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Zuli Shingala
Faculty of Pharmacy,
The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

Bhavik Chauhan
Faculty of Pharmacy,
The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

Jankhana Baraiya
Faculty of Pharmacy,
The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

Corresponding Author:
Bhavik Chauhan
Faculty of Pharmacy,
The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

A review on medicinal plants as a source of anti-inflammatory agents

Zuli Shingala, Bhavik Chauhan and Jankhana Baraiya

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Abstract
Natural plants are one of the most important sources of medicines, since ancient's time plants have been used to treat wide range of diseases. Nowadays, many drugs have been developed from traditional medicinal plants. Inflammation is body's immune response to any kind of injury. There are four primary indicators of inflammation: redness, heat or warmness, pain and swelling. This report constitutes an updated review of some medicinal plants and their marker compound having anti-inflammatory activity with in-vitro and *in-vivo* study models for assessing anti-inflammatory activity of medicinal plant, plant extract or pure compound.

Keywords: inflammation, medicinal plants, anti-inflammatory activity, *in-vivo* models, marker compound

Introduction
Inflammation is a nonspecific, defensive response of the body to tissue damage. Among the conditions that may produce inflammation are pathogens, abrasions, chemical irritations, distortion or disturbances of cells, and extreme temperatures. The four characteristic signs and symptoms of inflammation are redness, pain, heat, and swelling (Gerard J. Tortora, 2009) [20].
Inflammatory response has three basic stages:
1. Vasodilation and increased permeability of blood vessels
2. Emigration (movement) of phagocytes from the blood into interstitial fluid
3. Tissue repair (Gerard J. Tortora, 2009) [20].

These are the substances which are contributing into the vasodilation, increased permeability and other aspects of inflammatory response- Histamine, Kinins, Prostaglandins (PGs), Leukotrienes (LT) and different components of complement system. Two main types of inflammation are acute inflammation, associated with increased vascular permeability, capillary infiltration and emigration of leukocytes. Chronic inflammation, associated with infiltration of mononuclear immune cells, macrophasaes, monocytes, neutrophils, fibroblast activation, proliferation and fibrosis (S. Kumar, 2013) [69].
Adverse effects of long term using conventional anti-inflammatory drugs:
Many steroidal and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are available in the market. Among them NSAIDs are most widely used and most prescribed anti-inflammatory agents, but the use of these agents is harmful. Since they increase risk of Gastrointestinal (GI) and Cardiovascular complications compared with non-NSAIDs patients (Carlo S, 2010). NSAIDs acts by mechanism of inhibition prostaglandins, which are responsible for protection of gastric mucosa. Acidic properties of NSAIDs initiate gastric mucosal damage.

Anti-Inflammatory Herbal Drugs
Herbal medicine is one of the important aspects of complementary medicines. Herbal drugs have been used for prolong period of time for prevention as well as treatment of diseases including inflammation. Many people are now using herbal remedies for their day to day life as phytonutrients of nutraceuticals, because of those herbal drugs and phytonutrients or nutraceuticals continues to expand rapidly across the world. According to World Health Organisation (WHO) three quarters of people rely on traditional and plant based medicine for their day to day healthcare. Herbal drugs are now in more demand, as they have lesser side effects than the synthetic one. There are many medicinal plants available, which possessesanti-inflammatory properties, some of them are used since ancient's time and also some of them mentioned in Ayurveda and Traditional Chinese medicines.

Some medicinal plants with anti-inflammatory activity listed below in Table no.1 with their biological name, common name, plant part used as anti-inflammatory and chemical constituent from particular plant part responsible for anti-inflammatory activity.

Table 1: Medicinal plants having anti-inflammatory potential

Sr. No.	Plant name (Biological source)	Common name	Plant part used	Type of extract	Marker compound	References
1.	*Aegle marmelos*	Bael	Roots, fruits	Aqueous, Ethyl acetate	Marmelosin	(Pynam Hasitha, 2018) [58] (Jyoti M. Benni, 2011) [32]
2.	*Albizia lebbeck*	Shirish	Leaves, bark	Ethanolic chloroform, ether	Catechin	(N. Prakash Babu, 2009) [50] (Girish Gulab Meshram, 2016) [21] (S. C. Verma, 2013) [68]
3.	*Allium cepa*	Onion	Leaves and bulb	Methanolic	Quercetin	(Tatiane Teixeira Oliveira, 2015) [80]
4.	*Allium sativum*	Garlic	Leavse and cloves	Garlic clove powder	Allin, Allicin	(M.K. Jayanthi, 2011) [32] (Gaber El-Saber Batiha, 2020) [19]
5.	*Aralia cachemirica*	Kashmir spikenard	Whole plant	Hydroalcoholic extract (70% alcohol)	Octadec-6-enoic acid	(Neelofar Majid, 2021) [51]
6.	*Azadirachta indica*	Neem	Leaves	Methanolic extract	Azadirchtin, Nimbin	(Marc Schumacher, 2011) [44]
7.	*Borago officinalis*	Borage	Seed oil	Seed oil	Gama-lenoleic acid	(Amitava, 2019) [3]
8.	*Boswellia serrata*	Salai guggul	Gum resin	Hydroalcoholic	α–boswellic acid β–boswellic acid	(Venkata Krishnaraju Alluri, 2020) [84]
9.	*Bryophyllum pinnatum*	Goethe plant	Leaves	Ethanol extract	Rutin, Luteolin	(Lucas A. Chibli, 2014) [37]
10.	*Butea monosperma*	Flame of the forest tree, Palash	Flowers	Methanol extract	Butrin, Butein	(V.M. Shahavi, 2008) [82] (Mishra, 2016) [47]
11.	*Camellia sinesis*	Green tea	Leaves	Ehtanol extract	Catechin, Epigallocatechin	(Arina Novilla, 2017) [5]
12.	*Capsicum annum*	Chilli	Fruits	Ethyl acetate extract	Capsaicin	(Jolayemi AT, 2013) [30]
13.	*Cassia fistula*	Golden shower tree	Flowers	Isolated rhein	Rhein	(Paulrayer Antonisamy, 2019) [54]
14.	*Cinnamomum camphora*	Camphor tree	Leaves	Methanolic extract	Camphor, Linalool, Cineole	(Hye Ja Lee, 2006) [22]
15.	*Commiphora mukul*	Guggul	Gum resin	Hydroalcoholic	Guggulsterone	(Jayaraj A. Francis, 2004) [26]
16.	*Curcuma longa*	Turmeric	Rhizomes	Dichloromethane	Curcumin	(Andrew M. Anderson, 2000) [4] (Mou-Tuan Huang, 1991) [49]
17.	*Elaeagnus angustifolia*	Russian olive, Silverberry	Fruits	Methanol extract	Catechin, Epicatechin	(Rafie Hamidpour, 2017) [60] (Manijeh Motevalian, 2017) [43]
18.	*Eucalyptus globulus*	Nilgiri	Oil from leaves	Oil	1,8-cineole	(Jeane silva, 2003) [27]
19.	*Garcinia cambogia*	Malabar tamarind	Fruits	Ethanolis extract	Hydrocitric acid (HCA)	(Ramalingam Sripradha, 2015) [63]
20.	*Gaultheria procumbens*	American Wintergreen	Leaves and oil	Hydroalcoholic extract	Quercetin, Catechin	(Piotr Michel, 2014) [55]
21.	*Zingiber officinalis*	Ginger, Adrakh	Rhizomes, Oil	Essential oil	Gingerol	(Janet L. Funk, 2016) [25]
22.	*Glycyrrhiza glabra*	Licorice	Roots	Ethanol	Glycyrrhizin	(P. Thiyagarajan, 2011) [53]
23.	*Harpagophytum procumbens*	Devil's claw	Roots	Water	Harpagoside	(Marie-Claire Lanhers, 1992) [45]
24.	*Hibiscus tilliaceus*	Bhola	Leaves and Bark	Aqueous Methanol (90%)	Tiliaceic acid A α-Glucosidase	(Le Ba Vinh, 2019) [35] (S. M. Abdul-Awal, 2016) [71]
25.	*Linum usitatissimum*	Flaxseed, Linseed	Seeds	Oil from seeds	α-Linolenic acid	(Kaithwas G, 2010) [33]
26.	*Madhuca longifolia*	Mahudo	Seeds Leaves	Oil from seeds Aqueous extract of leaves	Oleic acid	(Jerine Peter Simon, 2018) [28] (Ramchandra D. Gaikwad, 2009) [65]
27.	*Mentha piperita*	Pudina, Mint leaves	Leaves	Ethanolic extract	Menthol	(YuXian Li, 2017) [89]
28.	*Moringa oleifera*	Drumstick plant	Leaves, Seeds, Roots	Ethanolic, Hydroalcoholic extract	β-carotene,	(Yong-Bing Xu, 2019) [88] (Mohsen Minaiyan, 2014) [48]
29.	*Ocimum sanctum*	Tulsi	Leaves	Essential oil from leaves	Eugenol	(Thamilvaani Manaharan, 2014) [81]
30.	*Oenothera biennis*	Evening primerose	Aerial parts	Oil, Methanolic extract	Linoleic acid	(Magdalena Timoszuk, 2018) [39] (Sebastian Granica, 2013) [79]
31.	*Olea europea*	Olive	Fruits	Methanolic extract	Oleuropein	(Shamim S, 2014) [74]
32.	*Panax ginseng*	Chinese ginseng	Roots, Calyx	Ethanol, Water-Methanol	Protopanaxadiol protopanaxatriol	(Sang Yun Han, 2018) [72] (Evelyn Saba, 2018) [14]
33.	*Persea americana*	Avocado	Fruit, Seed	Lipid extracted from fruits and seeds	Palmitic acid Oleic acid	(Maha I. Alkhalaf, 2019) [40]

					Linoleic acid	
34.	*Pinus roxburghii*	Chir pine	Bark	Alcoholic extract	α-pinene β-pinene	(Dhirender Kaushik, 2012) [9]
35.	*Pluchea indica*	Camphorweed	Leaves Roots	Ethanol Chloform	Quercetin Chlorogenic acid	(T. Sen, 1991) [79] (Doungnapa Buapool, 2013) [10]
36.	*Pluchea lanceolata*	Rasna	Aerial parts	Ethanol extract	Quercetin Quercitrin	(Pooja Srivastava, 2012) [56] (Vandita S, 1990) [83]
37.	*Podophyllum emodi*	Mayapple	Roots and rhizomes	Isolated podophyllotoxin derivatives	Podophyllotoxin	(Estela Guerrero, 2014) [13]
38.	*Ribes nigrum*	Blackcurrant	Berries Buds Leaves	Acetone/water/acetic acid(70:28:2) Ethanol extract	Cyanidin-3-O-glucoside Delphinidin-3-O-glucoside Concise Reviews & Hypotheses in Food Science Blackcurrants (Ribes nigrum): A review . . . Cyanidin 3-O-glucosi Concise Reviews & Hypotheses in Food Science Blackcurrants (Ribes nigrum): A review . . . Cyanidin 3-O-glucosid	(Jessica Tabart, 2012) [29] (Declume, 2002) [8] (Regina E. Cortez, 2019) [67]
39.	*Ricinus coumaris*	Castor bean Castor oil plant	Roots Leaves Seed oil	Methanol, Acetone, Hexane	Ricioleic acid Linoleic acid Kaempferol-3-O-beta-D-rutinoside	(Raju Ilavarasan, 2006) [62] (Vhutshilo Nemudzivhadi, 2014) [85] (Subramaniyan, 2020) [78]
40.	*Rosa canina*	Dog rose	Rose hip	Hydroalcoholic extract	Linoleic acid Alpha linoleic acid	(Francesca Lattanzio, 2011) [17] (Erik Larsen, 2003) [12]
41.	*Rosmarinus officinalis*	Rosemary	Aerial parts Essential oil	Ethanolic extract	Caffeic acid Rosmarinic acid Carnosol	(Raphaelle Sousa Borges, 2019) [66] (Jucelia Pizzetti Beninca, 2011) [31] (Mahboobeh Ghasemzadeh Rahbardar, 2017) [41]
42.	*Salix alba*	Willow	Bark	Ethanol extract	Salicin	(Edson Luis Maistro, 2019) [11]
43.	*Salvia officinalis*	Sage	Oil from aerial parts	Chloform extract	Borneol Camphor Caryophyllene Cineole	(Ahmad Ghorbani, 2017) [2]
44.	*Sesamum indicum*	Sesame	Oil from seeds	Oil	Sesamol Ferulic acid	(Pragney Deme, 2018) [57] (Marzieh Beigom Bigdeli Shamloo, 2015) [46]
45.	*Solanum xanthocarpum*	Kantakari	Fruits	Aqueous extract	Campesterol Chlorogenic acid	(Raman Preet, 2018) [64] (Shraddha Anwikar, 2010) [76]
46.	*Symphytum officinale*	Comfrey	Leaves Roots	Ethanol extract	Allantoin Rosmarinic acid	(Jacqueline Seigner, 2019) [23]
47.	*Tinospora cordifolia*	Guduchi Galo	Whole plant	Ethanolic, Aqueous extract	β-sitosterol sigmasterol	(Sheena Philip, 2018) [75] (Niraj S. Ghatpande, 2019) [52] (Biswajyoti Patgiri, 2014) [6]
48.	*Thymus vulgaris*	Thyme	Essential oil	Essential oil	Thymol, Carvacrol	(Fernanda Carolina Fachini-Queiroz, 2012) [16] (Ligia Salgueiro, 2019) [36] (A. Ocana and G. Reglero, 2012) [1]
49.	*Trigonella foenum-graecum*	Fenugreek	Seeds	Petroleum Ether Extract	Linolenic acid Galactomannan	(G. Sindhu, 2012) [18] (Kilambi Pundarikakshudu, 2016) [34]
50.	*Vitex negundo*	Nirgundi	Leaves	Methanol, Petroleum Ether extract	Caryophyllene epoxide	(Jaganathan Subramani, 2009) [24] (S. L. Khokra, 2008) [70] (R. R. Kulkarni, 2008) [59]
51.	*Withania somnifera*	Ashwagandha	Roots	Aqueous extract	Withanolides	(Singh, 2014) [77] (Y. P. Sahni & D. N. Srivastava, 1993) [87] (Mahmood Ahmad Khan, 2019) [42]

Screening of Anti-Inflammatory Activity

The main mechanism of action of Anti-inflammatory drugs is the inhibition of Cyclooxygenase (abbreviated as COX) enzyme which are responsible for the conversion of Arachidonic acid into Prostaglandins, which are responsible for inflammation. In mammalian cells, Cyclooxygenase enzyme exist in two isoforms COX-1 and COX-2. These COX enzymes are important target for design and development of novel anti-inflammatory agents as they play a crucial proinflammatory role (Rafik U. Shaikh, 2016) [61]. *In-vivo* and In-vitro models are vailable for screening of anti-inflammatory activity. In *In-vivo* method for evaluation there

is inducing chemical which induce inflammation in particular animal in particular part, then we treat that inflammation part to study anti-inflammatory actions of our ani-inflammatory drugs. *In-vivo* animal models for anti-inflammatory study are listed below in table.2.

Table 2: *In-vivo* animal models for screening of anti-inflammatory activity (Rafik U. Shaikh, 2016) [61], (Fabian Ifeanyi Eze, 2019) [15], (Vogel, 2002) [86], (Jeane silva, 2003) [27], (V.M. Shahavi, 2008) [82],

Sr. no.	Model	Inducing agents	Animals
1.	Paw edema	Carrageenan Brewers yest Formaldehyde Dextran Egg albumin Bradykinin Zymosan Serotonin Arachidonic acid Phorbol myristate acetate (PMA)	Sprague-Dawley Rats (100-150 gm)
2.	Ear edema	Croton oil Oxazolone	Mice (22 gm) Sprague-Dawley rats (70 gm)
3.	UV-erythema	UV light exposure	Guinea pigs (350 gm)
4.	Cotton wool granuloma	Sterilized cotton wool placed in scapular region	Rats (150-200 gm)
5.	Pleurisy test	2% carrageenan solution in pleural cavity	Sprague-Dawley rats (220-260 gm)
6.	Vascular pemeability	1% Evan's solution (i.v.)	Male Sprague-Dawley rats (160-200 gm)
7.	Granuloma pouch technique	Injection of 20 ml air in the middle of the dorsal skin followed by 1% croton or sesame oil	Male or female Sprague-Dawley rats (150-200 gm)

Conclusion

Medicinal plants are one of the most important aspects of complementary medicines. There are many studies available which claims the role of medicinal plants as anti-inflammatory activity. We have compiled some medicinal plants and their anti-inflammatory effects have been evaluated in clinical and experimental studies. It is known that synthetic anti-inflammatory drugs such as Opioids and NSAIDs are not suitable in all cases because of their side effects, so to overcome these side effects new medicines are necessary, and in plant derived natural products there is so many phytoconstituents are present having anti-inflammatory activity with lesser side effects. We can definitely consider plant derived products as a source of anti-inflammatory drugs and to study their anti-inflammatory activity there is number of screening methods are available, among them *In-vivo* screening methods are listed in this paper.

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