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## BRIEF REVIEW ON HERBAL PLANT USED IN ANTI-INFLAMMATORY TREATMENT

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**ABSTRACT:** Inflammation is a part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells or irritants. It is characterized by redness, swollen joints, joint pain, stiffness and loss of joint function. Inflammation is currently treated by NSAIDs. Unfortunately, these drugs cause increased risk of blood clot resulting in heart attacks and strokes. Therefore, the developments of potent anti-inflammatory drugs from the natural products are now under considerations. Natural products are rich source for discovery of new drugs because of their chemical diversity. A natural product from medicinal plants plays a major role to cure many diseases associated with inflammation. The conventional drug available in the market to treat inflammation produces various side-effects. Due to these side-effects, there is need for the search of newer drugs with less or no side-effects. There are hundreds of phytoconstituents reported to have many pharmacological activities although most of these reports are of academic interest and very few find entry in clinical trials. The present review is directed towards compilation of data on promising phytochemicals from herbal plants that have been tested in inflammatory models using modern scientific systems.

**INTRODUCTION:** Inflammation is a defense response of our body to hazardous stimuli such as allergens and/or injury to the tissues; on the other hand, uncontrolled inflammatory response is the main cause of a vast continuum of disorders including allergies, cardiovascular dysfunctions, metabolic syndrome, cancer, and autoimmune diseases imposing a huge economic burden on individuals and consequently on the society <sup>1</sup>.

There are various medicines for controlling and suppressing inflammatory crisis; steroids, non-steroid anti-inflammatory drugs, and immunosuppressant are the practical examples of these medications which are associated with adverse effects while in practice our goal is to apply minimum effective dose by the highest efficacy with the least adverse effects.

Thus, we need to apply natural anti-inflammatory factors within medication therapy to achieve increased pharmacological response and the lowest degree of unwanted side effects <sup>2, 3</sup>. Herbal medicines are promoting subjects in medicine and, of course, we have to increase our knowledge about them. Complementary, alternative, and traditional medicines are the pivotal source of herbal

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medication guidance, but surely modern medicine must prove these guidelines through scientific methods before using them in practice. In this review, we have endeavored to assess the plants and the most clinical evidence of their anti-inflammatory effects. Rheumatoid arthritis and osteoarthritis are the major inflammatory diseases affecting people worldwide. Rheumatoid arthritis is an inflammatory condition that usually affects multiple joints. It affects 0.3-1.0% of the general population and is more prevalent among women in developed countries. Persistent inflammation leads to joint destruction, but the disease can be controlled with drugs. Osteoarthritis, which is characterized by loss of joint cartilage that leads to pain and loss of function primarily in the knees and hips, affects 9.6% of men and 18% of women aged more than 60 years. Increases in life expectancy and aging populations are expected to make osteoarthritis the fourth leading cause of disability by the year 2020<sup>4,5</sup>.

Chronic inflammation leads to cancer development and in recent times experimental and clinical studies have supported this hypothesis, which is now globally accepted. Epidemiological studies have identified chronic infections and inflammation as major risk factors for various types of cancer. It has been estimated that the underlying infections and inflammatory reactions are linked to 15–20% of all cancer deaths<sup>6</sup>. Further studies have suggested that prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or of selective cyclooxygenase (COX)-2 inhibitors, delays the development of premalignant tumors and reduces the incidence of different forms of neoplasia. Cancer associated inflammation includes the presence of several mediators such as cytokines, chemokines, growth factors, lipid messengers, matrix degrading enzymes, and leukocytes infiltrating the tumor microenvironment<sup>7</sup>.

Natural products or natural product-derived compounds represent great structural diversity, which is not commonly seen in synthetic compounds. Of the 1184 new chemical entities reported during 01/1981 to 06/2006, 60% are derived from or based on natural products. Thus, natural products play a dominant role in the discovery of leads for the development of drugs for

treating human diseases<sup>8</sup>. Natural products (and traditional medicines) offer great hope in the identification of bioactive compounds and their development into drugs for the treatment of inflammatory diseases. Plants have been the basis of many traditional medicine systems throughout the world for thousands of years and continue to provide mankind with new remedies. The plant-based medicines initially dispensed in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations, now serve as the basis of novel drug discovery<sup>9</sup>.

There are several records in traditional medicine focusing on relief from pain and inflammation. Since ancient times many people suffering from inflammation were treated with phytochemicals, which is evident from the discovery of the first anti-inflammatory, analgesic drug aspirin. The discovery of aspirin was based on the known analgesic and antipyretic properties of the bark of willow-tree since 400 BC by the Greeks and Romans. In 1899 acetylsalicylic acid (aspirin) was introduced as the first potent drug to treat rheumatic diseases<sup>10</sup>.

#### **Plants as Natural Anti-inflammatory agents:**

Unlike modern allopathic drugs which are single active components that target one specific pathway, herbal medicines work in a way that depends on an orchestral approach. A plant contains a multitude of different molecules that act synergistically on targeted elements of the complex cellular pathway<sup>11</sup>. Medicinal plants have been source of wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions<sup>12</sup>. The use of herbal medicines is becoming popular due to toxicity and side-effects of allopathic medicines. Medicinal plants play an important role in the development of potent therapeutic agents. There are over 1.5 million practitioners of traditional medicinal systems using medicinal plants in preventive, promotional and curative applications<sup>13</sup>. India with its biggest repository of medicinal plants in the world may maintain an important position in the production of raw materials either directly for crude drugs or as the bioactive compounds in the formulation of pharmaceuticals and cosmetics *etc*<sup>14</sup>.

TABLE 1: PLANT HAVING ANTI-INFLAMMATORY ACTIVITY

Sr. no.	Plant Name	Family	Plant Part	Type of Extract
1	<i>Achillea millefolium</i>	Asteraceae	Whole Plant	Aqueous, Alcohol
2	<i>Aconitum heterophyllum</i>	Valeraneaceae	Root	Ethanol
3	<i>Adhatoda vasica</i> Nees	Acanthaceae	Leaves	Methanol
4	<i>Adansonia digitata</i>	Malvaceae	Fruit	Aqueous
5	<i>Aegle marmelos</i>	Rutaceae	Leaves	Ethylacetate and methanol
6	<i>Aloe vera</i>	Asphodelaceae	Leaves	Perether, Ethanol
7	<i>Azadirachta indica</i>	Meliaceae	Leaves	Hydro-alcohol
8	<i>Annona squamosa</i>	Annonaceae	Seeds	Ethanol
9	<i>Baccharis incarum</i>	Astereae	Whole plant	Ethanol
10	<i>Bacopa monnieri</i>	Scrophulariaceae	Whole Plant	Ethanol
11	<i>Barleria prionitis</i>	Acanthaceae	Whole plant	Methanol
12	<i>Bonafousia sananho</i>	Apocynaceae	Whole plant	Ethanol

***Achillea millefolium* Linn. (Asteraceae):** *Achillea millefolium* L. is a perennial herb native to Europe and highly recognized in traditional medicine for its anti-inflammatory properties. The plant has been traditionally used externally for treatment of wounds, burns, swollen and irritated skin. Studies have shown two classes of secondary metabolites, isoprenoids and phenolics, contribute mainly to the anti-inflammatory properties<sup>15</sup>. Aqueous and alcoholic extracts of *A. millefolium* are used in traditional medicine internally in treatment of gastro-intestinal and hepato-biliary disorders and as an antiphlogistic drug. The topical anti-inflammatory activity of sesquiterpenes is caused by inhibition of arachidonic acid metabolism. The three flavnoids present in the crude extract and enriched in flavnoid fraction are rutin, aspigenin-7-*O*-glucoside and luteolin-7-*O*glucoside. The crude plant extract and two fractions enriched in the dicaffeoyquinic acids and the flavnoids inhibit human neutrophil elastase as well as the matrix metalloproteinases, which are associated with anti-inflammatory process *in-vitro* studies<sup>16</sup>.



FIG. 1: *ACHILLEA MILLEFOLIUM*

***Aconitum heterophyllum* (Valeraneaceae):** *A. heterophyllum* is a plant which is commonly known

as 'Ativisha' or 'Patis' in Ayurveda. It is used for the treatment of diseases of nervous system, digestive system, fever and rheumatism. The ethanolic extract of root of *A. heterophyllum* contains alkaloids, glycosides, flavnoids and sterols. It has been reported that plants with these chemical classes of compounds possess potent anti-inflammatory effects through inhibition of prostaglandin pathways. The cotton pellet-induced granuloma is widely used to assess the transudative and proliferative components of chronic inflammation. The weight of the wet cotton pellets correlates with the amount of granulomatous tissue. The administration of *A. heterophyllum* extract has been observed to inhibit the weight of wet cotton pellet in a dose dependent manner and the higher dose of *A. heterophyllum* exhibited inhibition of inflammation very close to the inhibitory effect of diclofenac sodium. In literature it has been reported that ethanolic root extract of *A. heterophyllum* has potential to inhibit sub-acute inflammation by interruption of the arachidonic acid metabolism<sup>17</sup>.



FIG. 2: *ACONITUM HETEROPHYLLUM*

***Adhatoda vasica* (Acanthaceae):** *Adhatoda vasica* L. is an indigenous herb belonging to family Acanthaceae. The plant has been used in the



indigenous system of medicine in worldwide as herbal remedy for treating cold, cough, whooping cough, chronic bronchitis, asthma, sedative expectorant, antispasmodic, anthelmintic, rheumatism and rheumatic painful inflammatory swellings. The drug is employed in different forms such as fresh juice, decoction, infusion and powder. It is also given as alcoholic extract and liquid extract or syrup<sup>18</sup>. This plant contains alkaloids, tannins, flavonoids, terpenes, sugars and glycosides<sup>19</sup>. The anti-inflammatory potential of ethanolic extract has been determined by using carrageenan-induced paw edema assay, formalin-induced paw edema assay in albino rats. The ethanolic extract of *Adhatoda vasica* produced dose dependent inhibition of carrageenan and formalin-induced paw edema<sup>20</sup>.



FIG. 3: ADHATODA VASICA

***Bacopa monnieri* Linn. (Scrophulariaceae):** The *Bacopa monnieri* is a creeping, glabrous, succulent herb, rooting at nodes and habitat of wetlands and muddy shores<sup>21</sup>. Earlier, it is used as a brain tonic to enhance memory development, learning and concentration<sup>22</sup>. The plant has also been used in India and Pakistan as a cardio tonic, digestive aid and to improve respiratory function in cases of bronchoconstriction<sup>23</sup>. The plant possesses anti-inflammatory activity on carrageenan-induced rat paw edema and it has shown 82% edema inhibition when compared to indomethacin. *Bacopa monnieri* also significantly inhibited 5-lipoxygenase (5-LOX), 15 (LOX) and cyclooxygenase-2 (COX-2) activities<sup>24</sup>. *Bacopa monnieri* possesses significant anti-inflammatory activity that may well be relevant to its effectiveness in the healing of various inflammatory conditions in traditional medicine<sup>25</sup>. The anti-inflammatory activity of *Bacopa monnieri* is due to the triterpenoid and bacoside present in

the plant. The ability of the fractions containing triterpenoids and bacosides inhibited the production of proinflammatory cytokines such as tumour necrosis factor –alpha and interleukin-6. This was tested using lipopolysaccharide activated peripheral blood mononuclear cells and peritoneal exudates cells *in-vitro*. So, *Bacopa monnieri* has the ability to inhibit inflammation through modulation of pro inflammatory mediator release<sup>26</sup>.



FIG. 4: BACOPA MONNIERI

***Cassia fistula* L. (Caesalpiniaceae):** *Cassia fistula* tree is one of the most widespread in the forests of India. The whole plant possesses medicinal properties useful in the treatment of skin diseases, inflammatory diseases, rheumatism, anorexia and jaundice.

The bark extracts of *Cassia fistula* possess significant anti-inflammatory effect in the acute and chronic anti-inflammatory model of inflammation in rats. Reactive oxygen species (ROS) generated endogenously or exogenously are associated with the pathogenesis of various diseases such as atherosclerosis, diabetes, cancer, arthritis and aging process. ROS play an important role in pathogenesis of inflammatory diseases.



FIG. 5: CASSIA FISTULA

The main constituents responsible for anti-inflammatory activity of *Cassia fistula* are flavnoids and bio-flavnoids<sup>27</sup>.

***Daphne pontica* Linn. (Thymelaeaceae):** *Daphne* species are supposed to have anti-cancer activity since the time of AD 2nd century. Flavonoids constituents like daphnodorins were isolated from the roots of *Daphne pontica* which was reported to have antitumour activity. Several *Daphne* species have been used against inflammatory disorders. *Daphne pontica* has been used for the treatment of rheumatic pain and inflammatory ailments. The extracts inhibit the production of PGE2 and IL-1B<sup>28</sup>.



FIG. 6: DAPHNE PONTICA

***Emblica officinalis* (Euphorbiaceae):** *Emblica officinalis* is a tree growing in subtropical and tropical parts of China, India, Indonesia and Malay peninsula. It has been used for anti-inflammatory and antipyretic activities in these areas. In recent studies, anti-inflammatory activity was found in the water fraction of methanol extract of plant leaves. The effects of fraction were tested on the synthesis of mediators of inflammation such as leukotriene B4, platelet activating factor (PAF) and thromboxane. The water fraction of methanol extracts inhibited migration of human PMNs in relatively low concentrations<sup>29</sup>.



FIG. 7: EMBLICA OFFICINALIS

***Garcinia mangostana* Linn. (Guttiferae):** The fruit rinds of *Garcinia mangostana* have been used as a traditional medicine for the treatment of trauma and skin infections. The xanthonenes,  $\alpha$ - and  $\gamma$ -mangostins are major bioactive compounds found in the fruit hulls of mangosteen. The xanthonenes exhibit their biological effects by blocking inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). It was reported that two mangostins decrease prostaglandins (PGE2) levels through inhibition of COX-2 activity and NO production. It is reported that  $\alpha$ -mangostin shows a more potent inhibition of PGE2 release than either histamine or serotonin<sup>30</sup>.



FIG. 8: GARCINIA MANGOSTANA

***Lantana camara* Linn. (Verbenaceae):** The aerial parts of many species of *Lantana* are widely used in folk remedies like cancer and tumours. A tea prepared from leaves and flowers was taken against fever, influenza and stomachache. The other use of plants shows antimalarial, anti-bacterial and anti-diarrhoeal activities. From the studies it has been reported that aqueous extract of *Lantana camara* leaves is highly effective and safe for the treatment of hemorrhoids. It has been reported that aqueous extract of *Lantana camara* leaves has promising analgesic, anti-inflammatory and anti-hemorrhoidal activities<sup>31</sup>.



FIG. 9: LANTANA CAMARA



***Ricinus communis* Linn. (Euphorbiaceae):** *Ricinus communis* Linn. is found almost everywhere in the tropical and subtropical regions of the world. Anti-inflammatory and free radical scavenging activities of the methanolic extract of *Ricinus communis* root was studied by Iavarasan *et al.* in Wistar albino rats. The methanolic extract exhibited significant anti-inflammatory activity in carrageenan-induced hind paw edema model. The methanolic extract showed significant free radical scavenging activity by inhibiting lipid peroxidation. The observed pharmacological activity may be due to the presence of phytochemicals like flavonoids, alkaloids and tannins in plant extract<sup>32</sup>.

FIG. 10: *RICINUS COMMUNIS*

***Thespesia populnea* (Malvaceae):** The leaves and bark of *Thespesia populnea* are used to produce oil for the treatment of fracture wounds and as an anti-inflammatory poultice applied to ulcers and boils in southern India and Sri Lanka. Ethanolic extract of *Thespesia populnea* shows anti-inflammatory activity in both acute and chronic models. The phytochemical studies indicated that the ethanolic extract of bark contains alkaloids, carbohydrates, proteins, tannins, phenols, flavonoids, gums & mucilage, saponins and terpenes<sup>33</sup>.

FIG. 11: *THESPESIA POPULNEA*

***Sida cordifolia* Linn. (Malvaceae):** *Sida cordifolia* is a perennial subshrub of the mallow family Malvaceae. It has naturalized throughout the world and is considered an invasive weed in Africa, Australia, Hawaiian Islands, New Guinea and French Polynesia<sup>34</sup>. *Sida cordifolia* is used in folk medicine for the treatment of inflammation of the oral mucosa, blenorrhea, asthmatic bronchitis and nasal congestion<sup>35</sup>. It has been investigated as an anti-inflammatory<sup>36</sup>, for preventing cell proliferation<sup>37</sup> and for encouraging liver growth<sup>38</sup>.

FIG. 12: *SIDA CORDIFOLIA*

**Future Perspectives:** Although various types of conventional and non-conventional treatment options are available for inflammation, all of them are associated with few drawbacks such as safety, efficacy and high cost. Herbal products are alternative medicines being used for the treatment of various diseases and are comparatively safe as compared to synthetic drugs. As per the report by WHO, 80-85% of world population is using herbal products for management of various diseases as well as these being used in daily life as nutritional supplements. Although, a number of plants derived products had exhibited significant anti-inflammatory effect in preclinical studies, further investigation is required for their molecular mechanism as well safety profile to prove their efficacy in human beings.

**CONCLUSION:** Plants have played a significant role in human health care since ancient times. Traditional plants exert great role in discovery of new drugs. The majority of the human population worldwide is getting affected by inflammation related disorders. It is believed that current analgesia inducing drugs such as opiates and NSAIDs are not useful in all cases, because of their side effects like GIT irritation, liver dysfunction and much more.

There are a number of immuno-suppressing agents that have been developed based on their COX-1 inhibition mechanism, but they cause severe side effects on long term administration. So, selective inhibitors of COX-2 were developed to avoid side effects of COX-1 inhibitors.

However, one of these inhibitors has been reported to increase the risk of myocardial infarction and atherothrombotic events. Thus, it is likely that COX-2 inhibitors will not be suitable for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis. For rheumatoid arthritis currently available drugs are primarily directed towards the control of pain or the inflammation associated with synovitis. A large number of herbal species has been used traditionally or as folk medicines against inflammatory disorders. Many of them have been studied scientifically and proved to be beneficial anti-inflammatory agents. Despite the divergent bioactivities of the plant medicines against various diseases, active components of most plant extracts have not been elucidated thoroughly, due their complex mixtures.

However, the core chemical classes of anti-inflammatory agents from natural sources have been reported to engage a vast range of compounds such as polyphenols, flavonoids, terpenoids, alkaloids, anthraquinones, lignans, polysaccharides, saponins and peptides. From the study done so far, it has been elucidated that flavonoids are major anti-inflammatory agents. Some of them act as phospholipase inhibitors and some have been reported as TNF- $\alpha$  inhibitors in different inflammatory conditions. Biochemical investigations have also shown that flavonoids can inhibit both cyclooxygenase and lipoxygenase pathways of arachidonic metabolism depending upon their chemical structures. Alkaloids in asserted skeletal type based on pyridine ring system have been reported to have striking anti-inflammatory activity, e.g Berberine from *Berberis* is traditional remedy against rheumatism. Terpenoids significantly inhibit the development of chronic joint swelling. Terpenoids may affect different mechanisms relevant to inflammations arising in response to varied etiological factors. However, still many herbal medicines for inflammation and rheumatism have not undergone through scientific investigations. Hence, it is a need of time that all

such herbal medicines should consider for determination of their pharmacological activities, isolation of single entity responsible for anti-inflammatory activity and development of suitable formulation which would be beneficial against inflammatory disorders.

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