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Anti-inflammatory agents from plants – Part III

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Inflammation is the major condition associated with various diseases. Various molecules have been isolated from plants that have proven effective against inflammatory conditions. This review is a summary of different plant constituents which demonstrated anti-inflammatory activity.

Keywords: Inflammation, Paw oedema, Triterpenoids, Anti-inflammatory.

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Introduction

Inflammation is a local response of living mammalian tissue to injury. It is a body defense reaction in order to eliminate or limit the spread of injurious agent. There are various components of an inflammatory reaction that can contribute to the associated symptoms and tissue injury. Oedema formation, leukocyte infiltration and granuloma formation represents such components of inflammation[1]. Carrageenan-induced paw oedema is widely used for determining the acute phase of inflammation. Histamine, 5-hytroxy tryptamine and bradykinin are the first detectable mediators in the early phase of carrageenan induced inflammation[2]. Whereas prostaglandins are detectable in the late phase of inflammation[3]. It is believed that current analgesia inducing drugs such as opiates and non steroidal inflammatory drugs are not useful in all cases, because of their side effects and potency[4]. As a result, search for other alternatives seems necessary and beneficial. Anti-inflammatory agents from plants have been earlier reviewed by the author in two separate parts[5-6]. This chapter i.e. part-III is an extension of the earlier parts.

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Anti-inflammatory phytoconstituents and their sources

Terpenoids

E-phytol obtained from the leaves of *Aucuba japonica* Thunb. (Anacardiaceae) exhibited more potent action against histamine induced paw oedema in rats[5]. Triptoquinone A and B, isolated from *Tripterygium wilfordi* Hook. f. inhibited interleukin-1 in *in vitro* test systems[6]. Andrographolide from *Andrographis paniculata* (Burm. f) Wall. ex Nees reduced inflammation induced by various phlogistics in a dose dependent manner in rats[7].

Hexane extract of *Sideritis javalambrensis* Pau. (Lamiaceae)[8] yielded novel diterpenes like *ent*-13-*epi*-12-acetoxymanoyloxide (manoyl oxide F_1) and *ent*-8α-hydroxylabda-13(16), 14-diene (labdane F_2), which were non cytotoxic and inhibited prostaglandin E_2 generation in cultured peritoneal macrophages stimulated by zymosan A23187, melitin and PMA. However, labdane F_2 was found to be more potent.

Diterpenes kauronic acid from the root cortices of *Acanthopanax gracilistylus* W. Smith (Araliaceae)[9] and aethiopinone from the roots of *Salvia aethiopsis* L. (Lamiaceae)[10] were isolated and their anti-inflammatory activity was established in various models. The sesquiterpene lactones such as helenalin and 11, 13-dihydrohelenaline from *Arnica montana* L. have also been shown to attack inflammatory processes by inhibiting NF-κB and NF-AT at

micromolar concentrations[11] and by inhibiting neutrophil migration, lysosomal rupture, enzymatic activity, and prostaglandin synthesis[12].

The triterpenoids sorghumol, sorghumol acetate and boehmerol acetate from the roots[13], moretenol, moretenol acetate, neolupenol and neolupeol[14,15], psi-taraxasterol acetate[16] obtained from *Pluchea lanceolata* C.B.Clarke (Asteraceae) exhibited significant anti-inflammatory activity in carrageenan induced paw oedema model in wistar albino rats at 50 mg/kg p.o. dose level.

18α-glycyrrhetinic acid (30 mg/kg p.o.) obtained from *Glycyrrhizae radix* showed similar antigranulomatous action in normal and adrenalectomized rats. Whereas 18β-glycyrrhetinic acid (30 mg/kg p.o.) which exhibited the inhibitory effects in normal rats, showed no action in adrenalectomized rats. 18α-glycyrrhetinic acid was found to be more active than its 18β-isomer because of stereochemical structure of D/E *trans* conformation[17].

3β-Acetoxyolean-12-en-27-oic acid, 2α, 3α-dihydroxyoleana-5, 12-dien-28-oic acid; 2β, 3α-diacetoxyolean-5, 12-dien-28-oic acid and 2α, 3β-diacetoxy-18-hydroxyolean-5, 12-dien-28-oic acid isolated from *Vitex negundo* L. (Verbenaceae) seeds showed anti-inflammatory activity in carrageenan induced rat paw oedema model at 50 mg/kg p.o. dose level[18]. Betulin, betulinic acid and ursolic acid obtained from *Diospyros leucomelas* Poir. (Ebenaceae) exhibited anti-inflammatory activity against various phlogistic agents in rats[19]. However, the most potent activity was observed in betulinic acid obtained from the rhizomes of *Menyanthes trifoliata* L. against prostaglandin synthesis in *in vitro* at IC_{50} value of 101 μM compared to 1897 μM of aspirin[20]. The roots of *Bupleurum longeradiatum* Turcz. (Apiaceae) yielded arborinone which exhibited significant anti-inflammatory activity in a dose dependent manner[21].

Glycyrrhizin significantly decreased neutrophil generated O_2, H_2O_2 and OH in a dose-dependent manner. However, the drug did not reduce any of the ROS generated in a cell-free, xanthine-xanthine oxidase system. Therefore, glycyrrhizin is not a ROS scavenger but exerts its anti-inflammatory action by inhibiting the generation of ROS by neutrophils[22].

Triterpene saponins, named sativosides A and B isolated from the seeds of *Nigella sativa* L. showed significant inhibition of phorbol 12-myristate-13-acetate (PMA) plus calcium ionophore A23187-induced production of IL-6 in a human mast cell (HMC-1) line[23].

Saikosaponins a, b_1, b_2, d and their aglycones from *Bupleurum falcatum* L. [51], saikosaponin from the roots of *Bupleurum kaoi* Liu, Chao et Chuang [24] and a glycoside of saikogenin G containing three sugars from the roots of *Bupleurum gibraltaricum* Lam.[25] have shown significant anti-inflammatory activity in carrageenan induced paw oedema in rats. A bisdesmodic triterpenoid saponin, dulcin (1) having anti-inflammatory activity was isolated from the seeds of *Pithecellobium dulce* (Roxb.) Benth. (Mimosaceae) [26].

The dried leaf extract [methanol-water (1:1)] of *Wattakaka volubilis* (L.f.) Stapf. significantly inhibited the arachidonic acid-induced paw oedema in rats, indicating that the extract inhibited both the cyclo-oxygenase and lipo-oxygenase pathways of arachidonic acid metabolism. The extract also significantly enhanced the macrophage count in mice in a dose- and time-dependent manner. It is possible that the saponins present in the extract may be responsible for these activities[27].

An acylated triterpene saponin from the roots of *Silene jenisseensis* Willd. (Caryophyllaceae) exhibited inhibitory effect on cyclooxygenase assay for anti-inflammatory action[28]. Tubeimoside I isolated from the bulbs of *Bolbostemma paniculatum* Maxim. (Cucurbitaceae) inhibited the arachidonic acid induced mouse ear oedema when given intraperitoneally, but it was inactive through oral route[29].

In vitro and *in vivo* anti-inflammatory activity was demonstrated with esculentoside from *Phytolacca esculenta* Van Houtte (Phytolaceae) by inhibiting the production of interleukin-1 at a concentration of 1.0 μM/L and inhibition of antibody production challenged by sheep RBC at a concentration of 2.5-5.0 mg/kg, respectively[30].

Flavonoids

Flavonoids are known to inhibit the enzyme prostaglandin synthesis, more specifically the endoperoxide and reported to produce anti-inflammatory effect[31,32]. Naturally occurring flavonoids with diverse chemical structures as anti-inflammatory agents have been reviewed earlier[33-35]. The dose related response of 5,7,3'-trihydroxy-3,6,4'-trimethoxy flavone (Centaureidin) and 5,3'-dihydroxy-4'-methoxy-7-carbomethoxy flavonol from the aerial

parts of *Tanacetum microphyllum* DC. (Asteraceae) at 600 mg/kg was similar to phenylbutazone at 80 mg/kg in carrageenan induced paw oedema in mice[36].

Flavonoids apigenin, luteolin and quercetin contribute to chamomile's anti-inflammatory activity[37]. Gangetin, one of the Pterocarpans, isolated from the hexane extract of the root of *Desmodium gangeticum* (L.) DC. showed significant anti-inflammatory activity in the exudative and proliferative phases of inflammation in the doses of 50 and 100 mg/kg p.o.[38].

Flavonoids namely kaempferol, ombuin, kaempferol 7,4'-dimethyl ether 3-*O*-*β*-D-glucopyranoside, kaempferol 3-*O*-*β*-D-glucopyranoside, isorhamnetin 3-*O*-*β*-D-glucopyranoside and hesperidin, together with one triterpene caffeate, 3*β*-trans-(3,4-dihydroxycinnamoyloxy)olean-12-en-28-oic acid isolated from the non-woody aerial parts of *Bauhinia variegata* L. significantly and dose dependently inhibited LPS and IFNγ induced NO and cytokines [TNF*α* and IL-12][39]. Kaempferol-3-*O*-sophoroside isolated from the leaves of *Cassia alata* L. (Caesalpiniaceae) exhibited significant anti-inflammatory activity in carrageenan and cotton pellet granuloma inflammations at 50 mg/kg i.p. in mice, compared to phenylbutazone[40].

When applied topically, the flavonoids of *Matricaria recutita* L. (German Chamomile) were found to penetrate intact skin deeply to exert an anti-inflammatory effect. Compared to a hydrocortisone 1% cream, the anti-inflammatory effect of a chamomile cream was weaker[41].

Topical anti-inflammatory activity of 8-[C-*β*-D-[2-*O*-(*E*)-cinnamoyl] glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone from *Aloe barbadensis* Mill. (Liliaceae) at a dose level of 200 µg/ear was comparable to hydrocortisone in mice[42]. Taxifolin down regulated the expression of intercellular adhesion molecule-1. It impeded the calcium influx induced by fMLP (a receptor mediated activator) or AlF_4^- (a G protein mediated activator) and effectively inhibited the fMLP or PMA induced ROS production with IC_{50} less than 10 μM, possibly through impairing the activation of NADPH oxidase[43].

Ethanol fraction of *Cassia sophera* L. showed 69.7 % protection against acetic acid induced writhing. *C. sophera* contains flavonoids which modulate the oxidative stress[44]. Flavonoid enriched fraction of rhizomes of *Sophora flavescens* Ait. inhibited cyclooxygenase-2 catalyzed PGE_2 and inducible nitric oxide synthase catalyzed NO production by lipopolysaccharide treated RAW 264.7 cells at 10-50 µg/mL. Fraction also inhibited IL-6 and TNFα production. When tested against adjuvant-induced arthritis in rats at 10-100mg/kg/day p.o., fraction strongly inhibited arthritic inflammation[45].

The roots of *Xylopia africana* (Benth.) Oliver, yielded isouvarinol which is cytotoxic and antibacterial[46]. Quercetin-3-*O*-glucorhamno arabinoside from *Symphorema involucratum* Roxb. (Verbenaceae)[47], quercetin-*O*-coumaric acid from *Cedrela sinensis* A. Juss. (Meliaceae)[48] exhibited significant anti-inflammatory activity in rat paw oedema method. Quercetin and I3/II8-biapigenin from oil extracts of *Hypericum perforatum* L. exhibited anti-inflammatory activity similar to those of indomethacin as well as significant gastroprotective activity[49].

Galetin 3,6-dimethyl ether (**2**) (100 µmol/kg, i.p.) obtained from aerial parts of *Piptadenia stipulacea* (Benth.) Ducke protected the second phase of inflammation by 68.78%[50]. Axillarin, isoquercitroside, hyperoside from the aerial parts of *Xanthium* species (Asteraceae) exhibited significant topical anti-inflammatory activity in rats[51]. Hesperidin from the peels of *Citrus aurantium* L. (Rutaceae) exhibited significant anti-inflammatory and analgesic properties[52].

Prunin-6"-*O*-*p*-coumarate (30 and 100 mg/kg i.p.), a flavonoid glycoside isolated from the nut shells of *Anacardium occidentale* L. (Anacardiaceae) showed anti-inflammatory activity in carrageenin induced rat paw edema. Ibuprofen (50 mg/kg i.p.) was used as the reference drug[53]. Broussochalcone A (3) from *Broussonetia papyrifera* (L.) Hert. ex Vent. (Moraceae) exhibited most potent anti-inflammatory activity by inhibiting the arachidonic acid induced platelet aggregation at IC_{50} 6.5 µM[54].

Bavachinin A isolated from fruits of *Psoralea corylifolia* L. showed anti-inflammatory activity against carrageenan-induced edema in rats[55]. Licochalcone A isolated from the roots of *Glycyrrhiza inflata* Bat. (Fabaceae) exhibited significant anti-inflammatory activity against TPA induced mouse ear oedema[56].

Nepitrin (5,3',4'-trihydroxy-6-methoxy flavone) was found to possess significant anti-inflammatory activity in the exudative and proliferative phases of inflammation. This action can be due to its anti-bradykinin and anti-angiotensin action[57]. Biochanin-A (5,7-dihyddroxy-4-methoxy isoflavone) isolated from flowers of *Dalbergia sissoides* Wight & Arn. have

shown anti-inflammatory activity against PGE, bradykinin, 5-HT and histamine induced rat hind paw oedema in a dose dependent manner[58].

Phenolic compounds

Ethyl acetae and *n*-butanol fractions of ethanol extract of *Arceuthobium oxycedri* (DC.) M. Bieb. (Loranthaceae) showed significant inhibitory activity in the bioassay systems. (+)-catechin was isolated as the major component from the EtOAc fraction[59]. Curcumin's anti-inflammatory activity stems from inhibiting cyclooxygenase-2 (COX-2), prostaglandins and leukotrienes[60].

Curcumin from the rhizomes of *Curcuma longa* L. (Zingiberaceae) exhibited potent anti-inflammatory properties by the inhibition of nitric oxide synthase (NOS) in activated macrophages at IC_{50} 6 μM[61]. A number of different molecules involved in inflammation were inhibited by curcumin including phospholipase, lipooxygenase, cyclooxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor and interleukin-12 (IL-12)[62].

The anti-inflammatory activity of curcumin analogues namely triethyl curcumin (TEC), tetrahydro curcumin (THC) was compared with that of phenylbutazone (PB) using the carrageenin-induced rat paw edema and cotton pellet granuloma tests. The order of potencies of curcumin analogues in carrageenin-induced inflammation were THC greater than PB greater than TEC. These analogues decreased carrageenin-induced paw edema at low doses. However, at higher doses this effect was partially reversed[63]. A lignan, 6-hydroxy-4-(4-hydroxy-3-methoxy phenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-napthaldehyde from the seeds of *Vitex negundo* L. reduced the inflammation by 40.6% induced by carrageenan at a dose level of 50 mg/kg p.o. in rats[64]. The structure activity relationship indicated that the *o*-dihydroxy group of gallic acid is important for the inhibitory activity[65].

6-Gingerol and 6-paradol have been reported to possess a strong anti-inflammatory activity and to suppress the TNF-α production in TPA-treated female ICR-mice and rats[66, 67]. 6-Shogaol and gingerdiols isolated from 40 % ethanolic extract of *Zingiber officinale* var. *rubra* suppressed NO production from mouse leukemic monocytes (RAW264 cells). Proanthocyanidins also suppressed NO production at 100 μg/mL[68]. (+)-α-Viniferin obtained from *Caragana chalmagn* (Fabaceae) roots exhibited significant reduction in mouse hind paw oedema induced by carrageenan[69]. Hydnocarpin from *Hydnocarpus wightiana* Blume (Flacourtiaceae) exhibited anti-inflammatory activity at a dose level of 8 mg/kg i.p.[70]. Ferulic acid isolated from *Ligusticum wallichi* Franch. (Apiaceae) inhibited oedema induced by carrageenan, acetic acid and granuloma formation in rats at a dose level of 300 mg/kg p.o.[71]. 3'-*O*-methylbatasin obtained from *Bleitilla strjata* (Thunb.) Rchb. f. (Orchidaceae) showed 75.4% inhibition at 50mg/kg dose level in callidium induced inflammation[72].

Coumarins

Cleomiscosin A (4) from the methanolic extract of seeds of *Hyoscyamus niger* L. reduced dry and wet weight of cotton pellet granuloma in mice[73]. 11-*O*-galloylbergenin isolated from ethanolic extract of *Mallotus philippensis* Muell.-Arg. exhibited significant anti-inflammatory activity in carrageenan-induced paw edema model at doses of 10, 20 and 30 mg/kg[74].

Iridoids

6-Deoxyharpagide isolated from *Ajuga bracteosa* Wall. ex Benth. exhibited highest COX-2 inhibition while aajugarin I, lupulin A, withaferin A and reptoside exhibited weak to moderate COX-1 and COX-2 inhibition at 30 μM concentration[75]. Devil's claw is used for osteoarthritis and other inflammatory conditions because iridoid glycosides seem to have an anti-inflammatory effect[76].

Alkaloids

Nimbin and Nimbidin have been demonstrated to be equal effective anti-inflammatory agent as a standard over-the counter treatments, but without side-effects[77]. The prototype alkaloids,16-*epi*-pyrojesaconitine and pyrojesaconitine from the roots of *Aconitum napellus* L. (Ranunculaceae) showed more potent effect against adjuvant, air pouch granuloma in mouse than hydrocortisone and indomethacin in an angiogenesis in chronic inflammation[78,79].

Berberone hydrochloride, an alkaloid isolated from *Berberis aristata* DC. was found to have significant anti-inflammatory activity on acute, subacute and chronic types of inflammations produced by immunological and non-immunological methods[80]. Chronic oral (20 mg/kg) and intramuscular (2 mg/kg)

administration of Berberine sulphate to rats increased the duration of pentobarbitone-induced sleeping time and decreased serum cholesterol levels[80].

Tylophorine isolated from *Tylophora indica* (Burm. f.) Merrill significantly inhibited the primary and secondary responses of adjuvant-induced arthritis in rats[82]. Crotalaburnine (10 mg/kg s.c.) isolated from *Crotalaria laburnifolia* L. produced a similar degree of inhibition as 100 mg/kg p.o. of phenylbutazone in carrageenan-induced paw oedema model[83].

Xanthones

The xanthones isolated from *Calophyllum inophyllum* L. and *Mesua ferrea* L. namely, dehydrocycloguanandin, calophyllin-B, jacareubin, 6-desoxy jacareubin, mesuaxantbone-A, mesuaxanthone-B and euxanthone exhibited anti-inflammatory activity both by i.p. and oral routes in carrageenin induced rat hind paw oedema, cotton pellet granuloma and granuloma pouch techniques[84].

α-Mangostin and γ-mangostin isolated from the fruit hull of *Garcinia mangostana* L. significantly inhibited NO and PGE_2 production from lipopolysaccharide stimulated RAW 264.7 cells with IC_{50} values for the inhibition of NO production being 12.4 and 10.1 μM, respectively. The inhibitory activities of α- and γ-mangostins are not due to direct inhibition of iNOS enzyme activity. In *in vivo* study, α-mangostin significantly inhibited mice carrageenan-induced paw edema[85].

Polysaccharides

The polysaccharidic fraction (0.5 mg/kg i.v.) of *Echinacea angustifolia* DC. roots almost inhibited the carrageenan-induced oedema over 8 h and when topically applied, inhibited mouse ear oedema induced by croton oil[86].

Essential oils

The essential oil from *Artemisia caerulescens* subsp. *gallica* (Asteraceae) exhibited analgesic, anti-pyretic and anti-inflammatory activity in rats and mice at a dose level of $1/4^{th}$ to $1/3^{rd}$ of its LD_{50} (1.35 mL/kg)[87].

Crude essential oil of *Cinnamomum insularimontanum* Hayata and its dominant compound (citral) presented the significant NO production inhibitory activity. IC_{50} of crude essential oil and citral were 18.68 and 13.18 µg/mL, respectively. The expression of IKK, iNOS and nuclear NF-κB was decreased and IκBα was increased in dose-dependent manners. Citral also showed inhibition in croton oil-induced mouse ear edema at 0.1 and 0.3 mg/ear. The inflammation was reduced to 22 and 83 %, respectively[88].

Tannins

A mixture of tannins obtained from the bark of *Anacardium occidentale* L., on i.p. injection, demonstrated anti-inflammatory activity in carrageenan and dextran-induced rat paw oedemas, cotton pellet granuloma test and adjuvant-induced polyarthritis in rats. Tannins also inhibited acetic acid-induced writhing in mice and antagonised the permeability-increasing effects in rats of certain mediators of inflammation and inhibited the migration of leucocytes to an inflammatory site[89].

Miscellaneous Compounds

Bromelain shows anti-inflammatory activity by inhibiting the generation of bradykinin at the inflammatory site via depletion of the plasma kallikrein system as well as limiting the formation of fibrin by reduction of clotting cascade intermediates[90-92]. Cepharanone B, aristolactam AII, piperolactam A and norcepharadion B isolated from *Houttuynica cordata* Thunb. (Sauraceae) exhibited inhibitory effects on cyclooxygenase in *in vitro* at IC_{50} values of 150 µM[93].

The rhizomes of *Curcuma xanthorrhiza* Roxb. yielded *trans*-1,7-diphenyl-1,3-heptadien-4-one (alnustone); *trans*-1,7-diphenyl-1,3-heptadien-5-ol; 1*E*,3*E*-1,7-diphenylheptadien-5-one. These exhibited significant anti-inflammatory activity against carrageenan and ethyl phenyl propionate induced ear oedema in rats at ID_{50} value similar to that of oxyphenbutazone. The structure activity relationship of their semisynthetic derivatives indicated unsaturation at 1 and 3 positions and nature of oxygenation at position 5 of the C-7 chain was found to play a significant role in determining the *in vivo* activity[94,95]. The glycosides (5) and (6) isolated from the stems of *Sargentodoxa cuneata* (Oliv.) Rehd. et Wils. (Berberidaceae) inhibited prostaglandin synthase showing potent anti-inflammatory activity[96].

Rhazimine from *Rhazya stricta* Decne[97] (Rutaceae), fraxinellone and dictamine from the root bark of *Dictamus dasycarpus* Turcz.[98] (Rutaceae) exhibited significant anti-inflammatory activity against arachidonic acid and PAF induced platelet aggregation in *in vitro* test systems. Carboxypeptidase from *Aloe aborescens* Mill. var. *natalensis* (Liliaceae) exhibited significant analgesic and anti-inflammatory activity by intravenous administration[99].

Conclusion

Most of the studies of the plant extracts did not report the gastrointestinal side effects, which are common undesirable effects associated with almost all non steroidal anti-inflammatory drugs. Also studies did not report the effect of test drugs on prostaglandin biosynthesis. Since all the non steroidal anti-inflammatory drugs inhibit prostaglandin biosynthesis, which is supposed to be the principal mode of action of these drugs. Therefore, much of the work needs to be done in this area.

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