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Medicinal plants as a source of anti-inflammatory agent: a review

Sushma Kainsa[1], Reena Bhoria[2]

[1] Deptt of pharmacology, Himalyan college of Pharmacy, Kala-Amb, H.P.

[2]Kurukshetra University, Kurukshetra

Corresponding author- Sushma Kainsa Deptt of pharmacology, Himalyan college of Pharmacy, Kala-Amb, H.P.

Inflammatory diseases including different types of rheumatoid disorders are major worldwide problems. Gastrointestinal side effects are the problem associated with NSAIDs available allopathic drugs. Now a day's world population moves towards herbal remedies for treatment of such ailments. Numbers of plants have been screened for their anti-inflammatory activity. The review deals with the number of plants, their common name, family, extract used and dose showed significant results.

Introduction

More than two thousand years ago, the ancient Greeks used the term *phlogosis* and the Romans *inflammation* to designate the same phenomenon nowadays called inflammation. Since the first description of this phenomenon by Aulus Cornelius Celsus, the inflammation process has been described in many different ways. In the middle ages, inflammation was thought to be the heat accumulation originating in the heart, followed by blood flow, mucous, and bile; this was the humoral inflammation theory. This was then overtaken by the vascular theory in the 18th century. The concept of inflammation has evolved since the discovery of cells in the 19th century. By this time, inflammation was seen to be preceded by cell and tissue injuries, and that vascular changes including leukocyte emigration were secondary events. [1,2] Inflammation is a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes loss of function.[3] During the 1920s, the idea that the vascular system facilitated quick accumulation of great quantities of phagocytes and antibodies was reviewed. The first physical-chemical analysis of inflammation, cell stress and local tissue changes, promoted by an increasing concentration of oxidants and osmotic pressure, were also made at this time.[4] Therefore, modern investigators have considered inflammation a primary event of the host defense system.

Inflammation can be linked wide range of health conditions and overall health. The link between inflammation and illness typically begins with a circumstance that stimulates an over-expression of our body's own healing mechanisms. For example, TNF-α is an important component of the immune system that helps us kill bacteria, certain fungi, viruses and parasites and can even prevent cancer. TNF-α is also an inflammatory cytokine that becomes active during periods of inflammation. When inflammatory molecules are secreted continuously, they distrupt vital checks and balances that keep us healthy. An increase in inflammatory enzymes, for example, stimulates hormones production, specifically estrogen. An increase in estrogen activity has been directly linked to many hormone-dependent cancers such as breast, prostate and ovarian. That's one of many ways inflammation can contribute to cancer.

Anti-inflammatory allopathic drugs and their adverse effects :

The drugs used to reduce inflammation are NSAIDs. These drugs block COX-1 and COX-2 enzyme activity. COX enzymes assist with prostaglandin production. Prostaglandins influence blood flow, digestion and wakefulness. Therefore blocking prostaglandin production can result in a wide range of health problems. NSAIDs and other anti-inflammatory drugs simply mask symptoms-they do not correct the underlying cause or address the long term ramifications of an overactive inflammatory response. These drugs also have numerous side effects. NSAIDs can cause abdominal cramping, gas, Constipation, diarrhea, dizziness, fatigue, headaches, nausea, heartburn, ringing in the ears and many other ailments. It is estimated that upto 60% of individuals taking NSAIDs will experience side effects. The NSAIDs (naproxen) was shown to contribute to a 50% higher risk of heart attack and stroke with long term use. Although NSAIDs are often used to ease joint pain, the reality is that continuous use of them actually causes joints to deteriorate by

inhibiting the repair of joint cartilage. These drugs also destroy the lining of the stomach, causing ulcers severe enough to be deadly. COX-2 inhibitors are used to reduce inflammation but these have been shown to cause heart attacks and sudden cardiac deaths. For a short time these drugs are removed from the market, unfortunately they are back on the market. NSAIDs and COX-2 inhibitor drugs should be avoided whenever possible. These drugs do not safely reduce prolonged inflammation. Merely interfering with the inflammatory response, as with NSAIDs or COX-2 inhibitors carries too much risk of collateral damage in the long run, explains author and naturopathic physician (name: lise alschuler ND). Conventional medicine also falls short in effectively managing or even detecting a chronic inflammatory internal environment that has not yet manifested in acute symptoms of inflammation. Millions of Americans take these drugs every day. Estimates show that more than 100, 000 americans end up in the hospital each year because of ulcers and gastrointestinal bleeding due to NSAIDs use. [3]

Based on these data, in a recent back to nature move, modern man is searching for natural products with medicinal properties, particularly those from plants and bees. [5, 6, 7]

Several plants produce resinous exudates with strong anti-microbial, antiinflammatory and anti-necrotic properties[8] in addition to impermeability provided by populus - a substance from *Populus* sp.[9] Bees collect resin exudates from certain plants and add their secretion, wood fragments, pollen, and wax; this product from bees and plants is called propolis.

All these data have demonstrated the strong and different inhibitory action of several preparations or its isolated constituents on inflammation events. However, its anti-inflammatory effects depend mainly on the administration route and its potency.

In an attempt to establish quality standards for natural products, physical-chemical analysis studies have not been sufficient mainly for the great variety of compounds detected in plants from tropical regions. These standards should depend specifically on their different pharmacological activities.

There are many studies reporting on in *vivo* anti-inflammatory activity of medicinal plants or their derivatives. Based on these data, an evaluation of the anti-inflammatory potential of containing products from several phyto-geographic origins is of major importance for its indication in inflammatory processes. [10]

Plant name (biological name)	**Common name**	**Family**	**Extract used**	**Model**	**Dose /Result**	**Reference**
Solanum nigrum	black night shades	Solanaceae	Methanolic	Carrageenen induced edema	375 mg/kg b.wt, significant	11
Mitragyna parvifolia	Kadam b	Rubiaceae	Ethanolic	Carrageenen induced edema	300 mg/kg b.wt, significant	12
Rivea hypocrateriformis	Phang	Convolvulaceae	Ethanolic	Carrageenen induced edema	200, 400 mg/kg b.wt, significant	13
Cassia	Aragvadha	Caesalpinacea	Aqueous,	Carrageenen induced	250, 500	14

fistula		e	methanolic	edema, cotton pellet induced granuloma	mg/kg b.wt, significant	
Securidaca longipedunculata fres		Polygalaceae	Methanolic, petroleum ether	Topical edema on mouse ear with xylene	5 mg/ear significant	15
Rhododendron arboretum	Ardawal, burans	Ericaceae	Ethanolic, Aqueous, methanolic	Carrageenen, histamine, 5-HT, PGE_2	50, 150 and 600 mg/100g, significant	16
Bauhinia purpurea	Purple camel's foot	Leguminoaceae	Ethanolic,	Carrageenen, 5-HT induced edema	50, 100 mg/kg b.wt, significant	17
spilanthes acmella	Akarkara	Compositae	Aqueous,	Carrageenen, acetic acid induced paw edema	100, 200, 400 mg/kg b.wt, significant	18
sida cordifolia	flannel weed	Malvaceae	Chloroform, methanol, ethanol, butanol, dichloromethane, ethylacetate	Carrageenen, acetic acid induced paw edema	100, 200, mg/kg b.wt, significant	19
argyreia speciosa	Vridha daraka	Convolvulaceae	Methanol	Carrageenen	30, 100, 300 mg/kg b.wt, significant	20
vitex negundo	nirgundi	Verbenaceae	Methanol	Carrageenen	100 mg/kg b.wt, significant	21

Balanites aegyptiaca	Deset date	Zygophyllaceae	Ethanolic, petroleum ether	Carrageenen	300, 600 mg/kg b.wt, significant	22
Bambusa vulgaris	bamboo	Gramineae	Methanolic	Formalin, acetic acid, malondialdehyde, cotton pellet, Carrageenen	100,200, 400 mg/kg b.wt, significant	23
Adenenthera pavonina	Red sandalwood	Mimosoideae	Ethanolic	Carrageenen, castor oil, cotton pellet	250, 500 mg/kg b.wt, significant	24
Holoptelea integrifolia	Kanju	Urticaceae	Aqueous	Carrageenen	250, 500 mg/kg b.wt, significant	25
hypnea musciformis	Wulfen	Hypneaceae		Carrageenen,		26
Sida Rhombifolia	Mahabala	Malvaceae	Methanolic, aqueous	Carrageenen,	100, 500 mg/kg b.wt, significant	27
Silybum Marianum	Milk thistle	Compositae	Methanolic,	Carrageenen, formalin	100 mg/kg b.wt, significant	28
Stereospermum kunthianum	Cham, Sandrine petit	Bignoniaceae,	Aqueous	Carrageenen, leukocyte migration and granuloma air pouch test	100, 200, 400 mg/kg b.wt, significant	29
Lotus Pedunculat	Greater Bird's-foot	Fabaceae	Ethanolic	Carrageene	10, 25, 50	30

us	Trefoil			n	mg/kg, ip	
Ficus bengalensis	Mulberry	Moraceae	Ethanolic, petroleum ether	Carrageenen	300, 600 mg/kg b.wt, significant	31
Barleria cristata	Bluebell Barleria	Acanthaceae	Aqueous	Carrageenen, Acetic acid, prostaglandin inhibiting activity	125, 250, 500 mg/kg b.wt, significant	32
Simplocos spicata (alpha-spinasterol)	Lodhra	Simplocaceae	Aqueous	Carrageenen	10, 20 mg/kg, ip	33
Phyllanthus amarus	Bahupatra	Eubphorbiaceae	Methanolic	Carrageenen, cotton pellet	250mg/kg b.wt, significant	34
Rungia pectinata	Comb Rungia	Acanthaceae	Hydroalcoholic	Carrageenen	200,400, 800 mg/kg b.wt, significant	35
Rungia repens	Creeping Rungia	Acanthaceae	Hydroalcoholic	Carrageenen	200,400, 800 mg/kg b.wt, significant	35
Piper longum	Long papper	Piperaceae	Aqueous methanolic	Carrageenen	0.5 and 1 ml/kg, oral	36
Wattakaka volubilis	Sneeze Wort	Asclepiadaceae	Aqueous methanolic	Carrageenen, cotton pellet, croton oil, freund's adjuvant, arachidonic acid	50,100, 200 mg/kg b.wt, significant	37
Dillenia	Chulta	Dilleniaceae	Methanoli	Carrageenen, acetic	100, 200, 400	38

indica			c	acid	mg/kg b.wt, significant	
Sapindus trifoliatus	Soapnut Shells	Sapindaceae	Aqueous	Carrageenen, histamine, serotonin,zymosan-A, TPA, arachidonic acid, capsacin, 5-lipoxygenase assay,	20, 100 mg/kg b.wt,(po), 1,5mg/kg, topical, Significant	39
Carum copticum	Ajowan	Umbelliferae	Alcoholic, aqueous	Carrageenen, cotton pellet	100mg/kg b.wt, significant	40
Kalanchoe crenata	Dog's liver	Crassulaceae	Hexane, ethylacetate, n-butanol, aqueous	Carrageenen, histamine, serotonin, formalin	300, 600 mg/kg b.wt, significant	41
Plantago major	Greater Plantain	Plantaginaceae	Methanolic	Carrageenen,	5, 10, 20, 25mg/kg, ip	42
Tabernaemontana coronaria	Tagar	Apocynaceae	ethanolic, aqueous	Carrageenen, formalin	100, 250 mg/kg b.wt, significant	43
Gynadropsis pentaphylla	Cleome gynandra	Cleomaceae	Aqueous	Carrageenen	100 mg/kg b.wt, significant	44
Achillea millefolium		Asteraceae	Aqueous	Lipopolysaccharide induced inflammatory responses	25-300 µg/ml	45

The herbal medicines are getting more importance in the treatment of inflammation because of the toxic effect of the current therapy used to treat those inflammation using synthetic drugs. Herbal medicines are less toxic and less costly when compare to synthetic drugs. The various studies on plants will help the industry to produce herbal with less side effect, less costly affordable and more effective in the treatment of inflammation. Finally the phytochemical screening or elucidation of the bioactive compounds from the plants would be effective drug against inflammation.

Anti-inflammatory activity of various herbal formulations :

In the traditional systems of medicine, many polyherbal formulations are being prescribed for inflammatory conditions. Although these preparations have been claimed have anti-inflammatory activity and some of the individual ingredients of the formulations have been shown to have anti-inflammatory activity. Two polyherbal ayurvedic formulations chandraprabha vati and maha yogaraja guggulu in rat paw edema model. chandraprabha vati is a classical polyherbal formulation, which consist of 37 ingredients of plant and mineral origin. Maha yogaraja guggulu is a classical polyherbal formulation consisting of 31 ingredients. To the best of our knowledge, the pharmacological activity of these formulations has been reportd.methanolic extract of these herbal products and carrageen model. [46]

Herbal formulation (DRF/AY/4012) containing Vitex nigundo (nirgundi), Alpinia galangal (rasana patti), merremmia tridentate (prasarini), commiphora mukul, boswellia serrata have anti-inflammatory activity. DRF/AY/4012 showed anti-inflammatory effect against carrageenen or egg albumin induced edema and cotton pellet induced granuloma at dose 400, 800 mg/kg b.wt, significant. [47]

The anti-inflammatory activity of the polyherbal formulation Entox was investigated in rats for acute and subacute models of inflammation using carrageenan induced rat paw edema and cotton pellet granuloma methods respectively at a dose of 300 and 600mg/kg administered orally. The formulation in doses show significant inhibition of paw edema.[48] The polyherbal formulation Entox is constituted of fruits of terminalia chebula (combretaceae), embelica officinalis (euphorbiaceae), punica granatum (punicaceae), terminalia arjuna (combretaceae), rubia cordifolia (rubiaceae), withania somnifera (solanaceae), tinospora cordifolia (menisoermaceae) and curcuma longa (zingiberaceae).[48]

Fifteen plants were tested: Alangium salviifolium (Linn.f.) Wang. (seed), Albizia lebbeck (Linn.) Benth. (leaf), Aloe vera Linn. (juice), Alpinia zerumbet (Pers.) Burtt et R.M. Smith = A. speciosa (Wendl.) K.Schum. (root), Calophyllum inophyllum Linn. (seed), Cassia fistula Linn. (leaf), Celastrus paniculatus Willd. (whole plant), Erythrina variegata Linn. = E. indica Lam. (leaf), Evolvulus alsinoides (Linn.) Linn. (whole plant), Hemidesmus indicus (Linn.) R.Br. (whole plant), Hibiscus rosa-sinensis Linn. (flower), Myristica fragrans Houtt. (fruit), Sida acuta Burm.f. (whole plant), Solanum virginianum Linn. = S. xanthocarpum Schrad. et Wendl. (leaf), Vitex negundo Linn.(leaf); the anti-inflammatory activity was assayed in male albino rats, using the carrageenin-induced hind paw oedema method; the air dried powder of the plant materials was given orally at a dose of 1 gm/kg body weight at 24 hours and one hour prior to the carrageenin injection (suspended in 2\% gum acacia solution); the animals in the control group received orally 2\% gum acacia solution; Myristica fragrans, Celastrus paniculatus and Albizia lebbeck exerted a maximum anti-inflammatory activity in the second phase of the carrageenin inflammation, Solanum virginianum, Hibiscus rosa-sinensis and Alangium salviifolium in the first phase; the remaining plants were not effective.[49]

Anti-inflammatory experimental models :

Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms:

1. An acute, transient phase, characterized by local vasodilatation and increased capillary permeability
2. A subacute phase, characterized by infiltration of leukocytes and phagocytic cells
3. A chronic proliferative phase, in which tissue degeneration and fibrosis occur.

According to these phases, pharmacological methods have been developed. The various methods are given below.

1. UV-erythema in guinea pigs
2. Vascular permeability

3. Oxazolone-induced ear edema in mice
4. Croton-oil ear edema in mice and rats, paw edema in rats (with various modifications and various irritants)
5. Pleuristy tests
6. Granuloma pouch technique (with various modifications and various irritants) like cotton wool granuloma, glass rod granuloma, PVC sponge granuloma etc.
7. Paw edema (with various modifications and various irritants) like:

i) 0.05 ml undiluted fresh egg white [50]

ii) 0.1 ml of1% ovalalbumin solution [51]

iii) 0.1 ml of1% formalin [51]

iv) 0.1 ml of 0.2% carrageenam solution [52]

v) 0.1 ml of 1% carrageenam solution plus 100ng PGE_2 or PGI_2 [53]

vi) 0.1 ml of 1-3% dextran solution [51]

vii) 0.1 ml of 2.5% brewer,s yeast powder suspension etc.[54]

Conclusions

It is interesting to note that although a large number of plants have been studied and these investigations suggest selective anti-inflammatory activity of the said plants, a large number of these studies have not been pursued further upto the stage of clinical trials. This may be doing the fact that most of the research works in this field are purely academically oriented and there are no industrial supports behind these projects.

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