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Natural Anti-Inflammatory Agents: Recent Progress and Future Perspectives

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Abstract

Background: Although, various synthetic anti-inflammatory drugs were reported to be used for the treatment of inflammatory disorders but it is still a challenge for the medicinal chemists to develop more potent therapeutic agents. Since most of the clinically used anti-inflammatory drugs like NSAIDs, Coxibs, GCs and TNF inhibitors etc. are allied with considerable toxicity.

Method: A variety of medicinal plants are known to exhibit a wide range of interesting biological activities like antioxidant, anti-inflammatory, anticonvulsant, analgesic, antimicrobial, anticancer, antiprotozoal, antioxidant, antiparasitic, antiplatelet, cardioprotective, anthelmintic, antidiabetic, antitubercular, trypanocidal and anti-HIV. Reported literature survey has been studied to summarize medicinal plants which were utilized as potential anti-inflammatory agents.

Results: The search of novel anti-inflammatory agent is not an ending process. An array of herbal drugs targeting inflammatory cytokines has been identified in the past regained their popularity due to devoid of toxicity.

Conclusion: The present review summarizes recently explored anti-inflammatory herbal drugs and preparations which will be precious for the researchers to working in the field of anti-inflammatory natural chemistry.

Keywords: Inflammation; Herbal drugs; Anti-inflammatory agents; Phyto-constituents; COX

Abbreviations

NSAIDs: Non Steroidal Anti-inflammatory Drugs; ImSAIDs: Immune Selective Anti-inflammatory Derivatives; GCs: Glucocorticoids; TNF-α: Tumor Necrosis Factor–α; COX: Cyclooxigenase; ROS: Reactive Oxygen Species; H_2O_2: Hydrogen Peroxide; 5-LOX: 5-lipoxigenase; RNA: Ribonucleic Acid; DNA: Deoxyribonucleic Acid; CAPE: Caffeic Acid Phenethyl Ester; PGE2: Prostaglandin E2; NO: Nitric Oxide; IL-1β: Interleukin-1β; LPS: Lipopolysaccharide; TPA: Tissue Plasminogen Activator; AIA: Anti-inflammatory Activity; TLC: Thin Layer Chromatography; HPLC: High Pressure Liquid Chromatography; MPLC: Medium-pressure Liquid Chromatography; iNOS: Inducible Nitric Oxide Synthase; 5-HT: 5-Hydroxytryptamine; NF-kB: Nuclear Factor-kappa B; PAF: Platelet-activating Factor

Introduction

Inflammation is the body's first protective attempt that helps in healing of tissues against injurious stimuli or infection [1]. Sometimes when inflammation goes awry, it seems to produce quite serious events like occurrence of rheumatoid arthritis, heart attacks, colon cancer, Alzheimer's and a host of other diseases which may be life threatening. Current approaches to overcome the inflammation include the use of various synthetic drugs belongs to the class of Non Steroidal Anti-Inflammatory Drugs (NSAIDs), immune Selective Anti-Inflammatory Derivatives (ImSAIDs), synthetic forms of natural cortisol (glucocorticoids) GCs, selective glucocorticoid receptor agonist, resolvins and protectins, Tumor Necrosis Factor (TNF) inhibitors and many more [1]. However, various studies based on the clinical trial, suggest almost 90% of these synthetic molecules produce drug related toxicities including gastric irritation, ulceration, bleeding, renal failure, interstitial nephritis, hepatic failure, headache, thrombocytopenia, hemolytic anaemia, asthma exacerbation, skin rashes, angioedema, pruritis *etc* [2].

In contrast, numerous plant herbs and particularly plant food supplements receive great potential by European consumers as they can deliver significant health benefits at relatively lower

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cost. The field in which plant-based anti-inflammatory agents are being explored as a potential alternative tool in this era of 21st century has given rise to several varieties of beneficial compounds isolated from plants. In addition, a variety of chemical constituents such as alkamide [3,4], coumarins [5], carotenoid [6], flavonoids [7], steroids [8,9], fatty acids [8-10], stilbenes [11-12] and terpenoids [13] are isolated from plant origin which significantly shows anti-inflammatory activities in different animal models. Hence, this approach for treatment of inflammatory diseases by herbal drugs has keen interest to the researchers. A detailed classification of these herbal anti-inflammatory compounds is provided in Table 1.

Miscellaneous Anti-inflammatory Agents

Algae and sponges

In search for new biologically active anti-inflammatory natural products, a variety of isolated compounds derived from algae and sponges were evaluated. Out of these, two compounds palisol and dictyol C exhibited most prominent COX-II inhibitory activity [119]. *Spirulina fusiformis* (Oscillateriaceae), also known as "blue green algae", shows significant anti-inflammatory activity as compared to adjuvants in rats using carrageenan induced hind paw model [120]. In another study, methanolic extract of *Cheilanthes farinosa* (Adianthaceae), a fern grown indigenously in southeast Africa, showed significant anti-inflammatory activity. The main chemical constituents responsible for the activity was found to be rutin, cinnamic acids, caffeic acid and its quinic acid derivative, chlorogenic acid [121].

In addition, "marine red algae" obtained from *Neorhodomela aculeate* showed promising anti-inflammatory and antioxidant properties. The result indicates promising neuroprotective effect produced by glutamate-induced neurotoxicity and inhibition of ROS expression in murine hippocampal HT22 cell line, and inhibition of H_2O_2-induced lipid peroxidation in rat brain homogenates [122].

Fish oil

Fish oils obtained from marine organisms was found to possess remarkable therapeutic activity in various inflammatory disorders such as psoriasis, eczema, allergy lipid lowering activity. The main constituents responsible for the activity include eicosapentaenoic acid and docosahexaenoic acid. The proposed mechanism of action of oil includes reduction of lipid level which may be due to 5-LOX, 15-LOX, 15-HEPE inhibitory activity when examined on epidermal enzymes and basophilic leukemia cells of rat [123].

Fungal infected peanuts

Resveratrol derivatives are of interest as inhibitors of cyclo-oxygenase-2 and as anti-inflammatory agents. The prenylated resveratrol derivative 4-(3-methyl-but-1-enyl)-3,5,3′,4′-tetrahydroxystilbene was purified from fungally infected peanuts by thin layer chromatography and its structure was confirmed by mass spectrometry. 4-(3-Methyl-but-1-enyl)-3,5,3′,4′-tetrahydroxystilbene inhibited lipopolysaccharide-induced expression of cyclo-oxygenase-2 protein and cyclo-oxygenase-2 mRNA in mouse macrophages at concentrations that were non-cytotoxic. 4-(3-Methyl-but-1-enyl)-3,5,3′,4′-tetrahydroxystilbene warrants further evaluation as an anti-inflammatory agent [124].

Propolis

The ethanolic extract of propolis, with and without Caffeic Acid Phenethyl Ester (CAPE), and some of its components on cyclooxygenase (COX-I and COX-II) activity in J774 macrophages has been investigated. COX-I and COX-II activity, measured as prostaglandin E_2 (PGE_2) production, were concentration dependently inhibited by propolis (3 × 10–3–3 × 102 μgml–1) with an IC50 of 2.7 μgml–1 and 4.8 × 10-2 μgml–1, respectively. Among the compounds tested pinocembrin and caffeic, ferulic, cinnamic and chlorogenic acids did not affect the activity of COX isoforms. Conversely, CAPE and galangin were effective, the last being about ten-twenty times less potent. To better investigate the role of CAPE, we tested the action of the ethanolic extract of propolis deprived of CAPE, which resulted about ten times less potent than the extract with CAPE in the inhibition of both COX-I and COX-II. Moreover, the result suggests that both CAPE and galangin contribute to the overall COX inhibitory activity of propolis. However, CAPE was found to be more effective [125].

Herbal preparations

Wen-Pi-Tang-Hab-Wu-Ling-San (WHN): WHN preparation has been widely used traditionally in Korea for significant anti-inflammatory activity. The activity of the extract was is due to its strong inhibition of the excessive production of inflammatory mediators like NO, TNF-α, IL-1β and IL-6, respectively [126,127].

Seungma-Galgeun-Tang: Seungma-galgeun-tang, a promising Chinese herb has been widely used in China as a folk medicine recipe for broad-spectrum treatment of acute and chronic inflammatory disorders. It has been found to inhibit the generation of NO, PGE2, COX-II, TNF-α, IL-12, IL-1β, and activation of NF-kB competitively and to inhibit the secretion of NO in BV-2 microglia without affecting cell viability [128].

Cheng-Chi-Tang: Cheng-Chi-Tang, a Chinese traditional herbal decoction type formulation was reported to have significant anti-inflammatory activity in several inflammation and related disorders like pain and inflammation produced due to regular use of purgatives, painful abdomen, hard stools and fever [129].

San Huang-Xie-Xin-Tang: San Huang-Xie-Xin-Tang widely used traditionally oriental anti-inflammatory medicine in china. The prominent activity was found to be due to the presence of baicalin using LPS-induced inflammation models [130].

Bolengguazi: Bolengguazi, a formulation used widely in Tibetan medicine in the management of inflammation related disorders. It was reported to contain the seed extract of *Herpetospermum pedunculosum, Momordica cochinchinensis* and *Momordica charantia.* The activity of the extracts was evaluated using different animal models of inflammation like egg-albumin–induced paw edema and cotton pellet granuloma tests [131,132].

Kampo medicine, Shosaikoto: Kampo medicines are the traditional medicines that originated in Japan based on the silent concept of treatment of diseases. In a study conducted by Ara et al. [133], they evaluated the efficacy of this system of treatment through clinical trials in vitro against periodontal diseases, where inflammation was induced by LPS. The possible mechanism behind this may involve the inhibition of production of inflammatory mediators like PGE2, IL-6, IL-8 and COX-II in a dose-dependent manner. Trials showed that therapy is quite efficacious in reducing the disease progression upto 24 hr duration without any viable growth of human gingival fibroblasts by *Porphyromonas gingivalis* [133].

SK Ato formula: Flavonoid isolated from the extract of leaves and

Table 1: Herbs with active constituents having anti-inflammatory activity.

Plant	Family	Active Ingredient	Animal Model	Mechanism of action
Stereocaulon alpinum [3]	Stereocaulaceae	Alkamide	*In-vitro* inhibitory activity against the key enzymes of the major pathways involved in arachidonate metabolism.	Inhibition of COX-I, COX-II and 5-LOX enzyme
Grifola frondosa [8]	Meripilaceae	Ergosterol, ergostra-4,6,8(14),22-tetraen-3-one, 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, palmitic, oleic, and linoleic acids	---	Inhibition of COX-I and COX-II enzyme
Agrocybe aegerita [9]	Strophariaceae	Palmitic acid, ergosterol, 5,8-epidioxy-ergosta-6,22-dien-3β-ol, mannitol and trehalose	---	Inhibition of cyclooxygenase (COX) enzyme
Houttuynia cordata [10]	Saururaceae	Fattyacids (linolenic, linoleic, oleic, palmitic and stearic)	*In vitro* prostaglandin synthase inhibitory activity	Inhibition of cyclooxygenase (COX) enzyme
Aiphanes aculeate Willd. [11]	Arecaceae	Stilbenolignan (aiphanol, isorhapontigenin, piceatannol), flavone (luteolin)	---	Inhibitory activities against COX-I and COX-II
Dracaena loureiri [12]	Asparagaceae	Loureiriol, 4,3',5'-trihydroxystilbene, 4,3'-dihydroxy-5'-methoxystilbene and 4-hydroxy-3',5'-dimethoxystilbene	---	Inhibitory activities against COX-I and 2
Aralia continentalis [13]	Araliaceae	Kaurenoic acid	LPS-induced RAW264.7 macrophages cell lines	Inhibition of nitric oxide (NO) production, prostaglandin E_2 (PGE_2) release, cyclooxygenase-2 (COX-II) and inducible Nitric Oxide Synthase (iNOS)
Stephania tetrandra S. Moore [14-15]	Menispermaceae	Bisbenzyl isoquinoline alkaloids (Tetrandine, berbamine)	---	Inhibition of COX, LOX pathways, inhibitory activity on prostaglandin E_2 (PGE_2), suppresses the release and activity of inflammatory cytokines, TNF-α and lymphocyte transformation.
Buxus papillosa,[16] *Buxus senzpervirens* [17]	Buxaceae	Steroidal alkaloids	---	Not Known
Adhatoda vasica [18-19]	Acanthaceae	Alkaloids	Cotton pellet induced granuloma model of inflammation	Reduced histamine, 5-HT
Sida cordifolia [20]	Malvaceae	1,2,3,9-tetrahydro-pyrrolo [2,1-b]quinazolin-3-ylamine	Carrageenan-induced rat paw edema.	Not Known
Peumus boldus [21]	Monimiaceae	Boldine	Carrageenan-induced rat paw edema.	Not known
Harpagophytum procumbens [21]	Pedaliaceae	Glycosides	Carrageenan-induced pedal edema	Not Known
Muesa chisia [22]	Myrsinaceae	Aglycone tetrahydroxy triterpene of the oleanene series present in glycosidal fraction	Carrageenan-induced pedal edema in rat, cotton pellet granuloma	Not Known
Hypericum perforatum and *Hypericum reflexum* [23]	Hypericaceae	Hyperforin	Acetic acid induced writhing in mice and formalin-induced pain, tail-flick test in rats	Inhibit COX-I
Hydnocarpus annamensis [24]	Achariaceae	Phenolic glycosides I and II	---	Not Known
Dystaenia takeshimana [25]	Umbelliferae	Coumarins, phenethyl alcohol derivatives, and two major steroidal principles, beta-sitosterol and dacusterol	Examined in mouse bone marrow-derived mast cells	Significant COX-II, 5-LOX, PGD_2 and LTC_4 inhibitory activity
Andrographis stenophylla [26]	Acanthaceae	Glycosides	Acute pedal paw edema in rats induced by carrageenan and Freund's adjuvant	Inhibiting NF-kB binding to the DNA, and thus reducing the expression of COX-II
Aesculushippo castanum [27]	Hippocastanaceae	Triterpenoid saponin glycoside, aescin.	$CoCl_2$-induced inflammation and hypoxia in human vascular endothelial cells	Not Known
Codonopsis lanceolata [28]	Campanulaceae	Triterpenoid saponins (codonolaside I-III)	Xylene-induced mouse ear edema.	Not Known
Artemisia species [29] (*A. annua, A. sinica* and *A. asiatica*	Compositae	Diterpenoidal saponins like artemisin and artemisinin, sesquiterpene lactones such as artemisolide	LPS-induced inflammation in macrophage RAW 264.7 cells	Inhibitory action against nuclear factor kB (NF-kB) cells, PGE_2 and nitric oxide (NO) production
Curcuma species [30] (*C. longa, C. xanthorrhiza, C. domestica* and *C. ambada*)	Zingiberaceae	Curcumin and zingiberene	---	Not Known
Arnica montana [31]	Asteraceae	1,5-trans-guaianolide	*In vitro* as well as *in vivo* NF-kB EMSA cells and in the IL-8 ELISA cells	Inhibitor of NF-kB EMSA cells and IL-8 ELISA cells
Lavandula multifida [32]	Lamiaceae	Terpenoids	Croton oil induced ear edema in mice	Not Known

Styrax japonica [33]	Styraceae	Styraxosides A and B and lignans like eugenol and masutakeside I	LPS-induced NO and PGE_2 production by the RAW 264.7 macrophage cell line	Inhibition of NO and PGE_2 production and release of TNF-α and IL-1β
Egletes viscosa [34]	Asteraceae	Diterpenes (centipedic acid and tanabalin)	Dermal inflammation induced in mouse ear model	Not Known
Youngia japonica [35]	Asteraceae	Sesquiterpenoids	---	Not Known
Boswellia sp.[36-39] (*Boswellia serrata and Boswellia carterii)*	Burseraceae	Oleogum resin, boswellic acid	Carrageenan-induced pedal edema in rats, mice and in adrenalectomized rat model	Inhibition of leukotriene production, leukocyte elastase enzyme and oxygen radicals, 5-LOX.
Pistacia vera [40]	Anacardiaceae	Oleo gum resin, α-pinene	Carrageenan-induced hind paw edema model	Not Known
Sanguis draconis and Daemonorops draco [41]	Palmae	Oleo gum resin	LPS on RAW 264.7 cells	Inhibition of NO and PGE_2 by selective down-regulation of intrinsic nitric oxide synthetase (iNOS) and inhibition of COX-II gene expression via the suppression of NF-kB activation.
Pinus densiflora [42]	Pinaceae	Resin	Arachidonic acid induced ear edema and acetic acid induced writhing response	Not Known
Carlina acanthifolia [43]	Asteraceae	Essential oil	Carrageenan-induced rat paw edema model	Not Known
Cordia verbenacea [44]	Boraginaceae	Essential oil, sesquiterpene compounds like α-humulene and *trans*-caryophyllene.	Carrageenan-induced paw edema in rats induced by bradykinin, substance-P, histamine, and Platelet-Activating Factor (PAF)	Inhibition of bradykinin, substance-P, histamine, and Platelet-Activating Factor (PAF)
Gaultheria yunnanensis [45]	Ericaceae	Gaultherin (methyl salicylate diglycoside)	Carrageenan and croton oil in mice ear.	Not Known
Casearia sylvestris [46]	Salicaceae	Caryophyllene, thujopsene, α-humulene, β-acoradiene, germacrene-D, bicyclogermacrene, calamenene, germacrene-B, spathulenol and globulol	Carrageenan-induced paw edema in rats	Not Known
Rosmarinus officinalis [47]	Labiatae	Ursolic acid, oleanolic acid and micromeric acid	Croton oil induced inflammation in mice	Not Known
Echinacea purpurea and *Echinacea angustifolia* [48]	Asteraceae	Echinacin, alkamides	Croton oil induced inflammation	Significant COX-I and II inhibitory activities
Comarum palustre [49]	Rosaceae	Comaruman	---	Activates adhesion of peritoneal leukocytes for AIA
Artemisia tripartite [50]	Asteraceae	Sulfated polysaccharides like xylose, glucose, arabinose, galactose and galactosamine.	---	Alter macrophage function, neutrophil count, and complement fixation function
Quercus itex [51]	Fagaceae	Flavonol glycoside (Kaempferol-di-coumaroyl-glucoside)	Croton oil induced inflammation	Not Known
Populus tremula [52]	Salicaceae	Salicin	Chorion allantoic membrane of hen's egg	Not Known
Selaginella tamariscina [53]	Selaginellaceae	Flavonoids (quercetin, morin, oleanolic acid, ursolic acid, glycyrrhetic acid, and caffeine), Biflavonoids (sumantoflavone and robustaflavone)	TPA model of ear edema in rabbits	Inhibition of lipoxygenase, iNOS gene expression responsible for NO synthesis.
Caesalpinia pulcherrima [54]	Fabaceae	Flavonoids	LPS and IFN-γ induced inflammatory response in murine peritoneal macrophage cell lines	Not Known
Tephrosia spinosa [55-56]	Leguminosae	Flavonol glycoside (Eupalitin-3-O-β-D-glucoside), phenolic flavonoids, methoxyflavone and hydroxyflavone	Carrageenan-induced paw edema	Reducing the expression of adhesion molecules to TNF-α
Scutellaria baicalensis [57]	Lamiaceae	Flavonoid	Animal models with chronic type of skin inflammation induced by TPA	Suppression of proinflammatory gene expression
Gentiana scabra [57]	Gentianaceae	Flavonoid	Animal models with chronic type of skin inflammation induced by TPA	Suppression of proinflammatory gene expression
Ginkgo biloba [57-58]	Ginkgoaceae	Terpenes and biflavonoids (gingkolide A and B)	LPS-induced NO synthesis and PGE_2 production in RAW 264.7 macrophage cell line	Inhibition of NO, PGE_2 synthesis, COX-II
Sideretis tragoriganum [59]	Labiatae	Flavonoids (5-O-demethylnobiletin)	TPA in mouse ear and acute mouse paw edema induced by carrageenan	Inhibition of 5-LOX, leukotriene B_4 (LTB_4) and elastase
Artemesia copa [60]	Compositae	Flavonoids (spinacetin, jaceosidin, axillarin, penduletin, tricin and chrysoeriol)	LPS induced inflammatory mediators in mouse macrophage (RAW 264.7) cell line	Not Known
Achillea millefolium [61]	Asteraceae	Flavonoids and dicaffeoylquinic acids	---	Inhibit the production of proteases, human neutrophil elastase and matrix metalloproteinase

Allium spp. [62]	Alliaceae	Phenolic compounds (catechol, cepaenes and unsaturated thiosulfinates)	---	Inhibit 5-LOX against porcine leukocytes.
Tabebuia avellanedae [63-64]	Bignoniaceae	Lapachol	Carrageenan-induced pedal edema	Not Known
Sambucus ebulus [65]	Caprifoliaceae	Polyphenolic compound (caffeic acid)	Carrageenan-, serotonin-induced pedal edema	Not Known
Laggera alata [66]	Asteraceae	Phenolic compounds	Carrageenan-induced rat paw edema, xylene-induced mouse ear edema and acetic acid induced vascular permeability in mouse.	Inhibition of leukocyte migration, reduction of serum lysozyme levels, nitric oxide, PGE_2 and malondialdehyde levels
Cannabis sativa [67-68]	Cannabinaceae	Δ-Tetrahydro Cannabinol (Δ-THC), and olivetol, canniprene, olivetolic acid	Tetradecanoyl phorbol-acetate induced erythema in mouse ear	Inhibitory activity against COX, 5-LOX, prostaglandin synthesis and mobilization.
Ganoderma lucidum and *Ganoderma tsugae* [69]	Ganodermataceae	Steroidal and triterpenoidal saponins	---	Inhibiting the release of β-glucuronidase
Linum usitatissimum [70]	Linaceae	α-linolenic acid	Rat paw edema induced by arachidonic acid and carrageenan	Inhibition in leukotriene-induced paw edema
Ocimum sanctum [70]	Lamiaceae	α-linolenic acid, cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and eugenol	Rat paw edema induced by arachidonic acid	Inhibition in leukotriene-induced paw edema
Rhus verniciflua [71]	Anacardiaceae	Glycoproteins	LPS-induced inflammation on RAW264.7 cell lines.	Inhibitory effect on proteins inducing inflammation and on NO production
Rubia cordifolia [72]	Rubiaceae	Glycoproteins	---	Lipid peroxidation, glutathione depletion, superoxide dismutase, and catalase.
Phyllanthus amarus [73]	Euphorbiaceae	Phyltetralin, nirtetralin, niranthin, phyllanthin	Carrageenan-induced paw edema and neutrophil influx in rats	Increase in IL1-β level in tissues, Reduce bradykinins, Platelet Activating Factors (PAF) and endothelin-1 prominently
Piper kadsura [74]	Piperaceae	Neolignans	---	Inhibition of polymethacrylic acid induced production of Reactive Oxygen Species (ROS)
Achillea pannonica [75]	Asteraceae	Germacrane derivatives	Croton oil induced dermatitis in the mouse ear	Not Known
Kigelia Africana [76]	Bignoniaceae	Iridoid glycoside (Verminoside)	iNOS and NO release in mouse J774.A1 macrophage cell line.	Inhibiting the expression of iNOS and NO release
Nyctanthes arbortristis [77]	Oleaceae	Arbortristoside-A	Carrageenan-, serotonin-, and histamine-induced inflammatory reactions	Inhibition of arachidonic acid synthesis
Illicium tashiroi, Illicium anisotum, Illicium arborescens [78]	Illiciacae	Phenylpropanoids	Rat basophilic RBL-2H3 leukemia cells stimulated by A23187.	Inhibition of histamine release
Eleutherine Americana [79-80]	Iridaceae	Naphthoquinones, flavonoid (Phyllanthin, Niranthin, Pinobatol, Luteolin)	LPS in mouse macrophage RAW 264.7 cell lines	Not Known
Melicope semecarpifolia [81]	Rutaceae	Benzoic acid derivatives	AIA on human neutrophils	Inhibitory action on superoxide anion generation and elastase release
Perilla nankinensis [82-83]	Lamiaceae	Carotenoid compounds (Luteolin diglucuronide, apigenin diglucuronide, and semi-pure luteolin diglucuronide)	Carrageenan-induced inflammatory events in rat paw edema model, cotton pellet induced granuloma in rats	Temporary blockage of leukocyte infiltration and elevated level of 6-keto-PGF1α in the inflammatory exudates
Tagetes erecta [84]	Compositae	Luteins	Carrageenan- and dextran-induced acute paw edema in mice.	Superoxide radical scavenging action
Hinoki cypress [85]	Cupressaceae	Tropolone derivatives (Hinkitiol)	LPS-induced macrophage like RAW264.7 cell line	Inhibition of production of TNF-α
Smalianthus sonchifolia [86]	Asteraceae	Melampolides	LPS-induced murine macrophage RAW264.7 cells.	Inhibition of NO production
Evodia rutaecarpa [87]	Rutaceae	Evodiamine, rutaecarpine and goshuyuamide II	LPS-induced inflammation on RAW 264.7cell lines.	Inhibitory action on PGE_2 generation from COX-II
Gnetum cleistostachyum [88]	Gnetaceae	Stilbenolignans (gnetofuran A, gnetumontanin C, lehmbachol D, gnetifolin F, gnetucleistol F)	---	TNF-α inhibitory activity
Saussurea conica [89]	Asteraceae	Conicaoside (conicaols A and B), arctigenin and matairesinol	LPS-induced inflammation in rat macrophages.	Not Known
Polyozellus multiplex [90]	Thelephoraceae	Stilbene derivatives (Polyzellin and polysylvin)	LPS-induced inflammation on RAW 264.7cell lines.	Inhibit the LPS-induced NO and NF-kB production
Pinus densiflora [91]	Pinaceae	Stilbene derivatives	LPS-induced inflammation on RAW 264.7cell lines.	Inhibit the LPS-induced NO and NF-kB production
Euonymus laxiflorus [92]	Celastraceae	Laxifolone A	LPS-induced inflammation on RAW 264.7 macrophagial cell lines.	Not Known
*Gardenia jasminoides*93	Rubiaceae	Geniposide and genipin	Carrageenan-induced rat paw edema	Inhibition of vascular permeability

Zingiber cassumunar [94]	Zingiberaceae	Phenylbutenoids	---	Inhibiting the COX-II generation thus reduced the level of PGE_2
Nigella sativa [95]	Ranunculaceae	Dithymoquinone, thymo hydroquinone, and thymoquinone	Carrageenan-induced rat paw edema	Inhibition of COX-I and COX-II enzymes
Marrubium vulgare [96]	Lamiaceae	Marrubiin	Screening models of inflammation like Microvascular leakage in mice ears	Not Known
Cymbidium goeringii [97]	Orchidaceae	Gigantol	LPS-, NO-, and PGE_2-induced edema in RAW 264.7 cells	Suppress the expression of iNOS and COX-II along with inhibition of mRNA level
Smilax china [98]	Smilacaceae	Kaemperol glucopyranoside, engeletin, isoengeletin, kaempferol, dihydrokaempferolglucopyranoside, rutin, kaempferol- glucopyranoside, 3, 5, 4'-trihydroxystibene, vanillic acid, 3, 5-dimethoxy4-O-beta-D-glu-copyranosylcinnamic acid, beta-sitosterol, and beta-daucosterol	Egg-albumin–induced edema and its anti-nociceptive effects in mice, using hot-plate test and acetic acid induced abdominal constriction test	Not Known
Clematis mandshurica [99]	Ranunculaceae	Concanavalin A	LPS/IFN-γ induced inflammation	Inhibiting NO, PGE_2 and other pro-inflammatory mediators
Sanguisorba officinalis L. [100]	Rosaceae	Triterpenoids, phenols and flavonoids	---	Inhibitory action on myeloperoxidase enzymes and 2,4,6-trinitrobenzene sulfonic acid induced ulcerative colitis
Panax notoginseng and *Panax ginseng* [101,102]	Araliaceae	Ginsenosides Rg3 and Rh2	LPS induced inflammation RAW264.7 macrophages cell lines and LPS and INF-γ induced inflammation in murine BC-2 microglial cells.	Inhibited the LPS-induced synthesis of TNF-α, IL-6, NO synthesis and expression of mRNA of NO
Ligusticum chuanxiong [103]	Apiaceae	Phthalide lactones like Z-ligustilide and senkyunolide A	---	Inhibiting LPS and TNF-α induced inflammatory reaction
Solidago chilensis [104]	Asteraceae	Essential oil	Carrageenan-induced rat paw edema	Inhibitory activity against leukocytes, neutrophils, myeloperoxidase, adenosine-deaminase, and TNF-α
Rhizoma coptidis [105]	Ranunculaceae	Berberine, tannins, and terpenes	AIA in human keratinocytes	Significant translocation of NF-kB into the nucleus after stimulation with TNF-α
Lycopodium clavatum [106]	Lycopodiaceae	Lycopodine, clavatin and clavatoxine	Acetic acid induced increased capillary permeability in mice	Not Known
Pluchea quitoc [107]	Asteraceae	Phenolic compounds	Carrageenan-induced paw edema	Inhibited neurogenic pain in rats, induced by formalin
Kalanchoe brasiliensis [108]	Crassulaceae	Kalanchosine (3,6-diamino-4,5-dihydroxyoctanedioic acid)	---	Not Known
Gleditisia sinensis [109]	Fabaceae	Gleditsioside Z	---	Inhibitory effect on lipo-polysaccharide induced NO production
Cedrus deodara [110]	Pinaceae	Volatile oil	---	Not Known
Psacalium decompositum [111]	Asteraceae	Sesquiterpenes (cacalol and cacalone)	Carrageenan-induced rat paw edema	Not Known
Zostera japonica [112]	Zosteraceae	Palmitic acid, Palmitic acid methyl ester, linoleic acid methyl ester, oleic acid methyl ester and linoleic acid	LPS induced inflammation on J774A cell lines	Inhibit expression in LPS stimulated J774A cell line
Sargassum fulvellum and Sargassum Thunbergii [113]	Sargassaceae	Sulfated polysaccharides	---	Not Known
Acacia farnesiana [114]	Fabaceae	Glycosidal fraction	Cotton pellet induced granuloma model of inflammation	Not known
Hpericum perforatum [115]	Guttifereae	Hypericin, hyperforin	Cotton pellet induced granuloma model of inflammation	Not known
Ceiba pentandra [116]	Malvaceae	Vavain 3'-O-beta-d-glucoside and vavain, flavan-3-ol, (+)-catechin	---	Significant COX-I inhibitory activity
Apium graveolens Linn.[117]	Umbelliferae	Sedanolide, senkyunolide-N, senkyunolide-J, 3-hydroxymethyl-6-methoxy-2,3-dihydro-1H-indol-2-ol	---	Significant COX-I and 2 inhibitory activity
Cornus kousa [118]	Cornaceae	Kaempferol 3-O-rhamnoside, myricetin 3-O-rhamnoside, kaempferol 3-O-glucoside, cornin and stenophyllin	---	Significant COX-I and II inhibitory activity

roots of *Scutellaria baicalensis*, *Ginkgo biloba* and *Gentiana scabra* were reported to have topical AIA against chronic skin inflammation like atopic dermatitis. The preparation is being available in market as "SK Ato Formula" and is meant for topical application and contains flavonoids like gingkolide A and B (biflavonoids). It shows satisfactory effects in animal models with chronic type of skin inflammation induced by TPA treatment to mouse ear. The probable mechanisms behind its AIA are by inhibition of PGE2 synthesis, COX-II and consequent suppression of proinflammatory gene expression [57].

Kava kava: The roots of plant *Piper methysticum* (kava kava) was used traditionally for managing inflammatory pains. Ethyl acetate extract of *Piper methysticum* (kava kava) roots yielded seven biologically active compounds, dihydrokawain, demethoxyangonin,

flavokawain A, kawain, dihydromethysticin, yangonin and methysticin. All the compounds were purified using MPLC, preparative TLC and HPLC methods. Both Dihydrokawain and yangonin showed the highest COX-I and COX-II inhibitory activities at 100 microg/ml, respectively [134].

In another study, Milled root of *Piper methysticum* plant were extracted sequentially with hot water and methanol. The methanol extract yielded bornyl esters of 3,4-methylenedioxy cinnamic acid and cinnamic acid, pinostrobin, flavokawain B, and 5,7-dimethoxyflavanone. The aqueous extract contained previously reported kava lactones, as confirmed by TLC analysis. All these compounds show excellent COX-I and moderate COX-II enzyme inhibitory activities at 100 microg/mL. Flavokawain B showed the highest COX-I inhibitory activity at 100 microg/mL [135].

Safety/Toxicity aspects of herbal preparations

Herbal medicine generally uses various parts of plants or mixtures of plant extracts to treat illness, to promote health, to restore the body's ability to protect, regulate and heal by itself. However, quality and efficacy of herbal medicines and preparations remain a question of concern, and bottlenecks in risk and benefit assessments need to be solved yet plant kingdom received considerable attention due to their wide range of biological activities. But as far as the safety of these medicines is concerned, these do not mean that herbals products are safe to use. Literature survey reveals, about 40% of the anticancer drugs made from plant origin which have been used successfully to treat cancer, but they still have serious side effects. Apart from this, many herbal preparations are reported to possess serious adverse effects and some of them have a tendency to interact with the synthetic preparations [136]. For example, St. John's Wort is used in the treatment of depression, but it interacts with iron to reduce its therapeutic efficacy. However, several clinical trials of herbal drugs have been done, representing them as a better aid in the treatment of anti-inflammatory disorders [137].

Fish oils have been proposed as a reasonable alternative for the treatment of rheumatoid arthritis e.g. cod liver oil and other conditions as a consequence of the fact that they provide less cardiovascular risk than other treatments including NSAIDs [33]. Caution should be exercised in combining low dose aspirin with COX-II inhibitors due to potential increased damage to the gastric mucosa. COX-II is upregulated when COX-I is suppressed with aspirin, which is thought to be important in enhancing mucosal defense mechanisms and lessening the erosion by aspirin [37].

Conclusion

The search of novel anti-inflammatory agent is not an ending process. Although the use of synthetic anti-inflammatory agents often very effective, but long term use of these agents leads to various undesirable side effects like gastric ulceration, infrequently, myocardial infarction and stroke. Nowadays, interest with plant based anti-inflammatory medicine is revived due to the increasing awareness of the health risks linked with the reckless use of current allopathic medicines. Unfortunately, India is still behind to mark its footprints in international business of herbal industry because lack of scientific approach in herbal drugs. Therefore, exploration of the more effective, potent, less toxic therapeutic agents to treat as well as reduce the signs and symptoms of acute and chronic inflammatory diseases is still a challenge for the pharmaceutical chemists. Hence, expert key commentaries are required in the field of herbals regarding their production and marketing in terms of better regulatory checks. However, ongoing experiments and clinical trials should be continued to guide and provide their scientifically based effectiveness to reduce inflammation and promote wellness. It is hoped that this review article can serve as a lead for readers who are interested to work on inflammation and its treatment.

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