Medicinal plants with non-steroidal anti-inflammatory-like activity

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Abstract

Inflammation is a natural aspect of the immune system's response. Pain, redness, heat or warmth, and swelling are the four major symptoms of inflammation. Plants can generate a vast range of phytochemical substances as secondary metabolites, all of which have anti-inflammatory properties. Herbal medicines are significant cures for the treatment of a variety of disorders around the world. Medicinal plants are made up of roughly 7500 species, with representatives from about 17,000 higher flowering plant species. Even when synthetic chemistry has advanced beyond expectations, the utilization of natural products in the production of medications utilized in modern medicine is unrivalled. Anti-inflammatory medicines can help to reduce tissue damage and improve patient comfort by interfering with the pathophysiology of inflammation. As a result of the huge number of species available for investigation, the effective creation of new naturally occurring anti-inflammatory medications relies mostly on a multidisciplinary approach to finding new compounds. Despite the fact that many review articles have been written in this area, the vast majority of them only looked at the subject from a regional perspective. Various non-steroidal anti-inflammatory medicines have been proven to alleviate pain and inflammation by inhibiting the isoform of cyclooxygenase enzyme's digestion of arachidonic acid, hence lowering prostaglandin synthesis. Non-steroidal anti-inflammatory medicines come with a slew of negative side effects. Thus, there are, however, medicinal herbs that have anti-inflammatory therapeutic properties with a little or no negative side effects.

Keywords: Herbal medicine, inflammation, medicinal plants, natural products, non-steroidal anti-inflammatory activity, use.

Introduction

Inflammation is the body's severe reaction to any kind of damage. Pain, redness, heat or warmth, and swelling are the four primary indicators of swelling. The arterioles in the surrounding tissue dilate when a part of the human body is injured. This results in increased blood flow to the affected area (redness) [1]. Inflammation is a ubiquitous process that happens in a disturbed state of homeostasis such as damage, exposure to contaminating substances and infection, as well as is triggered by innate immune system receptors for the removal of pathogens when they are identified [2]. There are two types of inflammation: acute and chronic inflammation. Acute inflammation may be the body's first response to damaging stimuli. The inflammatory response is out of proportion in chronic inflammation, resulting in body harm. Cyclooxygenase (COX) is a major enzyme in the production of prostacyclins, prostaglandins and thromboxanes which play a role in inflammation, pain and platelet aggregation [3]. The permeability (pore size) of these arterioles is also increased by vasoactive chemicals, allowing blood cells, chemical substances, blood proteins and fluid to collect in that area. This fluid buildup produces swelling and can cause discomfort by compressing nerves in the area. Additionally, prostaglandins may cause nerve irritation and contribute to pain [4]. The major enzyme in the manufacture of prostaglandins, prostacyclins and thromboxanes, which are implicated in inflammation, pain and platelet aggregation is COX [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most often prescribed medications in the world [6] and they are used to treat acute and chronic pain caused by an inflammatory process [7]. NSAIDs cover a wide spectrum of medications and their actions are all linked to COX inhibition in the generation of prostaglandins and thromboxanes [8 - 11]. The central and peripheral inhibition of COX which interferes with the conversion of arachidonic acid to prostaglandins E_2, prostacyclins and thromboxanes is the major mechanism of action of NSAIDs. COX-1 and COX-2 which act in distinct locations are two enzymes involved in the action of NSAIDs. COX-1 is found in most cells including foetal and amniotic fluid and plays a role in physiological functions such as regulation and protection. Inflammation and pro-inflammatory cytokines, on the other hand, activate COX-2 [11, 12]. NSAIDs or non-steroidal anti-inflammatory medicines have been used in humans for a long time. As a result, long-term use of these drugs causes negative side effects and damages human biological systems such as the liver and gastrointestinal tract. Due to negative side effects such as gastric lesions, cardiovascular, renal and gastrointestinal damage [13 - 15].

Natural products (NPs) can be considered any substance in the cosmos. NP is a chemical compound or substance created by a living entity (animals, plants or microbes) that has pharmacological or biological activity and can be clinically beneficial either in crude form (traditional remedies) or isolated/modified form (modern system) [16]. Traditional herbs and their preparations for example were considered drugs in the Ayurvedic system of medicine; the “SushrutaSamhita” (an Ayurvedic classic) contains roughly 700 plants for the treatment of 1100 ailments. Numerous traditional medical systems (Chinese materiamedica, Greek, Arab, Egyptian and Mesopotamian) as well as folk medicine (ethnomedicine) provided a vast amount of

information. Serturner's (1804) separation of morphine from opium marked the beginning of modern NP chemistry. Many such findings led to the discovery of bioactive isolated chemicals such as quinine (1820) from cinchona bark, strychnine (1818), cocaine (1859), tubocurarine (1935), penicillin and other bioactive isolated compounds [16]. Over 80% of approved therapeutic medicines were made from naturally occurring chemicals or were prompted by a natural substance. NPs have extensively been studied and it was discovered that 33% of the 1394 small molecule approved drugs introduced between 1981 and 2019 were either natural products or derived from natural products and another 35% were built around a pharmacophore from a NP [17]. As secondary metabolites, plants can synthesis a diverse range of phytochemical substances. Several phytochemicals have successfully been employed to treat a variety of human disorders. The World Health Organization (WHO) has attempted to identify all medical plants used around the world and has compiled a list of over 20,000 species. The most of medicinal plant parts are employed as raw pharmaceuticals and have a wide range of clinical properties [18]. Plants have a huge potential for developing novel medications and for treating chronic and infectious disorders in traditional medicine [19]. The purpose of this review is to look into basic aspects of anti-inflammatory properties of many medicinal herbs.

Plants have non-steroidal anti-inflammatory activities

Aeglemarmelos (Rutaceae): The anti-inflammatory effect of an aqueous extract of Bilwa root bark was investigated in albino rats using a carrageenan induced paw edoema model and cotton pellet induced granuloma model as well as the standard medicine indomethacin and Bilwa. The results demonstrated that inhibition has anti-inflammatory activities [20].

Ajugalaxmannii (Lamiaceae): Polymorphonuclear leukocytes, total leukocytes, oxidative stress, and phagocytosis all decreased in response to the ethanolic extract of Ajugalaxmannii's anti-inflammatory properties. In testing, A. laxmannii extract at 50 mg/ml outperformed diclofenac in terms of anti-oxidative stress and anti-inflammatory properties. As a result, the findings strongly showed that A. laxmannii is a valuable source of bioactive compounds that can be employed as anti-inflammatory agents in a variety of herbal medicines [21].

Allium sativum (Amaryllidaceae): Garlic oil has anti-inflammatory properties because it inhibits the cytoskeleton's construction and disassembly processes [22].

Aloe ferox (Asphodelaceae): Aloe ferox extract's anti-inflammatory properties are ascribed to its gel, which contains three malic acid acylated polysaccharides (**Figure 1**). Aloeresin, an anti-inflammatory chemical found in the plant, is also present. In addition, it also contains carboxypeptidase and bradykinase, which are anti-inflammatory and anti-swelling enzymes [23].

Figure 1: Image for Aloe ferox (*Asphodelaceae*)

Anacardiumoccidentale (Anacardiaceae): Anacardiumoccidentale leaf extract can be used to treat inflammation and oleamide has been identified as one of the most bioactive components linked to the plant's anti-inflammatory properties [24].

Calaminthanepeta (Limiaceae): Calaminthanepeta has anti-inflammatory properties, since it inhibits COX-2 synthesis by 40.10% [25].

Cassia fistula (Caesalpiniaceae): In the acute and chronic anti-inflammatory models of inflammation in rats, Cassia fistula bark extracts have a substantial anti-inflammatory effect. Endogenous and exogenous reactive oxygen species (ROS) have been linked to the pathophysiology of diseases such as atherosclerosis, diabetes, cancer, arthritis and the ageing process. Inflammatory disorders are complicated by the presence of ROS. Flavonoids and bioflavonoids are the major components of Cassia fistula that have anti-inflammatory properties [26].

Cassia occidentalis (Caesalpiniaceae): Using an ethanolic extract, Sreejith and others assessed the anti-inflammatory properties of the overall Cassia occidentalis plant. To evaluate the anti-inflammatory potential of carrageenan, a dosage of 250 mg/kg was used in a carrageenan-induced paw edema model. At a dosage of 250 mg/kg, the results demonstrated a considerable reduction in malondialdehyde levels in murine hepatic microsomes and a significant reduction in carrageenan-induced inflammation in mice [27].

Cissampelossympodialis (Menispermaceae): The ethanolic extract and alkaloids total fraction derived from Cissampelossympodialis aerial parts have anti-inflammatory effect, as they reduced tumor necrosis factor- and interlukin-1 levels while increasing interlukin-10 and glutathione–glutathione levels [28].

Citrus limetta (Rutaceae): The main ingredient of Citrus limetta essential oils (Eos) is limonene, (**Figure 2**) which is a monoterpene hydrocarbon. Inhibition of the synthesis of pro-inflammatory cytokines such as interlukin-6, tumor necrosis factor- and interlukin-1 in lipopolysaccharide-induced inflammation and inhibition of the synthesis of ROS in H_2O_2-induced oxidative stress have also been observed when macrophages were pre-treated with the EOs of C. limetta. In

contrast, an in vivo investigation found that when the volatile oil was administered topically, it reduced 12-O-tetradecanoylphorbol-13-acetate-induced ear weight, ear thickness, pro-inflammatory cytokine generation, lipid peroxidation and improved histological damage in the ear tissue [29].

Figure 2: Image for citrus limetta (*Rutaceae*)

Citrus limon (Rutaceae): Oral administration of Citrus limon EOs at dosages of 50, 100 and 150 mg/kg significantly reduced the number of writhes, whereas the highest doses significantly reduced the number of paw licks, indicating anti-inflammatory effect [30].

Coriandrum sativum (Apiaceous): The ultraviolet erythema test in vivo revealed that coriander oil had anti-inflammatory properties [31].

Cuminumcyminum (Apiaceae): The anti-inflammatory capability of cumin volatile oil in carrageenan-induced rat paw edema revealed that at a dose of 0.1 ml/kg, i.p., the volatile oil of cumin inhibited rat paw edema in a dose-dependent manner compared to the control group. The anti-inflammatory activity has also been found to be comparable to that of diclofenac sodium [32]. Cumin EOs induced significant suppression of the mRNA expressions of inducible nitric oxide synthase, cyclooxygenase-2, interleukin-1 and IL-6 in lipopolysaccharide-stimulated RAW 264.7 cells, as demonstrated by real-time polymerase chain reaction, PCR, testing. Furthermore, Western blotting research revealed that cumin EOs inhibited the phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase in response to LPS-induced transcriptional activation of nuclear factor kappa (NF-) (JNK). As a result, it was established that cumin EOs inhibited NF- and mitogen-activated protein kinases ERK and JNK signaling in LPS-stimulated RAW264.7 cells resulting in anti-inflammatory actions [33].

Cynodondactylon (Poaceae): Carrageenan, serotonin, histamine and dextran produced rat paw edema and cotton pellet technique were used to test the anti-inflammatory efficacy of an aqueous extract of Cynodondactylon at various doses. The experiment was conducted at three dose levels: 200, 400 and 600 mg/kg, orally. When taken orally, the aqueous extract of C. dactylon was found to be safe at all doses tested with no mortality up to 4000 mg/kg of extract. In all of the models, C. dactylon demonstrated strong anti-inflammatory properties. After 3 and 5 hours, the extract was

observed to significantly diminish ($p < 0.001$) the production of edema produced by carrageenan, serotonin, histamine and dextran [34].

Cyperusrotundus (Cyperaceae): The anti-inflammatory impact of Cyperusrotundus EOs in carrageenan-instigated rats demonstrated a dose-dependent reduction in paw edema rats from the second hour after carrageenan injection ($p < 0.01$). At a dose of 500 mg/kg, this EO inhibited inflammatory pain ($p < 0.01$), although pain caused by inflammation was considerably ($p < 0.05$) prevented at lower doses [35].

Dendropanaxmorbifera (Araliaceae): The anti-inflammatory activity of methanolic extracts from two stages of Dendropanaxmorbifera (green and senescent leaves) revealed that they suppressed the production of LPS-induced pro-inflammatory cytokines and mediators by suppressing the expression of inducible nitric oxide synthase and COX-2, as well as inhibiting the ERK1/2 signaling pathway. Furthermore, high-performance liquid chromatography (HPLC) analysis of phenolic compounds revealed that leaf extracts contained active phenolic compounds such as myricetin, quercetin, rutin, chlorogenic acid, resveratrol, (+)-catechin and ferulic acid which were thought to be responsible for the anti-inflammatory properties [36].

Emblicaofficinalis (Euphorbiaceae): Emblicaofficinalis is a subtropical and tropical tree found in China, India, Indonesia and the Malay Peninsula. In these locations, it has been utilized for anti-inflammatory and antipyretic properties. The water fraction of methanol extract of plant leaves was revealed to have anti-inflammatory properties in recent research. The effects of fraction on the generation of inflammatory mediators including leukotriene B4, platelet activating factor (PAF) and thromboxane were investigated. Human PMN migration was reduced by the water fraction of methanol extract at low doses [37].

Glycyrrhizaglabra (Fabaceae): The roots of Glycyrrhizaglabra (liquorice) were known to Roman medics as Radixdulcis and to Arab physicians as a cough treatment and the plant has been grown in Europe for its distinctive taste since the 18th century. Glycyrrhizaglabra includes the anti-inflammatory triterpenes glycyrrhizin (6 - 13%) and glycyrrhizic acid [38].

Ipomoea pescaprae (Convolvulaceae): In experimental animals, leaf extracts of Ipomoea pescaprae were efficient in treating dermatitis caused by jellyfish stings and edema caused by ethyl phenyl propiolate [39].

Jasminum sambac Linn (Oleaceae): Jasminum sambac L is grown all over India and its roots and leaves have long been used to cure fever, discomfort and inflammation. Its leaves have been shown to have potent anti-inflammatory properties. Sengar and associates discovered in 2015 [4] that the root extract. Inflammation pathway was effective at a dose of 400 mg/kg. Thromboxane, nitric oxide, inducible nitrous oxide synthase, interferon, tumor necrosis factor, nuclear factor-B, mitogen activated protein kinase, Janus kinase, interleukin, adapted from [41]. The current state and future of medicinal plant anti-Inflammatory activity after 2nd, 3rd, 4th and 6th hours of treatment

in carrageenan-induced edema, 71 J. Sambac produced in ethanol showed outstanding anti-inflammatory effect and a 33.58 percent decrease in cotton pellet-induced granuloma development has also been reported at the same dose quantity (**Figure 3**). Furthermore, this extract produced remarkable ($p < 0.001$) suppression in arthritis induced by adjuvant [42].

Figure 3: Image for Jasminum sambac, (*Oleaceae*)

Leonotisocymifolia (Lamiaceae): After six hours of instigation with carrageenan, the anti-inflammatory action of 80% methanolic leaf extract of Leonotisocymifolia in mouse models reduced 75% paw edema. Furthermore, it was discovered that all of the extract doses tested significantly slowed granuloma synthesis [43].

Limoniumdensiflorum (Plumbaginaceae): In LPS-stimulated RAW 70 S. Chouhan and S. Guleria 264.7 cells, the shoot methanolic extract of the halophyte Limoniumdensiflorum displayed the highest anti-inflammatory action, blocking 80% nitric oxide release at a concentration of 160 g/ml [37].

Nicotianatobacum (Solanaceae): The extract of Nicotianatobacum leaves is utilized as an anti-inflammatory. Chemical elements such as 1,8-cineole, 4-vinylguaiacol, acetaldehyde, acetophenone, alkaloids, anabasine, nicotinic acid, nicotine, scopoletin, quercitrin, sorbitol, tocopherolstigmasterol, trigonelline and trigonelline are mostly effective [6, 44 - 46].

Oleaeuropaea (Oleaceae): In carrageenan-induced paw edema in rats, the anti-inflammatory activity of extra virgin olive oil from Oleaeuropaea was reported to be equivalent to that of dexamethasone treatment [47].

Origanumehrenbergii (Lamiaceae): In lipopolysaccharide-induced inflammation in RAW264.7 cells, the anti-inflammatory action of Origanumehrenbergii EOs was investigated and a considerable reduction in nitrous oxide generation was reported [48].

Persicariachinensis (Polygonaceae): The molecular mechanism behind the prevention of Hcl and or ethanol-induced gastric ulcers in mice due to the methanol extract of Persicariachinensis against lipopolysaccharide-induced PGE_2 and nitric oxide in RAW264.7 macrophages revealed that it significantly reduced the expression of lipopolysaccharide-induced pro-inflammatory cytokines

such as interleukin- interleukin-6 and tNF. In both differentiated U937 cells and lipopolysaccharide-stimulated RAW264.7 cells, activation and phosphorylation of activator protein-1 and mitogen-activated protein kinase were reduced. As a result, these findings strongly suggested that a methanolic extract of P. chinensis could be used as a treatment for mitogen-activated protein kinase (MAPK)/activator protein (AP-1)-mediated inflammation [49].

Phyllanthus acidus (Phyllanthaceae): Phyllanthusacidus has been used to treat respiratory issues, gastrointestinal issues, hepatitis, bronchitis, rheumatism and asthma for many years (**Figure 4**). In lipopolysaccharide-treated RAW 264.7 cells, Kim and others [49] discovered that a methanolic extract of P. acidus aerial parts inhibited nitric oxide and prostaglandin-E2 generation while also preventing morphological alterations. Furthermore, this extract suppressed the expression of inducible nitric oxide synthase and COX-2 and lowered the nuclear levels of NF-. In the methanolic extract of P. acidus aerial parts, quercetin and kaempferol were revealed to be somewhat active anti-inflammatory substances among the flavonoids discovered. As a result, it was determined that the methanolic extract of P. acidus aerial parts had anti-inflammatory effects in vivo and in vitro by suppressing Syk, Src and their downstream transcription factor, NF-gene [50].

Figure 4: Image for Phyllanthus acidus

Syzygiumcaryophyllatum (Myrtaceae): Through a heat-induced egg albumin denaturation bio assay technique, the in vitro capacity of different doses of aqueous root extract of Syzygiumcaryophyllatum to prevent inflammation has also been proven [51].

Sida cordifolia Linn (Malvaceae): Sida cordifolia is a perennial mallow subshrub in the Malvaceae family. In traditional medicine, Sida cordifolia is used to treat oral mucosa inflammation, blenorrhea, asthmatic bronchitis and nasal congestion [52]. It has been studied as an anti-inflammatory, a cell proliferation inhibitor and a liver growth promoter [53].

Solanummelongena (Solanaceae): The anti-inflammatory efficacy of an aqueous extract of Solanummelongena L leaves was examined. The percentage of inhibition of the aqueous extract of S. melongena L in doses of 200 mg/kg and 400 mg/kg was 42.62%, which is less than the 64.5% inhibition of the standard medicine aspirin. Chemical components such as ascorbic acid, alanine, arginine and caffeic acid have anti-inflammatory properties [44 - 46, 54].

Tephrosiapurpurea (purple tephrosia) (Fabaceae): Using carrageenan and the produced paw edema method, the anti-inflammatory effect of different dosages of 50% alcoholic extract of T. purpurea root was studied.

Zingiberofficinale (Zingiberaceae): Shimoda and coworkers [55] explored the anti-inflammatory effect of Zingiberofficinale by manufacturing a 40% ethanolic extract from dried red ginger and testing its anti-inflammatory efficacy in acute and chronic inflammation models. The findings revealed a potent suppressive effect on acute and chronic inflammation with macrophage activation inhibition appearing to play a role in this anti-inflammatory action [55].

Conclusion

Anti-inflammatory plants have been the focus of research in recent years. Inflammatory disorders are frequent in industrialized and developing countries' ageing societies, yet the treatments used to treat them, sometimes have major side effects. Several plant-derived compounds, such as curcumin, resveratrol, baicalein, boswellic acid, betulinic acid, ursolic acid, and oleanolic acid are now being investigated as potential anti-inflammatory medications. This review aids current and future researchers to identify anti-inflammatory medicinal plants from whose active ingredients can be isolated using various separation procedures. These types of studies could lead to the discovery of novel compounds that can help in treatment of inflammatory illnesses. However, more detailed investigation could be carried out to discover the actual mechanism(s) of action.

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