7 *Bryophyllum pinnatum* S. Kurz (Crassulaceae)

B. pinnatum is popularly known as “abamoda” in the Yoruba tribe of Nigeria. The leaves are used in folk medicine, rubbed with shell butter or palm oil on abscesses or other inflammatory conditions [46, 47]. It is also claimed to be used for the treatment of sprains, dysmenorrhoea and common cold. [48]

In experimental animal models, the anti-inflammatory activity of the methanolic leaf extract in acute and chronic inflammation has been demonstrated [49]. The extract significantly inhibited carrageenan-induced rat paw edema and inhibited the weight of granuloma tissue in cotton pellet test. The observed activity in cotton pellet granuloma test was attributed to the ability of the extract to decrease fibroblasts number and synthesis of

collagen and mucopolysaccharides [49], which are natural proliferative agents of granulation tissue formation [50].

2.8 *Butea frondosa* Koen. Ex Roxb. (Papilionaceae)

B. frondosa leaves are used in inflammatory conditions, skin diseases, worm infestations, and haemorrhoids [51, 52]. The aqueous leaf extract was shown to exhibit dose dependent anti-inflammatory activity in carrageenan-induced rat paw edema [53]. The observed activity was significant and comparable to that of ibuprofen. [53]

2.9 *Calligonum comosum* (L.) Hert. (Polygonaceae)

C. comosum is a shrub distributed throughout Arabia and growing in sandy deserts, and used by the local healers to treat stomach ailments. The stems and leaves are chewed as an ailment in toothache. [54]

Experimental evidence suggests that 10% ethanolic extract of the aerial parts of *C. comosum* significantly reduced increase in hind paw edema induced by carrageenan [55]. The extract was reported to significantly reduce increase in weight of cotton pellet, and exhibit anti-ulcer and cytoprotective effect against gastric ulcers induced experimentally by NSAIDs and necrotizing agents. [55]

2.10 *Calotropis procera* (Ait) R. Br. (Asclepiadaceae)

C. procera is a wild growing tropical plant. It possesses multifarious medicinal properties including anti-inflammatory effects [56, 57]. Extracts from different parts of the plant have been reported to possess anti-inflammatory effect. The ethanolic extract of flowers [58], the chloroform-soluble fraction of roots [59] and the dry latex [57] have been reported to possess anti-inflammatory activity. The petroleum ether,

acetone, methanol and aqueous extracts of the dry latex significantly inhibited carrageenan-induced paw edema in rats [60]. The acetone and aqueous extracts produced the greatest inhibition.

2.11 *Caralluma tuberculata* N.E. Brown. (Asclepiadaceae)

C. tuberculata is a plant largely grown in Pakistan and India [61]. It is consumed as food and used in ethnomedicine in the treatment of rheumatism, leprosy, blood disorders and as an anthelmintic [62-64]

The ethanolic extract has been reported to possess significant anti-inflammatory and analgesic activities [61]. Experimental data indicated that the ethanolic extract significantly inhibited carrageenan-induced inflammation in rats. The extract also decreased granuloma formation by cotton pellets in treated rats [61].

2.12 *Cassia* spp (Caesalpinaceae)

Plants of the genus *Cassia* are mainly tropical or subtropical trees, shrubs or very rarely herbs or scramblers [65]. They form an important source of medicinal decoctions [66]. Some of the species are cultivated on plantation scale and are known to be good fodder though the leaves and pods contain constituents found toxic to livestock [67, 68]. Species of this genus include - *Cassia absus* Linn, *C. alata* Linn, *C. occidentalis* Linn, *C. sieberiana* DC, *C. podocarpa* Guill and Perr. In native medicine, the leaves are used as dressing for ulcers, swellings or inflammatory conditions [66].

It has been reported that the ethanolic leaf extract of some of the *Cassia* spp (*C. sieberiana*, *C. spectabilis*, *C. siamea*, *C. alata* and *C. nodosa*) inhibited increase in paw volume induced by carrageenan [66].

2.13 *Cedrus deodara* (Roxb.) Loud. (Pinaceae)

C. deodara variously known as “Devadaru” in Sanskrit, “Deodar” in Hindi/Marathi, India and “Cedar” in English, is a graceful, ornamental evergreen tree growing extensively on the slopes of the Himalayas. Deodar forests are common from Kashmir (1500–3000 m altitude) especially, Krishnaganga, Kishtwar and Jhelum to Garhwal. [69]

The effect of the essential oil of *C. deodara* wood on 48/80 – and nystatin- induced paw edema in rats and membrane stabilization has been reported [70]. The wood oil significantly inhibited edema formation produced by 48/80, known to release histamine [70]. The oil also significantly inhibited nystatin-induced edema dose dependently. Further findings indicate that the wood oil exhibited membrane stabilization by inhibiting erythrocyte hemolysis induced by heat and hypotonicity.

2.14 *Centaurea cyanus* L. (Asteraceae)

C. cyanus flower-heads are used in European traditional medicine in the treatment of minor ocular inflammation [71]. A polysaccharide fraction of the aqueous extract of *C. cyanus* inflorescences has been reported to inhibit carrageenan and zymosan-induced paw edema in rats [72]. The effect of the extract compared favourably with those of indomethacin and acetylsalicylic acid. The extract also dose-dependently inhibited croton oil-induced ear edema in mice. The polysaccharide fraction also induced the formation of anaphylatoxin-like activity *in vitro*.

2.15 *Chasmanthera dependens* Hochst (Menispermaceae)

The leaves of *C. dependens* are used as a dressing for fractures and as an embrocation for sprains and muscular pains [47, 48, 73]. The methanolic leaf extract was reported to

significantly and dose-dependently inhibit paw edema induced by carrageenan in rats [74]. The extract inhibited cotton pellet granuloma in rats producing effect comparable to that of indomethacin.

The extract also reduced the intensity of peritoneal inflammation by reducing dye leakage induced by acetic acid in the mice peritoneum. The effect on peritoneal inflammation was attributed to the ability of the extract to inhibit the release of inflammatory mediators, which cause increase in vascular permeability of small blood vessels and enhance inflammation [74].

2.16 *Cissus trifoliata* Rott. (Vitaceae)

C. trifoliata commonly known as “bolontibi” is reportedly used by practitioners of traditional medicine in the northern states of Sonora, Mexico, as a cure against rheumatic arthritis [75]. The ethanol root extract exhibited marked anti-inflammatory activity in carrageenan-induced edema in rats and mice and in formaldehyde- and adjuvant-induced arthritis in rats [75].

The extract was found more potent than phenylbutazone in acute inflammation and has similar potency of phenylbutazone in chronic inflammation [75]. The extract inhibited heat-induced erythrocyte lysis, which is a biochemical index of anti-inflammatory activity [75].

2.17 *Culcasia scandens* P. Beauv (Araceae)

C. scandens is a tall climbing epiphyte [76]. The morphology and distribution have been fully described [77]. It is abundantly present in the Southern parts of Nigeria. *C. scandens* is widely acclaimed as a potent anti-inflammatory herb. A poultice of the leaves mixed with *Capsicum frutescens* is usually applied to the affected or inflamed part [78]. In the eastern parts of Nigeria, the leaves of the plant are chewed with seeds of *Aframomum melegueta* and swallowed

to treat tonsillitis. A poultice of the leaves is placed on an aching tooth to relieve toothache. A single treatment is claimed to be highly efficacious.

The anti-inflammatory activity of the methanolic leaf extract and TLC fractions in egg albumin-induced acute inflammation in rats has been reported [79]. In addition, the crude extract effectively suppressed increase in rat paw edema.

2.18 *Curcuma longa* Haldi (*Zingiberaceae*)

C. longa rhizome, also known as “turmeric” is cultivated in India, West Pakistan, China and Malaya [80]. It has been used as a household remedy for local application in inflammatory conditions and other painful afflictions, including sprain [81]. Intramuscular injection of a volatile oil fraction of the dried rhizome of *C. longa* was found to inhibit formaldehyde and carrageenan-induced paw edema in rats [82]. The volatile oil and a sterol fraction were shown to possess anti-inflammatory activity in the cotton pellet and granuloma pouch tests. [83]

Also, the anti-inflammatory activity of the volatile oil on Freund’s adjuvant-induced arthritis in rats and talc-induced teno-synovitis in pigeons are documented [84]. The results indicate that the volatile oil exhibited a highly significant early anti-inflammatory effect, probably related to its antihistaminic and histamine depleting effect [82, 83]. The effect was more marked than that obtained with cortisone acetate. The antiarthritic effect of the volatile oil of *C. longa* was attributed to a possible mediation through the hypophyseal adrenal axis [84].

2.19 *Dalbergia sissoo* Roxb. (*Fabaceae*)

Plants of the genus *Dalbergia* have been reported to be useful in the treatment of arthritis, gonorrhoea and rheumatic pains [85-87]. The scientific evidence for the anti-inflammatory activity of *D. sissoo* leaves has been recently

provided [88]. The ethanolic leaf extract inhibited the edema induced by carrageenan, kaolin and nystatin in the rat paw. The extract was reported to reduce the weight of granuloma, implying an effect on the proliferative phase of inflammation. It also reduced the intensity of the peritoneal inflammation produced by acetic acid in mice, indicating its ability to inhibit the permeability of small blood vessels [88].

The anti-inflammatory activity was attributed to possible inhibition of autocoids such as prostaglandins or lysosomal membrane stabilization [88]. The evidence seem more in favour of prostaglandin inhibition since a related species *D. odorifera* has been found to significantly inhibit prostaglandin synthesis and platelet aggregation induced by arachidonic acid. [89, 90]

2.20 *Dicliptera chinensis* Juss (*Acanthaceae*)

Aerial parts of *D. chinensis* is among the constituents of “Wuu-joa-jin-ing” used as folk medicine in Taiwan [91]. It is employed in the treatment of hepatitis, cystitis and jaundice. [92]

The anti-inflammatory activity of *D. chinensis* has been reported [91]. Aqueous extract of the aerial part inhibited increase in paw edema induced by carrageenan. The extract was found effective in inhibiting the two phases of inflammatory response induced by carrageenan. [91]

2.21 *Diodia scandens* Swartz (*Rubiaceae*)

D. scandens is a straggling woody perennial herb growing wild in Southern Nigeria. It has a remarkable activity to survive in the dry season. The botanical characteristics have been described [42]. The leaves of this plant are used in the folkloric treatment of snake bites, rheumatic inflammatory disorders, earache and venereal diseases [73]. The antivenom property of the plant has been reported. [93, 94]

The scientific evidence for the anti-inflammatory effect of the aerial parts has been documented [95]. The petroleum ether extract of the plant dose-relatedly suppressed the rat paw edema induced by egg albumin. The suppression of edema was significant from 30 min after edema induction and lasted for about 3 h. The effect of the extract was attributed to a possible inhibition of the release of mediators of inflammation [95]. This is consistent with earlier reports that *D. scandens* extract blocked the stimulant effect of 5-HT and histamine on guinea pig ileum [93].

2.22 *Emilia sonchifolia* (L.) DC (Asteraceae)

E. sonchifolia is a weed predominant in the grassland regions of West Africa. In the Igbo-speaking parts of Nigeria, the plant is used in folkloric medicine for inflammation, eye sores and convulsion [96]. It is commonly used by the tribes of Kerala in the treatment of inflammation, insect bites, conjunctivitis, rheumatism, cuts and wounds [97]. In Cameroon, fresh juice squeezed from the fresh leaves is utilized in the dressing of fresh wounds. [98]

The methanol leaf extract was reported to inhibit paw edema induced by carrageenan in rats [99]. The anti-inflammatory activities of the two extracts were attributed to their flavonoid contents. [99]

The pharmacological evidence for the anti-inflammatory effect of *E. sonchifolia* has been further provided [98]. Methanol and aqueous leaf extracts of the plant was shown to reduce paw edema induced by egg albumin. The aqueous extract was found more potent than the methanolic extract. [98]

2.23 *Entada abyssinica* Steud. ex A. Rich. (Mimosaceae)

E. abyssinica is a tree found all over tropical Africa [100]. The plant has been used for the

treatment of bronchitis, cough, and to alleviate arthritic pains [78]. The juice of *E. abyssinica* is employed as an instillation for eye inflammation. [47, 101]

The defatted methanolic leaf extract of *E. abyssinica* has been demonstrated to possess anti-inflammatory activity [100]. The results indicate that the methanolic extract significantly inhibited the development of paw edema induced by carrageenan. The extract also exhibited a dose dependent and significant inhibition of dry weight of the cotton pellet granuloma tissue formation in rats. The inhibition produced by the extract was greater than that produced by hydrocortisone. [100]

2.24 *Euphorbia royleana* Boiss (Euphorbiaceae)

E. royleana is a shrub growing up to 15 ft high and commonly found on the outer dry slopes of the Western Himalayas, India [102]. In traditional medicine, it is used as a remedy for joint pains [102]. The anti-inflammatory activity of the latex of *E. royleana* has been established [102]. The ethylacetate extract obtained from the residue of an 85% ethanol extract of the latex of the plant displayed marked anti-inflammatory activity in acute inflammation induced by various phlogistic agents.

The extract produced significant antiarthritic activity in subacute and chronic models of formaldehyde and adjuvant-induced arthritis. It also inhibited the exudate volume, leucocyte migration in rats and vascular permeability in mice. However, the extract exhibited poor inhibitory effect on the granuloma formation by cotton pellet and croton oil [102].

Subsequent investigation revealed that the hydrosoluble fraction of the latex significantly inhibited edema induced by dextran, and carrageenan, and dose dependently inhibited arthritis induced by formaldehyde in rats by as much as 35%. The extract displayed significant

and dose dependent inhibition of the exudate volume and the total leucocyte count in the pleural cavity [103]. The anti-inflammatory activity of the extract was attributed to possible multiple interactions with several components of the different acute and chronic inflammatory reactions e.g. leucocyte migration inhibition [103].

2.25 *Ficus platyphylla* Del- Holl (*Moraceae*)

F. platyphylla is also known as “gamji” among the Hausa tribes of Northern Nigeria [104]. It is a tree that commonly grows in the savannah region of West Africa. The soft gummy resin of the tree is popularly used in Northern Nigeria as a birdlime while cold water extracts, decoctions and powder made from the root and bark are used in the treatment of insomnia, pain, depression and persons said to be possessed by the spirits [104].

Experimental evidence suggests that the methanol bark extract of *F. platyphylla* markedly inhibited egg albumin-induced rat paw edema in a dose-related manner [104]. There was significant difference between the activity of the extract and acetylsalicylic acid. The activity of the extract was attributed to its flavonoid content [104].

2.26 *Gentianella achalensis* (Gilg.) T. N. Ho et S. W. Liu (*Gentianaceae*)

G. achalensis is a small herb distributed in the northwestern and central regions of Argentina [105] where it is locally known variously as “pasto amargo” (bitter grass), or “nencia”. The infusion of the aerial parts of the plant has been used in place of the European *Gentiana* preparation extensively as stomachic or appetite stimulant and bitter tonic for digestive and liver problems [106-108].

The anti-inflammatory activities of the petroleum ether, dichloromethane and methanol extracts and a fraction F₂ (obtained from

chromatographic separation of the dichloromethane extract) of *G. achalensis* have been reported [123]. In the mice ear edema induced by 12-0-tetradecanoylphorbol-13-acetate (TPA), only the dichloromethane extract produced significant inhibition. Of the seven fractions obtained from its chromatographic separation, one fraction exhibited activity comparable to that of indomethacin and the fraction was shown to contain two triterpenoids – oleanolic and ursolic acids as major constituents.

2.27 *Heterotheca inuloides* Cass (*Asteraceae*)

H. inuloides grows abundantly in the cooler temperate regions of Mexico. The flowers of this plant are widely used in traditional medicine in Mexico for the treatment of inflammatory diseases, fever, and other disorders [109].

It has been reported that an active fraction obtained from the purification of aqueous extract of *H. inuloides* exhibited potent anti-inflammatory effect [109]. The fraction inhibited inflammation induced by carrageenan and dextran and weakly reduced arachidonic acid induced edema, and also produced gastric erythema on gastric mucosa of rats [109]. It was concluded that inhibition of prostaglandin biosynthesis might be involved in the anti-inflammatory activity of *H. inuloides* though other mechanisms may also be involved [109].

2.28 *Holmskioldia sanguinea* Retz (*Verbenaceae*)

H. sanguinea also known as “Kapni” is a large scrambling shrub [110] distributed in regions of India. The antinociceptive and anticancer activities of *H. sanguinea* have been reported [111, 112].

The aqueous extract and chloroform fractions of the leaves were reported to have inhibited carrageenan-induced paw edema in rats [113].

The activities of the aqueous extract and butanol fraction were greater than that of hydrocortisone [113].

2.29 *Icacina trichantha* Pflanzfam (Icacinaceae)

I. trichantha ethanol tuber extract is a common medicine in many Nigerian homes [114]. Traditionally, the alcoholic extract of the tuber is drunk to relieve pains and other symptoms. It is also used to treat cases of poisoning, constipation and yellowness of the eye commonly associated with malaria and hepatitis [114, 115].

The liver and kidney protective activities of methanol the tuber extract in carbon tetrachloride-poisoned rats have been reported [116]. This effect of the extract was reportedly suspected to be associated with a free radical scavenging activity characteristic of many anti-inflammatory agents [117].

The inhibitory effect of the hexane, chloroform, ethylacetate, methanol and water extracts of the tuber on croton oil-induced ear edema in mice has been reported [117]. The chloroform extract, which exhibited the highest activity, was shown to have significantly inhibited ear edema in a dose dependent manner. The chloroform fraction also significantly inhibited paw edema induced by carrageenan. [117]

2.30 *Mitracarpus scaber* Zucc (Rubiaceae)

M. scaber is a herb indigenous to Nigeria, Senegal, Ghana and Gambia and generally found in the tropics. It is an annual woody weed up to 1 m high which grows erect with a highly branched tough stem [42]. In folkloric medicine, the powdered leaves are applied to arrow wounds and the decoction drunk as antidote to arrow poison [73]. Squeezed extract of the fresh leaves is used to treat eczema infections of the skin and as anti-inflammatory agent [118].

In experimental animal models, the anti-inflammatory and antimicrobial activities of the petroleum ether and methanol extracts of the leaves of *M. scaber* have been reported [118]. Both extracts progressively exhibited sustained inhibition of increase in paw edema induced by fresh egg albumin. The methanolic extract exhibited a higher antimicrobial activity than the petroleum ether extract. This was suggested probably to imply that the extract might be more effective in inflammation caused by infectious microorganisms [118]. The petroleum ether extract was however more potent than the methanolic extract [118].

2.31 *Moringa oleifera* Lam (Moringaceae)

M. oleifera grows on sandy soil to a small or medium-sized tree and is commonly planted as fence tree [119]. In India, it is cultivated mainly for its fruit, which is used in curries and its leaves, which substitute as fodder for cattle [25]. The leaves and young buds are used as vegetable in soup and rubbed on the temples to relieve headache. The root bark are regarded as anti-scorbutic and are used externally as counter irritants. A poultice of the root mixed with salt is effective against inflammatory swellings [73].

The methanol root extract inhibited carrageenan-induced paw edema in rats [119]. The extract dose-dependently inhibited increased paw weight comparable to indomethacin. The extract also produced inhibitory effects against Freund's adjuvant-induced chronic inflammation [119]. These findings suggest that the root extract is effective in both acute and chronic inflammation and inhibits both the cell and fluid accumulation to the same extent in both acute and chronic forms of pouch inflammation [119].

The aqueous root and root bark extracts have been reported to effectively decrease the rat paw edema induced by carrageenan [25]. The effect was comparable to that of ibuprofen.

2.32 *Myracrodroun urundeuva* Fr. All (*Anacardiaceae*)

M. urundeuva is a popularly used medicinal plant in Northern Brazil [120]. Experimental studies have demonstrated significant anti-inflammatory activity of the aqueous and hydroalcohol extracts of the bark in several animal models [121]. The ethylacetate extract has been reported to have demonstrated highest anti-inflammatory activity when compared to the activities of hexane, chloroform, ethylalcohol, methylalcohol and water extracts [120].

It has been reported that the ethylacetate extract has two main fractions - a predominant group of substances of a chalcone nature and another group of mainly catechin tannins [122].

The catechin tannin fraction obtained by column chromatography of the ethylacetate bark extract of *M. urundeuva* was reported effective in inhibiting carrageenan- and dextran-induced paw edema [120]. The tannin fraction also inhibited leucocyte and neutrophil migrations induced by carrageenan and N-formyl-methionyl-L-leucyl-L-phenylalanine (fMLP).

The tannin fraction was also demonstrated to inhibit vesicle oedema and increased vascular permeability that occur at the onset of cyclophosphamide-induced haemorrhagic cystitis [120]. The tannin fraction was suggested to act on polymorphonuclear and leucocyte dependent and independent inflammatory responses and may also inhibit the release of tumour necrosis factor alpha (TNF- α), interleukin-1 (IL-1) and other secondary mediators of inflammation [120].

2.33 *Newbouldia laevis* (*Bignoniaceae*)

N. laevis is a common tropical plant with vast therapeutic uses in traditional system of medicine in Nigeria [123]. A decoction of the bark is given to children in Ivory Coast and

Nigeria for epilepsy and convulsions [123]. A pulp of the bark is used in Senegal for rheumatism, especially painful arthritis in the knee [73]. In Ghana and Nigeria, the bark and leaves are used for the treatment of breast tumors [124].

Experimental evidence suggest that a 95% ethanol leaf extract reduced the paw edema induced by fresh egg albumin and was significantly more potent than indomethacin [123]. The effectiveness of the extract as an anti-inflammatory agent was attributed to possible suppression of the release of inflammatory mediators [123].

2.34 *Opuntia fiscus-indica* Mill (*Cactaceae*)

O. fiscus-indica, the “pricky pear” and also known as “cactus” is a native of America, sometimes grown as a hedge [80]. The fresh stems have been used in folk medicine for the treatment of burns, wounds, edema and indigestion [125]. Alcoholic stem extracts have been reported to possess anti-inflammatory activity [125, 126].

In a recent report, it has been shown that adjuvant-induced pouch granuloma guided fractionation of the methanolic extract has led to the isolation and identification of β -sitosterol as the active principle. The anti-inflammatory activity was however reported to be weak compared to hydrocortisone [127].

2.35 *Orbignya phalerata* Mart [*Arecaceae* (*Palmae*)]

The mesocarp fruits of *O. phalerata* is a food rich in carbohydrates and mineral salts [128], with acclaimed anti-inflammatory and analgesic properties. In traditional medicine, it has been used for the treatment of menstrual pains, arthritis, leukemia, rheumatism, ulcerations, tumors, and inflammation of uterus and ovarium [128].

The chloroform extract of the dried fruits was reported to have exhibited potent anti-inflammatory activity by inhibiting carrageenan-induced acute inflammation, cotton pellet granuloma and formalin-induced arthritis in rats [129]. In a recent report, the isolation of an anti-inflammatory and immunomodulatory polysaccharide from the powdered fruit mesocarp has been demonstrated [128]. The polysaccharide fraction, significantly inhibited the increase in vascular permeability caused by acetic acid. The polysaccharide was also reported to have enhanced phagocytosis *in vivo* [128].

2.36 *Pothomorphe peltata* (L.) Miq. (Piperaceae)

P. peltata leaves are extensively used as an anti-inflammatory agent throughout tropical South and Central America [128-133]. The *in vitro* antioxidant and free radical scavenging activities of different leaf extracts of the plant have been demonstrated [134-137].

The methanolic leaf extract has been demonstrated to significantly reduced the edematous response induced by carrageenan [137]. The effect was comparable to that of phenylbutazone. The methanolic extract was shown to contain 4-nerolidylcatechol (4-NC). The anti-inflammatory activity of the methanolic extract was attributed to the ability of 4-NC to suppress lipid peroxidation, which occurs during inflammation [137-138].

2.37 *Premna herbacea* Roxb. (Verbenaceae)

[Syn. *Pygmacopremna herbacea* (Roxb.) Mold. (Verbenaceae)]

P. herbacea is also known as “sirutekku” in Tamil and used in the traditional system of medicine practised in South India called “Siddha” [139]. *P. herbacea* is claimed to be useful in the treatment of fevers, inflammation, rheumatism, respiratory disorders and as a sedative [140, 141].

Experimental evidence suggests that the ethanolic root extract did not reduce paw edema induced by carrageenan [139]. However the extract produced a mild but statistically significant reduction in the weight of cotton pellets in treated animals. The results indicate that the extract of *P. herbacea* may be effective only in chronic inflammation upon repeated administration [139].

2.38 *Psidium guianense* Pers (Myrtaceae)

P. guianense is a small fruitiferous tree, largely grown in Northeast of Brazil and popularly known as “araca azedo” (sour araca) [142]. Infusions prepared from the leaves of *Psidium* spp are popular medicine used for the treatment of swollen gums, mouth ulcers, and to alleviate abdominal pain [143 – 145].

In experimental animals, the essential oil of *P. guianense* obtained by steam distillation of fresh leaves was reported to have exhibited dose-dependent inhibition of edema in the rats hind paw [142]. The anti-inflammatory activity was found to be comparable to that of indomethacin.

The major volatile constituents of the essential oil have been reported [146]. These were mainly terpenes and include – 1,8-cineole, α -pinene, β -pinene, elemol and sesquiterpenoid alcohols - γ -eudesmol and β -aidesmol.

2.39 *Rheo spathacea* (Swartz) (Commelinaceae)

R. spathacea also known as “maguey” in Mexico, is used by the local populace in Tabasco State. The powder of the aerial parts is used in the treatment of arthritis [37]. The leaves are boiled in water to obtain a cup of clear yellowish liquid, which is drunk daily for chronic inflammation [37].

The ethanolic leaf extract inhibited the development of croton oil induced granulomatous tissue and the early stages of formaldehyde-induced arthritis in rats. The extract also

significantly inhibited carrageenan induced inflammation in the rat paw and was found to be more active topically than orally [37].

2.40 *Sambucus ebulus* (Caprifoliaceae)

S. ebulus also known as “Dwarf elder”, grows extensively in the northern regions of Iran and is popular for its anti-inflammatory and analgesic effects in Iranian traditional medicine [147], where the leaves and rhizomes are used topically for treating inflammatory joint diseases. Coastal people of the Caspian sea use the leaves, rhizomes and roots for treating bee and nettle bites, arthritis and sore throats [148-152].

Pharmacological evidence indicates that the methanolic rhizome extract produced anti-inflammatory activity in both acute and chronic inflammatory tests [147]. *S. ebulus* extract inhibited the formalin induced edema to an extent not significantly different from the effect of sodium salicylate. The extract also chronically inhibited the development of formalin-induced edema. The observed activities were attributed to the plant constituents such as flavonoids, steroids, glycosides and tannins but most probably flavonoids and steroids [148].

2.41 *Sideritis spp* (Lamiaceae)

Different species of the genus *Sideritis* are used as folk remedy in the treatment of inflammatory disorders in Spain [153]. Some of these are native of Granada, Spain include – *Sideritis incana* L. var. *virgata* (Desf) Font Quer, *S. funkiana* Wilk. and *S. hirsuta* L. [153].

The anti-inflammatory and anti-ulcerogenic activities of 20% decoctions of the flowering apices of these *Sideritis spp* have been demonstrated [175]. The extracts clearly reduced plantar edema induced by carrageenan with *S. incana virgata* being the most active. This was followed by *S. hirsuta*. Only *S. hirsuta* and *S. incana* were orally active.

2.42 *Syzygium cumini* L. Skeels (Myrtaceae)

S. cumini is a medicinal plant also known as “Brahhaspati” in Sanskrit and “Jamun” or “Jaman” in Hindi. The bark is reportedly employed in folk medicine for the treatment of inflammation [154] and the anti-inflammatory and antiulcerogenic activities have been reported [155]. Ethanol bark extract of the plant demonstrated significant anti-inflammatory activity in the rat paw edema induced by carrageenan, kaolin-carrageenan and formaldehyde and in the cotton pellet granuloma test in rats.

In the ulcerogenic screening, the extract did not show any ulcerogenic effect in both acute and chronic tests. This suggests that prostaglandin inhibition or cyclo-oxygenase-1 may not be involved in the anti-inflammatory activity of *Syzygium cumini* bark. However, the observed anti-inflammatory activity was attributed to a possible inhibition of inflammatory mediators [155].

2.43 *Tanacetum parthenium* L. Schutz-Bip (Asteraceae)

T. parthenium also known as “feverfew” is a perennial herb with a strong smell and greenish yellow feather-like leaves [156].

In native medicine, the leaves of *T. parthenium* are eaten or the infusion drunk in the treatment of arthritis, migraine and asthma. It is also claimed useful for tinnitus, vertigo, fever, menstrual disorders, difficulty of labour, stomachache, toothache and insect bites [157, 158].

In carrageenan-induced rat paw edema, it has been reported that ethanolic leaf extract exhibited dose dependent anti-inflammatory activity comparable to that of nimesulide [156]. The observed activity was attributed to parthenolide, a sesquiterpene lactone and active anti-inflammatory constituent in fever few extract

[156]. Parthenolide is also considered the most important biologically active principle of feverfew [158, 159].

In earlier studies, feverfew has been shown effective in prophylactic treatment of migraine [159] probably due to its inhibition of platelet aggregation, histamine release from mast cells [160] and the production of prostaglandins, thromboxanes and leukotrienes [156]. These effects may be the mechanisms responsible for the anti-inflammatory activity of feverfew.

2.44 *Taxodium distichum* L. Rich (Taxodiaceae)

T. distichum is one of the most valuable trees of North America. It is native to Europe and United States and grows to about 40 m high [161, 162]. In Egypt, it is cultivated for ornamental and economic purposes [163, 164]. The leaves and seeds are used for the treatment of malaria and liver diseases [165]. The seeds were reported to possess antitumor activities [166, 167].

The anti-inflammatory activity of essential oil of the fruit has been reported [168]. The essential oil obtained by hydrodistillation of the fresh crushed fruits exhibited a strong anti-inflammatory activity in the rat paw edema test. The oil was as effective as diclofenac. The anti-inflammatory activity of the oil was attributed to the presence of α -pinene found to be the principal component of the oil [168].

2.45 *Teucrium buxifolium* Schreber (Lamiaceae)

The aerial parts of *T. buxifolium*, have traditionally been used for the treatment of rheumatic and other inflammatory effects in the Mediterranean region [169]. Also reported is the anti-inflammatory activity of the hexane and methanolic extracts against adjuvant-carrageenan-induced inflammation [170].

Further experimental evidence has been provided for the anti-inflammatory activity of

T. buxifolium [169]. The hexane and methanol extracts inhibited both the acute and chronic phases of arthritis. The methanolic extract was more active against the chronic than the acute phase. The aqueous extract was, however, effective against both phases with activity comparable to phenylbutazone.

In carrageenan-induced plantar edema, all the extracts were found effective. The methanolic extract was the most active. The activities of the hexane and aqueous extracts were comparable to that of phenylbutazone. The extracts also exhibited antiulcerogenic effect indicating a possible selective COX II inhibition by the extracts [169].

2.46 *Tithonia diversifolia* (Hemsl.) Gray (Compositae)

Aerial parts of *T. diversifolia* are among the constituents of the herbal remedy "Wuu-jao-jih-ing" [171] used in folk medicine in Taiwan [172]. It is employed in the treatment of hepatitis, cystitis and jaundice [173]. The anti-inflammatory activity of aqueous extract of the aerial part has been reported [172]. The results show that the aqueous extract inhibited paw edema induced by carrageenan. The extract was found effective in the two phases of the carrageenan-induced inflammatory response [172].

2.47 *Trema* spp (Ulmaceae)

Many species of the genus *Trema* are used in traditional medicine [174]. Infusions prepared from the fruits and flowers of *T. guineense* (Schum et Thonn) are administered to children as therapy for bronchitis, pneumonia and pleurisy, in Tanzania [175].

The petroleum ether, ethanolic and aqueous leaf extracts were found active in carrageenan-induced edema and produced significant antiarthritic activity. In acute inflammation, *T. micrantha* ether extract caused the highest

percent inhibition comparable to that of indomethacin [174]. The observed anti-inflammatory and antiarthritic activities were attributed in part to the β -sitosterol in these species and perhaps to contributions from other constituents e.g. flavonoids triterpenes etc [174].

2.48 *Tripterygium wilfordii* Hook. F. (Celastraceae)

T. wilfordii, also known as “Thunder-God-Vine”, is a popular remedy for rheumatism in Southern China [176]. It is a type of vine-like plant mainly grown in the Southern province of China [177]. An ethanolic roots wood extract has been used in the treatment of various kinds of rheumatism and autoimmune diseases including rheumatoid arthritis [177, 178]. The extract was reported to have significantly improved joint symptoms in arthritic patients with onset of symptoms relief ranging from 3 days to 2-3 weeks [178].

There are evidence that the ethanolic root wood extract significantly inhibited carrageenan-induced paw edema in rats [179] and inhibited adjuvant-induced paw inflammation [176]. The extract exerted modulatory effect on mediators of inflammation, inhibited lysozyme release, decreased superoxide production and significantly reduced prostaglandin levels [176].

2.49 *Turner ulmifolia* L. (Turneraceae)

T. ulmifolia also known as “Chanana” is a weed widely distributed in Brazil [180]. Some *Turnera* species are employed for the treatment of inflammatory diseases in traditional medicine [181 - 183]. Among these species, *T. ulmifolia* is widely used as an anti-inflammatory agent [184].

The hydroalcoholic extract of *T. ulmifolia* and the ethylacetate, aqueous and ethanol fractions have been reported to exhibit anti-inflammatory effect in acute edema induced by carrageenan [208]. The crude hydroalcoholic extract and the

aqueous and ethanolic fractions inhibited edema in the rat paws at 3 h.

In antiedematogenic response in carrageenan-induced inflammation, the hydroalcoholic extract and ethanolic fraction inhibited the inflammation with an ED₅₀ of about 3 g/kg and 150 mg/kg respectively [84] while a marked inhibition of the transudative phase and the proliferative phase was observed in cotton pellet granuloma test.

The ethanolic fraction was reported to inhibit leucocyte migration, and markedly reduced the vascular permeability induced by PGE₂, histamine and 5-HT but not bradykinin [185]. The anti-inflammatory activity of the extract and fractions was attributed to inhibition of mediators of early or immediate inflammatory response. This suggestion is consistent with the activity observed in the cotton pellet granuloma test. Also consistent with the suggested mechanism of action is the effect of the hydroalcoholic extract on gastric lesions [184].

The extract inhibited gastric lesions induced by pyloric ligation, indomethacin and ethanol but was not effective in that induced by stress. The antiulcerogenic effect of the extract was postulated to be due to inhibition of histamine (pyloric-ligation ulcers) and enhancement of mucosal defensive factors such as gastric mucus (ethanol and indomethacin induced ulcers) [184]. The extract was also found effective in inhibiting arachidonic acid induced platelet aggregation thought to be due to a selective cyclooxygenase II inhibition and consistent with the anti-ulcerogenic effect [184].

3. Isolated anti-inflammatory plant constituents

3.1 *Fagaramide and DBA*

Fagaramide (piperonyl-4-acrylicisobutylamide) and DBA (3,4-dihydro-2-dimethyl-

2H-1-benzopyran-6-butyric acid), a benzopyran butyric acid derivative of xanthoxylol, are extractives from fagara plant, *Zanthoxylum zanthoxyloides* (Rutaceae) [185]. Root extracts of fagara plant are widely used locally in the treatment of fevers of various aetiologies and sickle cell [185].

DBA is a benzopyran butyric acid derivative of xanthoxylol from the fagara plant. Fagaramide, an unmodified extractive from fagara plant was found effective against carrageenan-induced paw edema in rats at a potency approximately twenty times less than that of indomethacin [185].

Fagaramide was also effective against the prostaglandin phase of acute inflammatory response where it dose-dependently inhibited *in vitro* prostaglandin synthesis. However, it showed no effect on PGE₁-induced potentiation of carrageenan edema in indomethacin treated rats. [185]

3.2 Lupeol and lupeol lineolate

The isolation of an anti-inflammatory triterpenoid, lupeol, from the n-hexane stem bark extract of *Crataeva religiosa* Forst. F. (Caparidaceae) has been reported [186]. It has also been documented that lupeol is a major triterpene constituent of the stem bark of *Crataeva nurva* Buch-Ham (Caparidaceae) [11]. *C. nurva* had been shown to possess anti-inflammatory and antiarthritic activities [187].

In an extensive and detailed anti-inflammatory activity studies, it was reported that lupeol exhibited anti-inflammatory effect in a variety of acute and chronic anti-inflammatory test models in rats and mice [186]. The highest oral activity was obtained in the carrageenan-induced edema. Lupeol exhibited significant anti-inflammatory effect in developing adjuvant

arthritis in rats to a degree better than that of acetylsalicylic acid. The same activity was obtained in mice arthritis model.

In formaldehyde arthritis, lupeol was effective in the development and pattern of inflammation compared to a similar dose of acetylsalicylic acid. Lupeol also reduced exudate volume, inhibited vascular permeability induced by acetic acid in mice and also reduced total leucocyte count.

However, lupeol was not effective in inhibiting cotton pellet granuloma in rats. It exhibited no ulcerogenic, analgesic and antipyretic effects [186]. It was thus suggested that the anti-inflammatory activity of lupeol might be due to immunosuppression and inhibition of cell migration into sites of inflammation [186]. The latter, in turn, reduces proinflammatory chemotactic factor release.

Further experimental evidence has been provided for the anti-inflammatory activity of lupeol and also lupeol lineolate which is an ester of lupeol [11]. Lupeol lineolate was obtained from esterification of lupeol with linoleoyl chloride [188].

In adjuvant-induced arthritis, lupeol and lupeol lineolate caused inhibition in paw diameter by 39 and 58% respectively [11]. The synovial cavity of lupeol treated arthritic joint was found more or less obliterated with granuloma-like lesion consisting of fibrin, and inflammatory cellular infiltration. Arthritic rats treated with lupeol lineolate showed synovial cavity with less cellular infiltration. These findings suggest that the antiarthritic activity of lupeol lineolate is greater than that of lupeol.

The reason for lupeol's lack of activity in cotton pellet granuloma test [186] and the activity observed in adjuvant-induced arthritis [11] is not known. However, it may be due to differences in pharmacological characteristics of the two models of chronic inflammation.

3.3 Parthenolide and the methoxyflavones (jaceosidin, eupatorin, chrysoeriol and diosmetin).

Parthenolide and the methoxyflavones (jaceosidin, eupatorin, chrysoeriol and diosmetin) have been isolated and identified from dichloromethane and methane extracts of aerial parts of *Tanacetum vulgare* (Asteraceae) [189].

These constituents have been reported to be responsible for the anti-inflammatory activity of the plant against 12-0-tetradecanoylphorbol-13-acetate (TPA) induced mouse ear edema. Parthenolide caused inhibition of mouse ear edema ($ID_{50}=0.18\mu\text{m}/\text{ear}$). The methoxyflavone jaceosidin caused inhibition with ID_{50} of $0.5\mu\text{m}/\text{ear}$. Parthenolide was reportedly found to be nearly three times (in molar terms) more potent than that of the most active of the flavones. [189]

3.4 (+) – Pinitol

Abies pindrow Spach (Pinaceae) known as the “Talisapatr” tree in Sanskrit and “Morinda” in Hindi is found in abundance in the deciduous forests of Himalayas [112]. The leaves have been used in Ayurvedic medicine for fever, respiratory and inflammatory disorders [190]. The leaf extracts and fractions of have been reported to possess anti-inflammatory, analgesic, hypnotic and antiulcerogenic activities in rats, hypotensive effect in dogs and endurance enhancing in swim stress in mice [191-193].

(+)-Pinitol inhibited edema induced by carrageenan in the rat paw in a dose-related manner [194]. The activity of the highest dose was comparable to that of phenylbutazone [194].

3.5 Premnazole

Premnazole is an isoxazole alkaloid derivative isolated from the leaves of *Gmelina arborea* Roxb and *Premna integrifolia* Linn (Verbenaceae) [195].

G. arborea was introduced into West Africa from tropical Asia as a shade and fuel tree [33] and is important in afforestation programme in the savannah zones of Nigeria [76]. The drupes, leaves, flowers, roots and bark are used in medicine [186]. A leaf paste is applied on the head to relieve headache in fever [196].

P. integrifolia tender plant is used for rheumatism and neuralgia [197]. The leaves also possess carminative and galactagogue properties. The leaf decoction is used for colic and flatulence [195].

Premnazole, an alkaloid was earlier prepared by total synthesis [198]. The isolated premnazole was shown to significantly reduce cotton pellet granuloma weight in treated animals [195]. It also reduced the weight of adrenal gland and spleen and also reduced ascorbic acid content in adrenal glands. The action of premnazole was attributed to a probable control of the activity of adrenocorticotrophic hormone and inhibition of bradykinin synthesis through reduction in the activities of glutamate pyruvate transaminase and glutamate oxaloacetate transaminase [195].

3.6 Sarsanquol

The isolation of an anti-inflammatory 3, 4-secotriterpene alcohol, sasanquol, from the non-saponifiable lipids of seed oil of *Camellia sasanqua* THUNB has been reported [199]. The structure was established by spectroscopy as 3, 4-seco-D:B-friedobacchara-4, 21-dien-3-ol. In anti-inflammatory test, sasanquol inhibited ear edema induced by TPA with ID_{50} of $0.4\text{ mg}/\text{ear}$ [199].

3.7 Triterpene alcohols

The isolation of seven novel naturally occurring triterpene alcohols from non-saponifiable lipids of seeds of *Camellia japonica* L. and sasanqua oil from seeds of *C. sasanqua* has equally been documented [199]. The compounds include tirucall-5, 7, 24-triene-3-beta-ol, lemmaphylla-7,

21-dien-3-beta-ol, isoeuphol, isotirucallol, (24R)-24, 25-epoxybutyrospermol and its 24S-epimer, and isoaglaiol. The anti-inflammatory effect of these compounds in the mouse ear has been reported [200].

Isoeuphol, isotirucallol, a mixture of (24R)-24, 25-epoxybutyrospermol and its 24S-epimer and a mixture of isoaglaiol and its 24S-epimer (aglaiol) inhibited mouse ear edema induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) with an ID_{50} of 0.2–0.9 mg/ear.

3.8 (+)-Usnic acid

(+)-Usnic acid has been isolated from the whole plant of the lichen *Roccella montagnei* Bel. (Fam. Roccellaceae) [201]. Activities of (+)-usnic acid earlier reported include antibacterial [202], antitubercular [203–205], analgesic and antipyretic [206] and other pharmacological activities [207, 208]. The anti-inflammatory activity of (+)-usnic acid has been studied [196].

(+)-Usnic acid produced dose-dependent inhibition of carrageenan-induced paw edema and also produced dose-dependent reduction in the weight of cotton pellet after chronic treatment. The activity of (+)-usnic acid was attributed possibly to uncoupling of oxidative phosphorylation [209] likened to acetylsalicylic acid [201].

3.9 Zanhasaponins A and B, and cyclitol pinitol

The methanolic extract of *Zanha africana* was found active against arachidonic acid acute edema, 12-O-tetradecanoylphorbol-13-acetate (TPA) induced chronic inflammation and oxazolone delayed-type hypersensitivity in mice [210]. The extract also exhibited significant inhibitory activity against *Naja naja* phospholipase A_2 using polarographic method [210]. Oleanane-type triterpene saponins zanhasaponins A, B and C and the cyclitol pinitol

were isolated from the methanolic extract of *Zanha africana* [210].

Out of the four isolated constituents, zanhasaponins A and B and the cyclitol pinitol were reported to inhibit phospholipase A_2 enzyme necessary for the release of arachidonic acid. Phospholipase A_2 inhibition prevents the formation of prostaglandins, thromboxanes and leukotrienes and is the main basis for the anti-inflammatory effect of steroids [211–214].

4. Discussion

It is evident from the documentations that a number of medicinal plants are employed in the treatment of inflammatory disease conditions. These anti-inflammatory plants have demonstrated effect in acute and chronic inflammation in experimental animal models. The effect of these various family of herbs may be due to the different structurally complex active principles or constituents present in these plants and the possible multiple targets for drug action in the complex inflammatory response.

The anti-inflammatory activity of plants is attributed mainly to the constituents such as alkaloids [195], flavonoids [215–226], tannins [227], sterols [216], triterpenes [186, 228–233], sesquiterpenes lactones [234], volatile oils [222, 235], resins [222], carbohydrates or polysaccharides [70, 128, 222, 236–238], flavone glycosides [240], polyunsaturated fatty acids e.g. palmitic, oleic and linoleic acids [240]. These structural forms have variously been shown to exhibit pharmacological activity in the inflammatory response process - naturally by interfering with the response pathway.

Consequently, flavonoids have been reported to inhibit arachidonic acid metabolism [241, 242] and prostaglandin synthetase [243, 244]. Tannins inhibit prostaglandin synthesis [227] while plant catechols e.g. 4-nerolidyl-catechol

(4-NC) have been shown to exhibit peroxy radical scavenging and lipid peroxidation [135, 245 - 247]. Glucan-type polysaccharides have been reported to inhibit increase in vascular permeability [128] while polysaccharides exhibited anti-complementary activity [70, 236, 237].

Of all the mechanisms for the anti-inflammatory effects of these plants, their actions on endogenous pro-inflammatory mediators are remarkable. The inflammatory reactions induced by the phlogistic agents used in the screening of these herbs are mediated by different endogenous mediators.

Carrageenan-induced edema is mediated by histamine, 5-HT [248], kinin, polymorphonuclear leukocytes, prostanoids, nitric oxide, neuropeptides and cytokines [249 - 253]. Substance P, bradykinin, histamine, 5-HT and prostaglandins mediate formaldehyde edema [254]. Zymosan edema is mediated by complement system, mast cell amines, polymorphonuclear leukocytes, prostanoids and PAF-acether [252, 255, 256] while prostanoids and leukocytes mediate croton oil-induced inflammation [257].

Inhibition or modulation of edema induced by these agents as well as membrane stabilization often imply inhibition of the action or release of these endogenous mediators. Inhibition of leukocyte (cell) migration can also lead to inhibition or modulation of edema formation [258]. These apply to inflammation whether acute or chronic.

However, in chronic inflammation models, such as adjuvant-induced arthritis, inflammation is attenuated through the inhibition of leukocyte (cell) migration [259] and immunosuppression. Adjuvant-induced arthritis exhibits clinical and pathological changes comparable to those seen in human rheumatoid arthritis [260].

It is thus obvious that the efficacy of anti-inflammatory plants in the treatment of inflammatory diseases possibly derive from a multifaceted assault on the inflammatory response cascade. The mechanism of action varies from plant to plant and certainly determines the observed potency of the plant. In addition to anti-inflammatory activity, some of these plants also possess antinociceptive, antiulcer and antimicrobial activities.

Ageratum conyzoides [32], *Chasmanthera dependens* [74], *Culcasia scandens* [79, 263], *Diodia scandens* [95], *Premna herbacea* [139], and *Tanacetum parthenium* [156] have all been reported to possess analgesic as well as anti-inflammatory properties. Analgesic property is essential in relieving pain associated with inflammation and is a beneficial effect of the NSAIDs.

However, NSAIDs by inhibiting the cyclooxygenase induce gastric lesions [261]. Therefore, plants that possess antiulcer property in addition to anti-inflammatory effect are immensely valuable in the search for ideal anti-inflammatory agent. *Euphorbia royleana* [103], *Calligonum comosum* [55], *Sideritis hirsuta var virgata* [53], etc have all been shown to possess antiulcer and cytoprotective properties in addition to anti-inflammatory effect. This effect confers advantage on these medicinal plants over available NSAIDs.

Also this effect is of greater importance for plants, which have shown activity in chronic inflammation. Perhaps the safety of such plants in chronic use may be better appreciated by considering the severe limitations experienced in short term use of NSAIDs.

Antimicrobial activity has been exhibited by *Cyphostemma natalitium*, *Rhoicissus rhomboidea* and *R. tomentosa* in addition to cyclooxygenase (prostaglandin syntheses)

inhibition [262]. Desirability of antimicrobial effect derives from modulation of inflammation caused by microbial infections. All these contributory mechanisms add to the efficacy of these anti-inflammatory herbs.

In a continued effort to develop more effective anti-inflammatory agents from plant sources, a number of active principles have been isolated and identified. The anti-inflammatory activity of β -sitosterol isolated from *Cactus, Opuntia ficus-indica* has been reported [127].

Parthenolide, a sesquiterpene lactone isolated from *Tanacetum vulgare* [189] and active principle of *Tanacetum parthenium* (feverfew) [156] has demonstrated potent anti-inflammatory and analgesic properties [156, 189]. Lupeol, an anti-inflammatory triterpenoid compound has been shown to possess antiulcer property [186].

Besides their inherent anti-inflammatory and other pharmacological activities, these active

principles could serve as “leads” for the development of drugs with enhanced activity profile. Already, lupeol lineolate, an ester of lupeol, obtained by esterification of lupeol with linoleoyl chloride, has been reported to exhibit greater antiarthritic activity than lupeol [11].

5. Conclusion

The existence of multiple targets for drug action in the inflammatory response pathway offers numerous sites of action to the multitude of active constituents of these medicinal plants. Due to their efficacy in the herbal treatment of inflammatory disease conditions, these plants have continued to serve as alternative and complementary therapies. Mounting experimental evidence has continued to lend credence to this fact and to establish rationale for the ethnomedicinal use.

In addition, these medicinal plants will continue to serve as reservoir for development of potent drugs with less serious and life-threatening adverse effects.

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