Review Article

Anti-inflammatory Herbal Plants – A Review

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ABSTRACT

Medicinal plants and their secondary metabolites are progressively used in the treatment of various diseases as a complementary medicines . Most of the synthetic drugs used as anti-inflammatory agents cause many side effects and toxic effects. Anti-inflammatory drugs obtained from several plant origins have been used against inflammation without adverse effect. Inflammation is a process by which our body's white blood cells and the things they make will protect from infection caused by outside invaders, such as bacteria and viruses. This review mainly focuses on several herbal plants, their constituents used in combatting the inflammation and also emphasized on several studies carried out in the past. The review concludes that herbal products are natural, safe, eco-friendly, free from side effects and there is a need to promote them to save human lives as human lifestyle is moving away from nature and getting techno-savvy.

Keywords: Anti-inflammatory drugs, Inflammation, Medicinal plants, Metabolites, Synthetic drugs.

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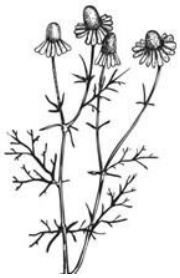
INTRODUCTION

Inflammation is a positive Defence mechanism of our body. Ddysregulated and prolonged inflammatory reaction has been well recognized as underlying causes for several disorders, namely, cardiovascular dysfunctions, metabolic syndrome, cancer and autoimmune diseases imposing a vast economic burden on individuals and consequently on the society [1,2]. Extend inflammation is implicated in the onset and progression of various pathologies including cardiovascular diseases and cancer[3]. Medicinal plants have shown variety of biological activities and used for the treatment of inflammation[4]. The current treatment of inflammatory disorders require extensive use of non-steroidal anti-inflammatory drugs and corticosteroids. Although use of modern drugs for inflammation has a relieving effect, it is now unsatisfactory[5, 6] . Macrophages located in various tissues of our body plays a central role in the regulation of inflammation by the production of large amount of inflammatory cytokines, such as interleukin(IL)-1, IL-6 and tumour necrosis factor α (TNF-α) and inflammatory mediators, including reactive oxygen species (ROS), nitric oxide (NO) and prostaglandin E_2 (PGE_2), which are generated by inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2). Regulated production of pro-inflammatory cytokines and mediators can lead to cytotoxicity, inflammation, autoimmune disorders and neoplastic changes of the inflammed tissue, suppression of immune response by inhibiting their production constitutes an important target for the treatment of many inflammatory-related diseases[7] . Inflammation can be classified as acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by increasing the movement of plasma and leukocytes from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation is known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation, such as mononuclear cells and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process[8].

The Article Reviews about Several Medicinal Plants, their Constituents, Mechanism of Action and Anti-inflammatory Studies Carried out in the Past:

Matricaria chamomilla



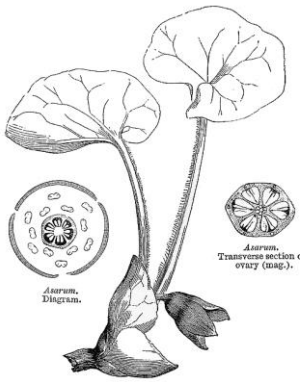
The flowers of chamomile contains 1–2% of volatile oils including alpha-bisabolol, alpha-bisabolol oxides A & B and matricin which possess anti-inflammatory properties. A study in human volunteers demonstrated that chamomile

flavonoids and essential oils penetrate below the skin surface into the deeper skin layers. This is important for their use as topical anti-inflammatory agents. One of chamomile's anti-inflammatory activities involve the inhibition of LPS-induced prostaglandin E (2) release and attenuation of cyclooxygenase 2 enzyme activity without affecting the constitutive form which suppress both the inflammatory effect and the leukocyte infiltration[9]. *Matricaria chamomilla* was assessed for its anti-inflammatory activity on intact rats by measuring the suppression of carrageenan-induced paw edema produced by 1/10th of the intraperitoneal LD50 dose for the 80 % ethanol extract. Results showed that the plant possessed good anti-inflammatory activity[10]. Intragastric and parenteral administration of heteropolysaccharides of *Matricaria chamomilla* L is found to normalize developing of the immune response upon air cooling and enhance (but do not normalize) this process upon immersion cooling. The immunomodulating effect of the heteropolysaccharides upon cooling is attributed to initiation of immunostimulating properties of heavy erythrocytes, activization of immuno regulation cells of peripheral blood and increased sensitivity of effector cells to helper signals[12].

Arnica montana

Arnica montana is used since centuries in homoeopathic system of medicine. It is used for the treatment of 66 different pathological conditions, but frequently used for contusion, wounds, rheumatism and inflammation.[13] The plant possesses numerous medicinal activity. The flowers of the plant shows greater medicinal value and are used as antiphlogistic, inotropic, antibiotic, anti-inflammatory, immunomodulatory, antiplatelet, uterotonic, anti-rheumatic and analgesic in febrile conditions[14]. *Arnica montana* has proved its worth as anti-inflammatory agent. *Arnica montana* extract (3–30%) when blended with one or more therapeutic or pharmaceutical agents, i.e. camphor, menthol, eucalyptus oil, mint oil, guaifenesin, topical analgesics, non-steroidal anti-inflammatory drugs or either transdermal opioid analgesics in a petroleum base or pluronic lecithin organogel, reduces inflammation.[15] Arnica in combination with *Ruta graveolens, Aconitum napellus, Bellis perennis, Hamamelis virginiana, Hypericum perforatum*, *Calendula officinalis*, *Ledum palustre, Bryonia alba* is effective for treating inflammation[16]. Various analytical methods such as gas chromatography with mass selective detection (GC-MSD), spectrophotometric, reverse-phase liquid chromatography (RPLC) and proton nuclear magnetic resonance spectroscopy (HNMR) have been used for analysing the quantity of lactones presents in the plant[17]. *Arnica montana* has significant anti-inflammatory potential. Huber et al. in 2011 disclosed that the molecular mechanism of sesquiterpene lactones differs from that of non-steroidal anti-inflammatory drugs, these lactones significantly decrease NF-kappaB mediated inflammation as they pass through the skin easily[18]. Arnica 6c has been investigated for its anti-inflammatory potential on carrageenan and rat paw oedema induced by nystatin. Arnica 6c significantly reduced inflammation in case of histamine-induced oedema, the action of histamine was inhibited and the vascular permeability was increased[19]. Researchers also investigated that when a solution of *A. montana* 6cH, dexamethasone or 5% hydroalcoholic solution is injected into male adult Wistar rats, they show marked anti-inflammatory activity. It was concluded that rats that presented oedema after a long time exhibited minor oedema, less degranulation of mast cells and increase in diameter of lymphatic vessels [20].

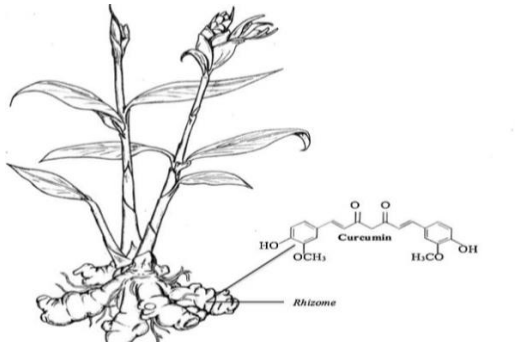
Aristolochia indica



Aristolochia species refers to several members of genus (family-Aristolochiaceae). *Aristolochia indica* (Indian Birthwort) is a perennial climber with greenish white woody stems found throughout India in the plains and low hills[21]. The roots of *Aristolochia indica* contains aristolindiquinone, ristololide, 2-hydroxy-1-methoxy-4Hdibenzo quinoline-4,5-(6H)-dione, Cephradione, aristolactum IIa, β-sitosterol-β-D-glucoside aristolactum glucoside I, stigmastenones II and III, methyl aristolate, ishwarol, ishwarone and aristolochene[22] . Aristolochia indica L is used to treat cholera, fever, bowel troubles, ulcers, leprosy, poisonous bites (Achari et al, 1983) and also used as emmenagogue, abortifacient, antineoplastic, antiseptic, anti-inflammatory, antibacterial, antioxidant and phospholipase A2 inhibitor. The leaves and barks are used in intermittent fever. It is used ethanomedically as an antitumor, anti-inflammatory, antibacterial, antioxidant and antimicrobial. The present study reveals that, *Aristolochia indica* effectively inhibit both α-amylase and α- Glucosidase enzymes. The methanolic extract of dried whole plant powder *Aristolochia indica* inhibited both the

enzymes alpha-amylase and alpha-glucosidase and the maximum inhibition was 60.12% at the concentration of 300µg/ml and 57.28% at the concentration of 400µg/ml respectively[23]. Immuno - modulation is the process of alteration in immune response due to foreign intrusion of molecules inside the body. Aristolochic acid also played a regulatory role in prostaglandin synthesis. It inhibited inflammation by both immunological and non-immunological agents. One mechanism of activity was thought to be as a direct inhibitor of phospholipase A2, decreasing the generation of eicosanoids and platelet-activating factors. Another anti-inflammatory mechanism may be the effect on arachidonic acid mobilization in human neutrophils. The active fractions of *Aristolochia indica* were found to neutralize rattle snake venom actions (Samy et al., 2008). Anti-inflammatory activity of antidote *Aristolochia indica* to the venom of *Heteropneustes fossilis* in rats was studied by Das et al. in 2010. The dried extract of plant showed analgesic activity against the venom extract of *H. fossilis* which is present in the glandular cell (Poison gland) at the base of pectoral spine. The LD50 of an *H. fossilis* extract in oral and intravenous doses were about 40 mg/kg/day and 29mg/kg/day respectively.

Curcuma longa



Research shows curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP) and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases[24]. Curcumin is thought to suppress NF-kb activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IκB). Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis[25]. Curcumin's inhibition of inflammatory cytokines is achieved through a number of mechanisms. In vitro studies indicate curcumin regulates activation of certain transcription factors such as activating protein-1 (AP-1) and NF-κB in stimulated monocytes and alveolar macrophages, thereby blocking expression of cytokine gene expression. Down-regulation of intercellular signalling proteins, such as protein kinase C, may be another way in which curcumin inhibits cytokine production[26,27].

Rosmarinus officinalis

The main constituents of *Rosmarinus officinalis* essential oil are camphor,1,8-cinole, α-pinene, borneol, camphene, beta-pinene and limonene in proportions that vary according to the vegetative stage and bioclimatic conditions. In an open-label trial, the effects of rosemary extract have been assessed in patients with osteoarthritis (OA), rheumatoid arthritis (RA) and fibromyalgia during 4 weeks; hs-CRP (an index for inflammation presence) was decreased noticeably in patients who had demonstrated augmentation in this index; by the way, reduction in inflammation related to pain score was observed during the treatment but remission has not occurred in fibromyalgia scores [28] . Furthermore, rosemary's extract has shown gastro protective action against gastric ulcer, even better than Omeprazole; this advantage is because of inhibition activity of rosemary in neutrophils infiltration and reduction in proinflammatory mediators: TNF-α and IL-1[29] .The anti-inflammatory effects of R. officinalis extract and rosmarinic acid were evaluated by assessing the levels of some spinal inflammatory markers including cyclooxygenase-2 (COX2), prostaglandin E2 (PGE-2), interleukin 1 beta (IL-1β), matrix metallopeptidase 2 (MMP2) through western blotting and nitric oxide (NO) production via Griess reaction on days 7 and 14 post-surgery[30]. The study indicates that rosemary essential oil dietary application is able to affect murine experimental inflammatory models depending on the concentration used. Obviously, it is necessary to study in greater detail the immunomodulatory properties of rosemary extracts. The study, however, conclude that the anti-inflammatory effects of rosemary essential oil should be interpreted with caution, due to its contradictory dose-related effects[31].

Urtica dioica

The main constituents of Urtica dioica are flavonoids, tannins, volatile compounds and fatty acids,

polysaccharides, isolectins, sterols, terpenes, protein, vitamins and minerals. Anti-inflammatory effects of orally administered U. dioica in animal models showed pharmacological evidence for its folkloric use in painful and inflammatory disorders[32].Urtrica dioica contain several Anti-inflammatory compounds such as cyclooxygenase, lipoxygenase and substances that affect the secretion of cytokines[33]. Anti-inflammatory activity of the test extracts was measured against acute paw edema induced by formalin. The extract produced a significant and dose-dependent inhibition of formalin induced inflammation [34].

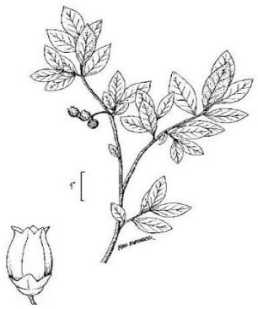
Zingiber officinale

Zingiber officinale is primarily known for its anti-emetic properties, However, it has also been used medicinally since antiquity as an anti-inflammatory agent[35]. Crude extracts containing both of ginger's secondary metabolites, the gingerols and the essential oils, were even more potent in inhibiting joint swelling than gingerols alone[36]. *Zingiber officinale* is a compound having a wide spectrum of biological functions. Safety evaluation studies indicate that *Zingiber officinale* are well tolerated even at a very high dose without any toxic effect[37].The earlier report suggested that in Rheumatoid arthritis (RA) and Osteoarthritis(OA) patients, use of powdered ginger for 3-month to 2.5-year period, reduce pain and inflammation in 75% patients without any adverse effect and suggested ginger is an anti-inflammatory agent[38].

Olea europaea

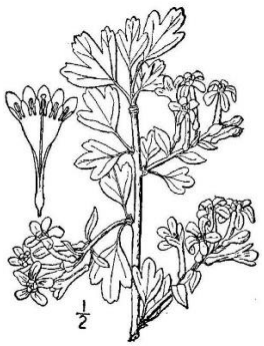
The olive tree (*Olea europaea L.*) is cultivated in many parts of the world, but the Mediterranean region is the main area of agricultural production, it represents approximately 98% of the growing around the world[40]. Phytochemical investigation on *Olea europaea* have revealed the presence of various phytochemicals such as oleuropein, hydroxytyrosol, verbascoside, apigenin-7-glucosides and luteolin-7- glucosides, flavonoids, secoiridoids, triterpenes, bio phenols, benzoic acids and sterols. The bioactive components of Xorialyc ®, a standardized olive leaves extract was characterised for testing its anti-inflammatory action compared to other similar extracts[39]. The anti-inflammatory effect of oleuropein in spinal cord trauma was tested in mice that were divided in 4 groups, one of them received 20 mg/kg of body weight of oleuropein soon after the spinal cord injury and the other one after 1 hour. The pro-inflammatory cytokines TNF-α and IL-1β are synthesized immediately after the spinal cord injury worsening the post traumatic condition by the increase of vascular permeability, recruitment of inflammatory cells and induction of iNOS and COX-2. Thus, the study suggests that oleuropein modulates the inflammatory reactions after spinal cord injury[41].

Vaccinium myrtillus L.



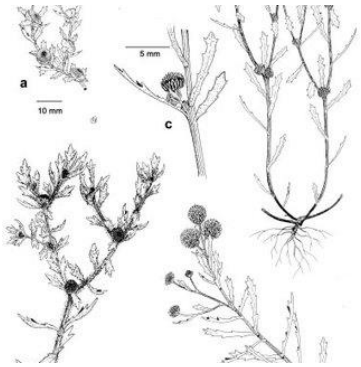
Bilberry fruit (*Vaccinium myrtillus L.*) belongs to the Ericaceae family and has been used in folk medicine for centuries. Anthocyanin rich bilberry extracts are traditionally used as ingredients of food supplements, mainly to treat ocular health and vasculopathy[42]. The study investigated the anti-inflammatory effects of bilberry (*Vaccinium myrtillus*) extract (BE, containing 42.04% anthocyanin) on Propionibacterium acnes (P. acnes) plus lipopolysaccharide (LPS) induced liver injury and croton oil-induced ear edema in mice. Moreover, BE administration markedly suppressed the increase of liver mRNA levels of iNOS, TNF-α, IL-1β and IL-6, and the protein levels of iNOS, TNF-α and NF-κB. In addition, liver malondialdehyde and NO contents were significantly reduced by BE treatment. These results indicated that BE has potent protective effects on acute and immunological inflammation, which might contribute to the study of the anti-inflammatory effects of natural products and healthy food. however, most of the biological activities investigated *in vitro* need to be confirmed *in vivo* [42,43].

Ribes glaciale



Ribes glaciale extract contains 2,2-azino-bis (3-ethybenzothiazoline -6-sulfonic acid), 1,1- diphenyl 2-picrydrazyl (DPPH), flavonoids, pyranoanthocyanins, phenolic acid and nitrile groups. The anti-inflammatory and analgesic activity was assessed by carrageenan induced rat paw edema and acetic acid induced writhing model respectively. The extract (500 µl) was diluted appropriately and mixed with 1 ml NaNO2 (5%). After standing for 6 min, 1 ml of 10% AlCl3 and 10 ml of NaOH (1 M) were added to the mixture. The mixture was adjusted to 25 ml with 70% ethanol and allowed to rest for 15 min[44]. The absorbance was measured at 510 nm, with 70% ethanol as a blank. Different concentration of extracts (50-500 µg/ml) in 1 ml of alcohol was mixed with 2.5 ml phosphate buffers (0.2 M, pH 6.6) and 2.5 ml of 1% potassium ferricyanide. The mixture was incubated at 50 °C for 20 min and 2.5 ml of 10% trichloroacetic acid was added. The reaction mixture was then centrifuged for 10 min. Further, 2.5 ml of the supernatant solution was mixed with 2.5 ml of distilled water and 0.5 ml of 0.1% FeCl3. The absorbance was measured at 700 nm [45]. The methanolic extract exhibited significant anti-inflammatory and analgesic activity and indicate the need for its further phytochemical evaluation[46].

Centipeda minima



Centipeda minima has been used since centuries as a traditional medicinal plant in treating a number of disease conditions. More than one hundred secondary metabolites, classifying as terpenoids, flavonoids, mono-phenols, fatty acids, amides and other types, were isolated from this plant[47]. Among them, sesquiterpene lactones are dominant in either C. minima species or numerous plants of genus *Centipeda*. These phytochemical groups also possessed various biological results like anti-cancer, anti-bacterial, anti-allergy, anti-virus, anti-inflammation, hepatoprotective activities, etc[48]. The plant *Centipeda minima* contains 7,4-dt-0-methyldihydrokaempferol, iristectorin-A, tricine,2-amino-3-phentl-propionicacid,4-amino-4-carboxychroman-2-one, arnicolide D. The flavonoids fractions was isolated from *Centipeda minima* leaves extracts to assess anti-inflammatory and anti-arthritis activity in rats. In anti-inflammatory study. Animals were fasted for 24 hours before the experiment with free access to water. Approximately 50µl of a 1% suspension of carrageenan in saline was prepared 1hr before each experiment and was injected into the plantar side of right hind paw of rat. 0.2 g of herbal gel containing *Centipeda minima* extract was applied to the plantar surface of the hind paw by gently rubbing 50 times in the index finger. Rats of the control groups received the plain gel base and 0.2 g of 1% *Centipeda minima* gel applied in the same way was used as a standard. Drugs were applied 1hour before the carrageenan injection. Paw volume was measured immediately after carrageenan injection and at 1,2,3 and 4 hours' intervals after the administration of the noxious agent by using plethysmometer[49].

CONCLUSION

The advancement of allopathic medication shifted scientific and general people's interest from conventional medicinal preparations. However, in recent years, a significant paradigm change has taken place. Attraction has re-focused in traditional medicine, simply because of the higher cost of modern drugs, time and expenditure which is essential to bring a drug to market after proper clinical tests, severe side-effects of a variety of modern drugs and drug-resistance developing in both microorganisms and parasites. So, researchers are currently taking an active interest in traditional medicinal preparations of native peoples, which are plant-based. In recent years' researchers are working on anti-inflammatory plants. Inflammatory diseases are common in the ageing society of developed and developing countries; yet the drugs used to combat inflammatory diseases like rheumatoid arthritis often have serious side-effects. Several leads from plant sources, like curcumin, resveratrol, baicalein, boswellic acid, betulinic acid, ursolic acid and oleanolic acid are now studied as possible drugs for the future against inflammation. This review will help the recent and future researchers in their research work as they could select the anti-inflammatory medicinal plants from which they can isolate active constituents by using various separation techniques. These types of research works may unveil some new molecules which help us to fight against inflammatory disorders. Most of the researchers concluded their study by mentioning that the anti-inflammatory activity may be due to inhibition of the enzyme cyclooxygenase leading to inhibition of prostaglandin synthesis. But more extensive study could be conducted to determine exact mechanism(s) of action.

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