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# Reveiw Article

# Potential anti-inflammatory bioactives from medicinal plants of Western Ghats, India

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ABSTRACT: Natural products have long been a thriving source for the discovery of new drugs because of their chemical diversity. With increased use of herbal remedies, traditionally used medicinal plants are receiving increased attention from scientific and pharmaceutical communities. The newer work on medicinal plants is mostly the rediscovery of traditional effects at cellular and molecular levels. Development of standardized, safe and effective herbal formulations as multi-target therapeutics and prophylaxis could be a tenable approach for the future. Hundreds of plant metabolites are reported to have many pharmacological activities although most of these reports are of academic interest and very few find entry at clinical trials. Compilation of the information would help promote wider acceptance and use of these plant based drugs in main stream of medicine. The present review is directed towards compilation of the pharmacological attributes of medicinal plants of Western Ghats, India in the drug discovery and development process as it could be a driving force to identify lead molecules providing an attractive strategy for novel and improved therapeutics.

KEY WORDS: Herbal medicine, Plant bioactives, LOX, COX, iNOS

## INTRODUCTION

The pharmaceutical industry currently faces unprecedented drug discovery challenges as research and development is becoming more expensive and the number of new drugs entering the market continues to remain low. The average cost of developing a new drug has risen to US $1.3 billion. Due to the toxic and adverse side effects of synthetic drugs traditional herbal medicine has the potential as a source of new bioactive molecules.[1]

In India, Western Ghats is a major biodiversity hotspot along the Western coast covering an area of 159,000 sq km. It is a niche for 4500-15,000 plant species.[2] Several of them are endemic to this region and many of them have been identified to have potential medicinal value. Due to over exploitation several species are also categorized as threatened.[3,4] Plants like lemon grass (*Cymbopogon Citratus*), patchouli (*Pogostemon cablin*), wild yam (*Dioscorea* spp.) and the lemon grass (*Vetiver* spp.) originated in this area. *Rauvolfia serpentine, Saraca asoca*, *Gymnema sylvestre*, *Gloriosa superb*, *Strycnos nux-vomica, Myristica malabarica, Garcinia indica, Utleria salicifolia*, *Coscinium fenestratum* and *Vateria indica* are included in the International Union for Conservation of Nature (IUCN) Red List.

Documentation of traditional medicinal plants and remedies is becoming increasingly important. The key efforts to document the diversity of Western Ghats include threatened endemic tree species of the Western Ghats;[5,6] Flora of Karnataka;[7] Sasya Sahyadri released by ATREE;[8] SAHYADRI: Western Ghats Biodiversity Information System (database of Western Ghats flora and Fauna and Critical Ecosystem Partnership Funded Ecosystem profile of Western Ghats and Sri Lanka Biodiversity hotspot (www.cepf.net; cepf@conservation.org). In this article the medicinal plants with anti-inflammatory activity has been compiled.

## INFLAMMATION

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,

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swollen joint that is warm to touch, joint pain, its stiffness and loss of joint function. Inflammation is either acute or chronic. Under specific circumstance, it could turn into a chronic state and subsequently become a causative factor in the pathogenesis. Inflammation is a self-defense reaction in its first phase, hence regarded as the main therapeutic target and often, the best choice to treat the disease and alleviate the symptoms.

### Acute inflammation

Acute inflammation may be an initial response of the body to harmful stimuli. An increased movement of plasma and leukocytes, especially granulocytes from the blood into the injured tissues is observed. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system and various cells within the injured tissue.

Mast cells in the tissues, the key players of inflammation, are loaded with mediators of inflammatory response. When their toll-like receptors interact with pathogen associated molecular patterns these cells discharge the chemical mediators recruiting white blood cells to the site of inflammation. These include neutrophils, monocytes (that become macrophages when they leave the blood and enter the tissue), antigen-presenting dendritic cells, lymphocytes (B cells and T cells leading to an adaptive immune response) and natural killer cells.

The Inflammatory response stimulates release of TNF-α from stimulated mast cells[9]. Other cells involved in inflammation have receptors for TNF-α.[10] They are activated by the binding of TNF-α. Activation of these recruited cells produces their own mediators of inflammation. This positive feedback quickly amplifies the response. Phagocytes (macrophages and neutrophils) produce reactive oxygen species (ROS). Macrophages and activated platelets release interleukin (IL)-1, a cytokine. IL-1 causes fever by stimulating the release of prostaglandins (PGs), which act on the temperature control center of the hypothalamus[11]. IL-1 is synthesized from a larger precursor that is cleaved by a caspase-1. Caspase-1 is part of two (or more) multi-protein complexes in the cytosol of macrophages and neutrophils that are called inflammasomes[12]. Inflammasomes are activated by several different products produced by invading bacteria that interact with toll-like receptors (TLRs) thus providing a link between the innate immune system and inflammation. Chemical mediators such as histamine and bradykinin induce the production of PGs and leukotrienes with a role to potentiate the plasma exudation[13]. These potent mediators of inflammation are derivatives of arachidonic acid (AA), a 20-carbon unsaturated fatty acid produced from membrane phospholipids.

Arachidonic acid released from membrane phospholipids is catalyzed by phospholipase A2 (PLA2) esterified at the second carbon in the glycerol backbone. It is subsequently metabolized by COX and LOX. The COX-1 is constitutively expressed and produces PGs involved in basic housekeeping for normal functioning of the body. The COX-2 is inducible and expressed in response to cytokines, mitogens and endotoxins.[14]

### Chronic Inflammation

In chronic inflammation, the inflammatory response is out of proportion resulting in damage to the body. The different types of allergies and many autoimmune diseases viz, asthma, rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus are a few examples.

### Cell signaling network

The cell signaling network that mediates the inflammatory response is very well documented. Lipopolysaccharide (LPS) initially bind to the LPS-binding protein in the plasma. It can also interact with transmembrane signal transduction receptor TLR-4[15]. Multiple mammalian receptors for LPS have been identified such as $\beta_2$-integrins CD11/CD18, the macrophage scavenger receptor for acetylated LDL, L-selectin and the most important CD14. LPS activates a number of intracellular signaling pathways, including IκB kinase-nuclear factor κB (NFκB) pathway and three mitogen-activated protein kinase pathways[16,17]. These pathways phosphorylate and activate various transcription factors, including NFκB/Rel proteins, activator protein 1 (AP-1) and nuclear factor-IL-6 (NF-IL6). This initiates a rapid gene induction and expression of inflammatory mediators as discussed above[18]. Inflammatory marker enzymes such inducible nitric oxide synthase (iNOS), cyclooxygenases (COX) -1, -2; 5-lipoxygenase (LOX) and matrix metalloproteinase (MMP)-9 and adhesion molecules are expressed[19].

### Animal models

Inflammation research involves a number of experimental models that can be broadly classified into two types: acute inflammatory models and chronic inflammatory models.[20] Acute models are designed to test drugs modulating erythema, changes in vascular permeability, leukocyte migration, measurement of local pain, local analgesic action and rat paw edema.[21] Chronic models are designed to find drugs modulating disease process induced by sponge, pellet implants, granuloma pouches and adjuvant induced arthritis.[20]

## ANTI-INFLAMMATORY ACTIVITY

### NSAIDS

Inflammation is currently regularly treated by non-steroidal anti-inflammatory drugs (NSAIDS). The NSAIDs achieve their effect by blocking the activity of COX involved in

blocking PGs secretion resulting in reduced fever and pain of inflammation[22]. However, prolonged use of NSAIDS results in side effect viz., a tendency to develop side effects due to inhibition of constitutive COX-1 as well COX-2 induced during inflammation. Specific COX-2 inhibitors viz., rofecoxib and celecoxib have been also used as drugs. Unfortunately these drugs cause increased risk of blood clot resulting in heart attacks and strokes as they do not block the synthesis of thromboxane $A_2$ by platelets which contain only COX-1[23].

## Natural products

Phytomedicine could be in the form of crude preparations (extracts, tinctures, essential oils) containing a wide variety of compounds or could be pure molecules with a strong and specific activity. Identification of chemical compounds and the molecular targets of these compounds helps validate the use of these medicines. Plant extracts or their constituents are responsible for the protective effect with powerful antioxidant capacity and protective properties.

## Plant-derived bioactives

Chemical compounds from plants have been screened for their capacity to modulate the expression of pro-inflammatory signals thereby assessing their capacity as anti-inflammatory agents. Polyphenols, flavonoids, terpenes, quinines, catechins, alkaloids and antioxidants are phytochemical compounds targeted for anti-inflammatory activity. Potent anti-inflammatory plant compounds include guggulsterone [4,17(20)-pregnadiene-3,16-dione], a plant sterol from *Commiphora mukul*,[24,25] boswellic acid, a pentacyclic triterpenic acid and its derivatives viz., acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid,[26,27] curcumin from turmeric, resveratrol from red grape seeds, genistein from Soy, quercetin (onions), silymarin (artichoke), withanolides (*Ashwagandha*), tea polyphenols, cranberries and peanuts[25]. The mechanism of anti-inflammatory activity for these bioactives was identified by inhibition of NF-κB activation and down-regulating the expression of inflammatory marker enzymes viz., COX-2, 5-LOX and MMP-9[25].

Vast resources of medicinal plants with anti-inflammatory activities are reported needs further attention. The aim of this review is to compile and present this information on medicinal plants (Table 1) and report the pharmacological targets in inflammatory reaction (Figure 1) for the bioactives (Figure 2) reported from them.

## Promising plant sources of anti-inflammatory bioactives

***Abrus precatorius* L:** Abruquinone A is a naturally occurring isoflavoquinone. It was originally isolated from the roots of *A. precatorius* (family Leguminosae).[28] The roots of *A. precatorius* have been used as a folk medicine for dieresis, treatment of fever, sore throat, bronchitis and hepatitis[29]. The anti-inflammatory effect of Abruquinone A was found to be partly via prevention of vascular permeability and inhibition of platelet aggregation[30]. It could influence the release of chemical mediators from mast cells *in vitro* and to suppress plasma extravasation caused by these chemical mediators *in vivo*.[30]

***Acacia catechu* L:** *A. catechu* (known as *grar*) is used as a cure for rabies in traditional medicine in Asia. This activity was attributed to catechin, a natural flavonoid isolated from *A. catechu*[31]. It was tested for COX-2 and 5-LOX inhibition via enzyme, cellular, and *in vivo* models. Catechin inhibited both ovine COX-1 and COX-2 at $IC_{50}$ of 15μg/mL[32]. In *in vivo* studies, human osteosarcoma cells expressing COX-2 showed decreased production of $PGE_2$[31]. It could also inhibit leukotriene production in human cell lines viz., immortalized THP-1 monocyte and HT-29 colorectal adenocarcinoma.[31] *A. catechu* flavans (epicatechin, quercetin, catechin) with reported anti-inflammatory activity had dual specificity for inhibiting COX-2 and 5-LOX experimented in air pouch model created on the back of Balb/C mice.[33,34]

***Alstonia scholaris* (L.):** Three main alkaloids, picrinine, vallesamine and scholaricine from *A. scholaris* leaf produced anti-inflammatory and analgesic effect. In *in vitro* tests, alkaloids inhibited inflammatory mediators viz., COX-1, COX-2 and 5-LOX[35]. Further indole alkaloids, 16-formyl-5α-methoxystrictamine, picralinal, and tubotaiwine isolated from this plant exhibited COX-2/5-LOX dual inhibition. They reduced inflammatory symptoms in xylene-induced ear edema and carrageenan-induced air pouch inflammatory model in mice.[36]

***Andrographis paniculata* Wall:** *A. paniculata* (commonly known as Kaalmegha) was reported to exhibit analgesic, anti-pyretic and anti-inflammatory effect[37]. Bioactivity-guided chromatographic fractionation was applied to identify bioactives with anti-inflammatory activity. Eight pure compounds viz., 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8-dimethoxyflavanone, a mix of beta-sitosterol and stigmasterol, ergosterol peroxide, 14-deoxy-14,15-dehydroandrographolide, a new compound, 19-O-acetyl-14-deoxy-11,12-didehydroandrographolide, 14-deoxy-11,12-didehydroandrographolide and andrographolide were identified[38]. They were analyzed for anti-inflammatory activity in *in vitro* studies using RAW 264.7 (Mouse leukaemic monocyte macrophage cell line) stimulated for inflammatory response by LPS/interferon (IFN)-γ[39]. A significant decrease in the levels of NFκB mRNA by compounds 5, 11, 12, decreased levels of tumor necrosis factor (TNF)-α, IL-6, MIP-2 and nitric oxide (NO) by all the compounds was recorded.[40,41]

***Artocarpus heterophyllus* Lam:** *A. heterophyllus* is a large evergreen tree cultivated throughout Southeast Asia for its

**Table 1: Therapeutic targets for phytochemicals with anti-inflammatory activity isolated from medicinal plants**

| Sl. No | Plant name | Phytochemical isolated | Therapeutic targets |
|---|---|---|---|
| 1. | *Abrus precatorius* Linn.<br>**Family -** Fabaceae<br>**CN/*AN*** -Crab's eye, *Gunjaa* | Abruquinone A | ↓plasma extravasation [30] |
| 2. | *Acacia catechu* (Linn. f.)Willd<br>**Family -** Mimosaceae<br>**CN/*AN*** - Catechu, *Khadira* | Epicatechin, quercetin, catechin | ↓COX-2, ↓LOX [33, 34] |
| 3. | *Aegle marmelos* (L.) Corr.<br>**Family** – Rutaceae<br>**CN/*AN*** - Bael tree, *Bilva* | Petroleum ether fraction | ↓NFκB, ↓AP-1, ↓CREB [72] |
| 4. | *Aglaia elaeagnoidea* Benth.*<br>**Synonyms** - *Aglaia roxburghiana* Miq. Hiern Benth.;<br>**Family -** Meliaceae<br>**CN/*AN*** – *Priyangu* | Roxburghiadiol A and B | ↓COX-2 [78] |
| 5. | *Alstonia scholaris* (L.) R. Br.<br>**Synonym-** *Echites scholaris* (Linn.).<br>**Family**- Apocynaceae<br>**CN/*AN*** - Devil's tree, *Saptaparna* | Picrinine, vallesamine, scholaricine, 16-formyl-5α-methoxystrictamine, picracinal, tubotaiwine | ↓COX-1, ↓COX-2, ↓ 5-LOX [35,36] |
| 6. | *Andrographis paniculata* Wall.<br>**Synonyms -** *Justicia latebrosa* Russ.,<br>**Family -** Acanthaceae<br>**CN/*AN*** - Creat, *Kaalmegha* | 5-hydroxy-7,8-dimethoxyflavone (**1**), 5-hydroxy-7,8-dimethoxyflavanone (**2**), beta-sitosterol (**3a**) and stigmasterol (**3b**), ergosterol peroxide (**4**), 14-deoxy-14,15-dehydroandrographolide (**5**), a new compound, 19-O-acetyl-14-deoxy-11,12-didehydroandrographolide (**6a**); 14 – deoxy - 11,12-didehydroandrographolide (**7**) and andrographolide (**8**) | Compounds **1-8** - ↓TNF α, ↓macrophage inflammatory protein (MIP)–2, ↓NO and ↓IL-6;<br>Compounds **5**, **11**, **12** - ↓NFκB [40, 41] |
| 7. | ***Artocarpus hirsutus*** Lam.*<br>**Synonym -** *Artocarpus hirsuta* Lam.<br>**Family** – Moraceae | Artocarpesin | ↓iNOS, ↓NO, ↓COX-2 [43, 44, 45] |
| 8. | *Bacopa monnieri* (L.) Penn.<br>**Synonyms-** *Gratiola monnieria* L. *Herpestes monnieria* (L.) Kunth<br>**Family-** Scrophulariaceae<br>**CN/*AN*** - Thyme-leaved Gratiola, *Braahmi* | Methanol extract | ↓COX-2, ↓5-LOX, ↓15-LOX ↓TNF-α [79] |
| 9. | *Bauhinia variegata* Linn.<br>**Synonyms**- *Phanera variegata* (L.) Benth.;<br>**Family –** Caesalpiniaceae<br>**CN/*AN*** -Mountain Ebony, *Kaanchanaara* | Ombuin, kaempferol 3-*O*-β-D-glucopyranoside, isorhamnetin 3-*O*-β-D-glucopyranoside | ↓LPS, ↓IFN-γ, ↓NO, ↓cytokines [46] |
| 10. | *Berberis tinctoria* Lesch.<br>**Family** -Berberidaceae | Berberine | ↓NFκB, ↓IL-1, ↓IL-8, ↓COX-2; ↓androgenic platelet α -2 receptor [80] |
| 11. | *Biophytum sensitivum* DC.<br>**Synonym** – *Oxalis sensitiva* Linn.<br>**Family** – Oxalidaceae<br>**CN/*AN*** -*Lajjaalu* | Amentoflavone | ↓COX-1, ↓COX-2, ↓NFκB [48] |

*Continued...*

**Table 1: *Continued***

| Sl. No | Plant name | Phytochemical isolated | Therapeutic targets |
|---|---|---|---|
| 12. | *Boswellia serrata* Roxb.<br>**Family -** Burseraceae<br>**CN/*AN*** -Indian Frankincense, *Shallaki* | Boswellic acids, 3-O-acetyl-11-keto-β-boswellic acid (AKBA) | ↓5LOX [81]<br>↓NFκB, ↓LOX ↑p42 MAPK, ↑p38 MAPK [25] |
| 13. | *Butea monosperma* (Lam.) Taub.<br>**Synonym -** *Butea frondosa* Koenig ex Roxb.<br>**Family –** Fabaceae<br>**CN/*AN*** -Flame of the forest, *Paalasha* | Isobutrin, butrin, butein<br>Isobutrin | TNF-α, IL-6, IL-8, ↓NFκB<br>↓IκBα, ↓IKK;<br>↓NFκBp65 [53] |
| 14. | ***Caesalpinia sappan* Linn.**<br>**Synonym -** *Biancaea sappan* Todaro<br>**Family –** Caesalpiniaceae<br>**CN/*AN*** -Sappan, *Pattanga* | Methanolic extract | ↓PGE2, ↓NO, ↓iNOS [82] |
| 15. | *Celastrus paniculatus* Willd.<br>**Synonym-** *Celastrus dependens* Wall.<br>**Family-**Celastraceae<br>**CN/*AN*** - *Jyotishmati* | Methanolic extract | ↓COX-1 [83] |
| 16. | *Centella asiatica* (Linn.) Urban<br>**Synonym -** *Hydrocotyle asiatica* L.<br>**Family -** Apiaceae<br>**CN/*AN*** -Asiatic Pennywort, *Manduukaparni* | Asiaticoside, terminoloside, madecassoside | ↓iNOS [84] |
| 17. | *Cyperus rotundus* Linn.<br>**Synonyms-** *Chlorocyperus rotundus* (L.) Palla, *Pycreus rotundus* (L.) Hayek<br>**Family**- Cyperaceae<br>**CN/*AN*** - Nut Grass, *Musta* | Sesquiterpenes -β -selinene, isocurcumenol, nootkatone and aristolone, triterpene-oleanolic acid | ↓ iNOS [85] |
| 18. | *Eclipta prostrata* Roxb.<br>**Synonym** - *Eclipta alba* (L.) Hassk.<br>**Family** - Asteraceae<br>**CN/*AN*** - Trailing Eclipta Plant, *Bhringaraaja* | Methanolic extract | ↓LOX [86] |
| 19. | *Embelia ribes* Burm. f.<br>**Family** - Myrsinaceae<br>**CN/*AN*** - Embelia, *Vidanga* | Embelin and its 2, 5-isobutylmine salts | ↓NFκB, ↓TNF-α, ↓ COX-2, ↑apoptosis [55] |
| 20. | *Ficus benghalensis* Linn.<br>**Family** - Moraceae<br>**CN/*AN*** - Banyan tree, *Vata* | Aqueous extract | ↓SOD, ↓ iNOS [87] |
| 21. | *Garcinia indica* (Thouars) Choisy*<br>**Synonym** - *Garcinia purpurea* Roxb.<br>**Family** - Clusiaceae<br>**CN/*AN*** - Kokam Butter tree, *Vrkshaamla* | Garcinol and its derivatives | ↓cPLA2, ↓ERK1/2 kinase; ↓iNOS, ↓JAK / STAT-1, ↓NFκB, ↓p38 MAPK, ↓COX-2, ↓5LOX, ↓HAT [60, 61] |
| 22. | *Gloriosa superba* Linn.<br>**Family** - Liliaceae<br>**CN/*AN*** - Glory Lily, *Laangali* | Extracts | ↓5-LOX [88] |
| 23. | *Morinda citrifolia* Linn.<br>**Synonym** - *Morinda bracteata* Roxb.<br>**Family** - Rubiaceae<br>**CN/*AN*** - Indian Mulberry, *Ashyuka* | Extracts | ↓5-LOX, ↓15-LOX, ↓COX-1, ↓COX-2, ↓IL-1β, ↓IL-6, ↓TNF-α [89, 90] |

| Sl. No | Plant name | Phytochemical isolated | Therapeutic targets |
|---|---|---|---|
| 24. | *Myristica fragrans* Houtt<br>**Family** - Myristicaceae<br>**CN/*AN*** - Nutmeg, *Jaatiphala* | Macelignan | ↓iNOS, ↓TNF-α, ↓COX-2 [64] |
| 25. | *Phyllanthus amarus* Schum. & Thonn.<br>**Family -** Euphorbiaceae<br>**CN/*AN*** - *Bhuumyaamalaki* | Ethanolic/water, hexane extracts | ↓NFκB; ↓iNOS; ↓COX-2 [91] |
| 26. | *Phyllanthus emblica* Linn.<br>**Synonyms** - *Embelica officinalis* Gaertn.<br>**Family -** Euphorbiaceae | Gallic acid, methyl gallate, corilagin, furosin, geraniin | ↓COX-2, ↓iNOS [72] |
| 27. | *Pterocarpus marsupium* Roxb.<br>**Family** - Fabaceae<br>Indian Kino Tree, *Asana* | Extract | ↓COX-2 [66] |
| 28. | *Rubia cordifolia* Linn.<br>**Synonym** - *Rubia munjesta* Roxb.<br>**Family** - Rubiaceae<br>**CN/*AN*** - Indian Madder, *Manjishthaa* | Extract | ↓iNOS, ↓NO [92] |
| 29. | *Saraca asoca* (Roxb.) De Wilde<br>**Synonym** - *Saraca indica* auct. non L.<br>**Family** - Caesalpiniaceae<br>**CN/*AN*** - Ashoka tree, *Ashoka* | Extract | ↓NFκB, ↓AP-1, ↓CREB [72] |
| 30. | *Semecarpus anacardium* Linn. f.<br>**Family** - Anacardiaceae<br>**CN/*AN*** - Marking Nut, *Bhallaataka* | Anacardoside | ↓NFκB, ↓COX-2, ↓TNF-α [70] |
| 31. | *Sida cordifolia* Linn<br>**Family**- Malvaceae<br>**CN/*AN*** - Country Mallow, *Balaa* | 5′-Hydroxymethyl-1′-(1,2,3,9-tetrahydro-pyrrolo [2,1-b] quinazolin-1-yl)-heptan-1-one | ↓COX-2 [93] |
| 32. | *Terminalia arjuna* (Roxb.) W. & A.<br>**Family** - Combretaceae<br>**CN/*AN*** - Arjun Terminalia, *Arjuna* | Extract | ↓NFκB, ↓GATA, ↓AP-1, ↓CREB [72] |
| 33. | *Terminalia chebula* Retz.<br>**Family** - Combretaceae<br>**CN/*AN*** - ChebulicMyrobalan, *Haritaki* | Chebulagic acid<br>Padma 28 [74, 75] | ↓ COX-2, ↓ LOX, ↓NFκB [72]<br>↓iNOS [75] |
| 34. | *Tribulus terrestris* Linn.<br>**Family** - Zygophyllaceae<br>**CN/*AN*** - Land-Caltrops, *Gokshura* | Extract | ↓COX-2, ↓iNOS, ↓NFκB [73] |
| 35. | *Woodfordia fruiticosa* Kurz.<br>**Synonym** - *Woodfordia floribunda* Salisb.<br>**Family** - Lythraceae<br>**CN/*AN*** - Fire-flame Bush, *Dhaataki* | Methanol and water extract | ↓5-LOX [94] |

* = Endemic to Western Ghats; CN/*AN* = Common names/ *Ayurvedic names*
↓ = inhibited/downregulated
↑ = improved activity/upregulated

fruits. Its leaves and roots have been used for medicinal purposes. Three phenolic compounds viz., artocarpesin [5,7,2',4'-tetrahydroxy-6-(3-methylbut-3-enyl) flavone][42] , norartocarpetin (5,7,2',4'-tetrahydroxyflavone) and oxyresveratrol [trans-2,4,3',5'-tetrahydroxystilbene] were reported[43,44]. Among them, artocarpesin suppressed the LPS-induced production of NO and $PGE_2$ through the down-regulation of iNOS and COX-2 protein expressions in LPS-activated RAW 264.7 murine macrophage cells.[45]

***Bauhinia variegata* L:** Six flavonoids, namely kaempferol, ombuin, kaempferol 7,4'-dimethyl ether 3-*O*-*β*-D-glucopyranoside, kaempferol 3-*O*-*β*-D-glucopyranoside, isorhamnetin 3-*O*-*β*-D-glucopyranoside and hesperidin,

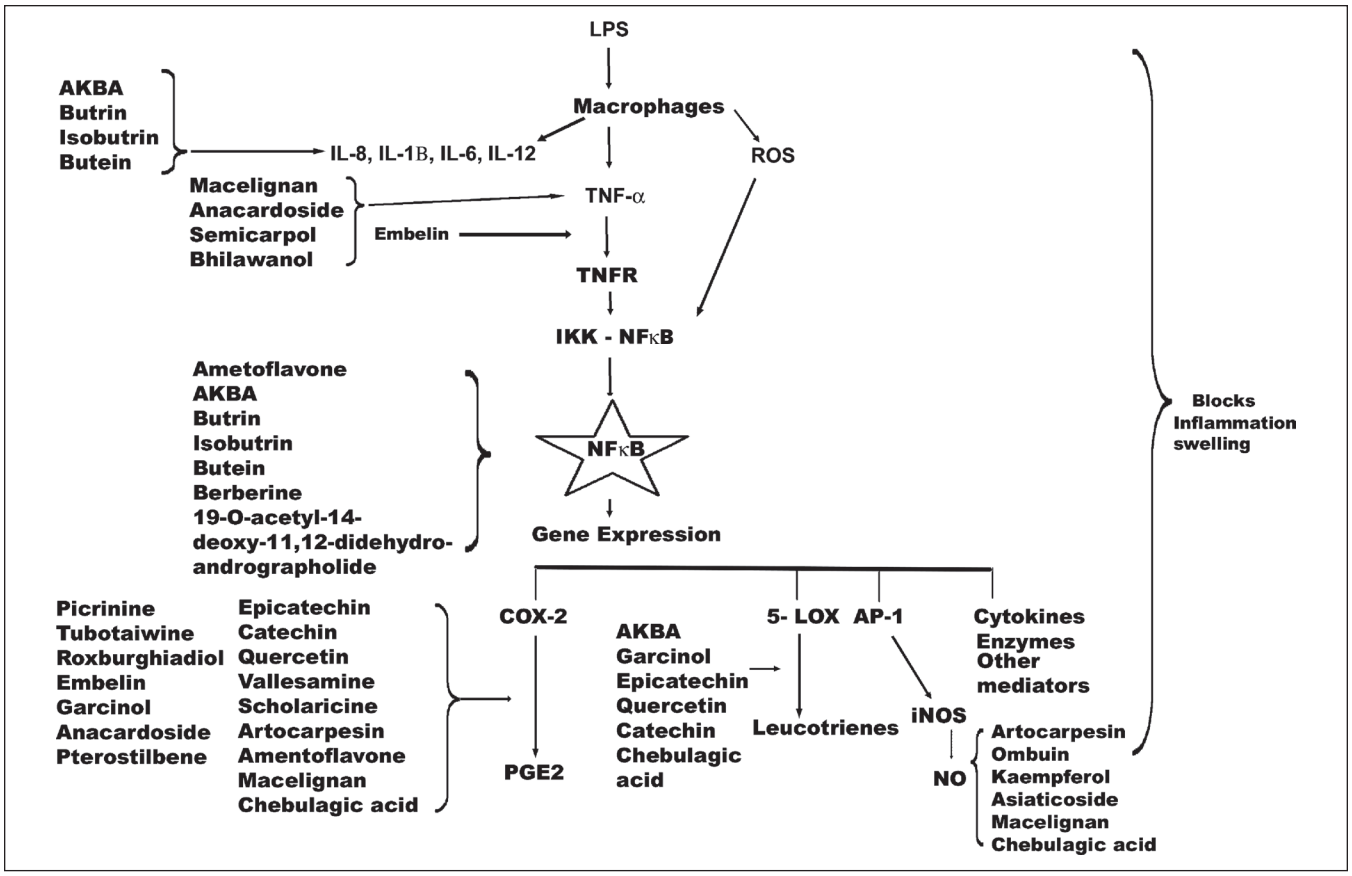


**Figure 1:** Phytochemicals isolated from medicinal plants exhibiting inhibitory activity at various sites in inflammatory pathway blocking inflammation/ swelling

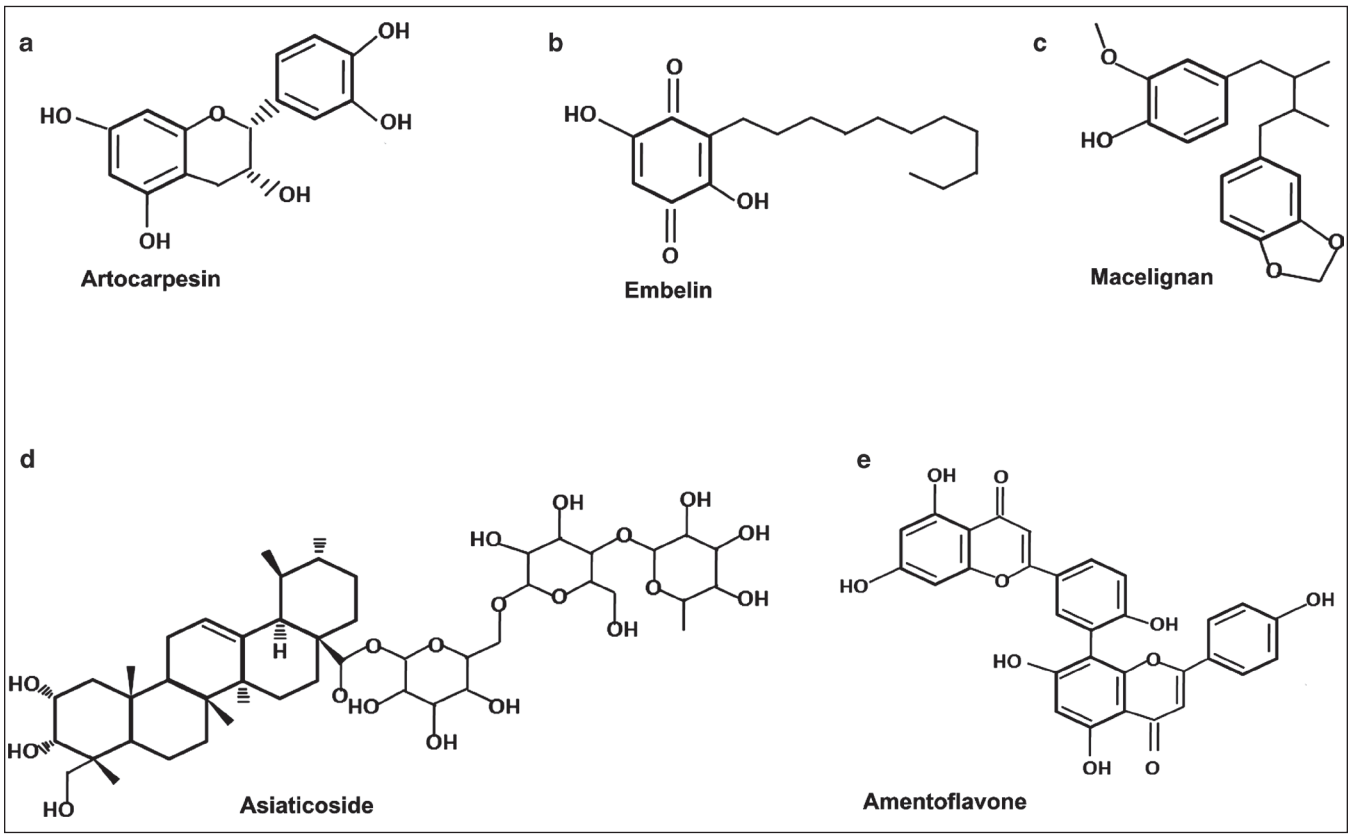


**Figure 2:** Chemical structure for a few therapeutically active bioactive with anti-inflammatory property.

together with one triterpene caffeate, 3*β-trans*-(3,4-dihydroxycinnamoyloxy)olean-12-en-28-oic acid were isolated from the non-woody aerial parts of *B. variegata*[46]. All the seven compounds were tested in LPS/IFN-γ induced macrophages. These compounds inhibited LPS and IFN-γ induced NO and cytokines (TNF-α and IL-12) production all of which play a crucial role in inflammation.[46]

***Biophytum sensitivum* DC:** Amentoflavone, a biflavonoid with anti-inflammatory activity isolated from *B. sensitivum,* downregulated COX-2 expression in TNFα-activated A549 cells with concomitant inhibition of NF-κB mediated signaling cascades[47]. Amentoflavone inhibited NF-κB/DNA binding activity with inhibition of degradation of IκBα and NF-κB translocation into nucleus in TNFα-activated A549 cells[48]. It may be of therapeutic value for several lung diseases where COX-2 plays an important role.[48]

***Boswellia serrata* Roxb:** Frankincense, the gum resin of *B. serrata* and *B. carterii* has been used for the treatment of inflammatory diseases in the traditional medicine in many countries. Boswellic acid (BA), which belong to the ursane type pentacyclic triterpene saponines was identified as the active principle[49]. It could inhibit leukotriene biosynthesis in intact cells.[25,50] Boswellic acid and its derivatives acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid have been extensively studied[51]. *In vitro*, BAs selectively blocked the leukotriene, IL-12 and IL-6 generation down regulating NFκB activation.[25] In animal models of inflammation, BA has been shown to be an effective adjuvant mitigating BSA-induced arthritis.[25]

***Butea monosperma* (Lam.) Taub:** *Butea monosperma* is a well known medicinal plant in India used to treat cuts, wounds and skin diseases[52]. Anti-inflammatory activity was credited to the presence of polyphenols- butrin, isobutrin, isocoreopsin and butein[53]. All these polyphenols could significantly reduce the phorbol 12-myristate 13-acetate and calcium ionophore A23187 induced inflammatory response in HMC-1 human mast cells[53]. The anti-inflammatory potential was measured through decreased production of TNF-α, IL-6 and IL-8 in HMC-1 cells mediated by inhibiting the activation of NF-κB. In addition, isobutrin was most potent in suppressing the NF-κB p65 activation by inhibiting IκBα-degradation, whereas butrin and butein were relatively less effective. Kinase activity assay revealed that isobutrin was a potent inhibitor of IKK (Inhibitor Kappa B Kinase) activity.[53]

***Embelia ribes* Burm.:** Embelin, identified primarily from *E. ribes*, exhibited chemopreventive, anti-inflammatory and apoptotic activities[54]. Embelin inhibited IL-1, IL-6, TNF-α binding TNF receptor (TNFR) and activation of NFκB[55]. Embelin could also down regulate both inducible and constitutive NFκB activation when stimulated by diverse stimuli such as IL-1β, LPS, phorbol myristate acetate, okadaic acid, $H_2O_2$ and cigarette smoke condensate. A sequential inhibition of the TNF-α induced activation of the inhibitory subunit of NFκB, the IαBα kinase, IαBα phosphorylation, IαBα degradation and p65 phosphorylation and nuclear translocation were reported. Embelin also suppressed NFκB-dependent reporter gene transcription induced by TNF α, TNF receptor-1 (TNFR1), TNFR1-associated domain protein, TNFR-associated factor-2, NFκB-inducing kinase and IαBα kinase, down-regulate gene products involved in cell survival, proliferation, invasion and metastasis of the tumor. Down-regulation was associated with enhanced apoptosis by cytokine and chemotherapeutic agents.[55]

***Garcinia indica* (Thouars) Choisy:** *Garcinia indica* extracts, especially from the rind, are rich in polyisoprenylated benzophenone derivatives such as garcinol[56]. Garcinol shows strong antioxidant activity which has been credited to both phenolic hydroxyl groups as well as a β-diketone moiety[57,58]. The effects of garcinol was associated with lowered concentrations of intracellular ROS, significant inhibition of 5-LOX and microsomal $PGE_2$ synthase (mPGES)-1 in cell-free assays[59]. Cell line studies recorded significant inhibition of COX-1 enzyme and as well as thromboxane B2 production by human platelets.[60,61]

***Myristica fragrans* Houtt:** Macelignan was isolated from *M. fragrans*[62]. It exhibited potent anti-inflammatory activity *in vitro* in microglial cells[63]. One of the important features in neurodegenerative disease was the failure to regulate oxidative stress and inflammation[63]. Macelignan could suppress COX-2 and iNOS expression in microglial cells activated by LPS. A subsequent reduction of NO and significant suppression of pro-inflammatory cytokine TNF-α and IL-6 was recorded.[64]

***Pterocarpus marsupium* Roxb:** Pterostilbene was identified as an active principle of *P. marsupium* (PM) extract with potent anti-inflammatory activity[65]. A decreased PGE2 production indicated specific COX-2 inhibition in LPS-stimulated human peripheral blood mononuclear cells with $IC_{50}$ of approximately 1.0μM[66]. A short term human trial did not identify abnormal blood cell counts or blood chemistry. The authors suggest the need for clinical studies using the PM extract to corroborate the *in vitro* observed inhibitory activity on PGE2 production in order to resolve the potential use of PM extract in inflammatory disorders and/or inflammatory pain.[67]

***Semecarpus anacardium* Linn:** *S. anacardium* extract showed a remarkable scavenging capacity of nitrate/nitrite radicals[68]. Flavonoids viz., semicarpol and bhilawanol in the nuts inhibited acute tuberculin reaction in inflammatory sensitized rats with a decreased level of arthritic condition.[69]

In rheumatoid arthritis, these flavonoids inhibited the release of chemical mediators viz. histamine and serotonin reducing the symptoms. It was thought to be mediated through decreased monocyte infiltration and fibroblast proliferation, blocked TNF-α and inhibition of COX.[70]

***Terminalia chebula* Retz.:** Preliminary studieshave indicated anti-inflammatory activity for the ethanolic extracts of fruits of *T. chebula*[71]. The extracts could inhibit COX-1, COX-2 and 5-LOX. However the inhibitory quotient showed a strong preference to inhibit COX-2 and 5-LOX. Chebulagic acid was subsequently isolated from this extract. *In vitro* studies showed potent COX–LOX dual inhibition activity with $IC_{50}$ values of 15 ± 0.288, 0.92 ± 0.011 and 2.1 ± 0.057μM for COX-1, COX-2 and 5-LOX respectively. Downregulation NFkB was observed.[72]

### Other plants

Inhibition of DNA-transcription factor (TF) interactions was hypothesized to be a strategy for the development of anti-inflammatory, anti-tumor and anti-viral therapeutic agents. Several TFs viz., NFκB, AP-1, STATs, cAMP response element binding protein (CREB) and GATA-1 are involved in inflammatory processes. Their intervention in human pathologies related to inflammation, such as rheumatoid arthritis, chronic asthma and inflammatory bowel diseases was analyzed by electrophoretic mobility shift assay performed using [γ-$^{32}$P] 50-end-labeled oligonucleotides.

*Terminalia arjuna*, *Saraca asoca* and *Aphanamixis polystachya* extracts were the most effective extracts inhibiting AP-1/DNA interactions. Extracts of *Embelica officinalis, Hemidesmus indicus*, *T. arjuna*, *Aegle marmelos*, *Saraca asoca* and *A. polystachya* showed high NFκB/DNA inhibitory activity. *A. marmelos*, *S. asoca*, *A. polystachya* extracts were the most active in inhibiting interaction between GATA-1 and DNA. *T. arjuna*, *S. asoca* and *A. polystachya* inhibited STAT-3/DNA interaction. *T. arjuna*, *S. asoca* and *E. officinalis* possessed an intermediate activity regarding the CREB/DNA interaction studies.[72]

### Herbal compositions with anti-inflammatory activity

Practitioners of traditional Indian medicine use 'Dashamoola' a combination of roots of ten plants, as a standard Ayurvedic medicine for inflammatory diseases. A WIPO patent application reports on a synergistic herbal composition for treatment of rheumatic and musculo-skeletal disorders comprising of medicinal plants *viz*., *Withania somnifera*, *Tribulus terrestris*, *Phyllanthus emblica* and *Boswellia serrata* to reduce pain, inflammation, stiffness and degeneration of bones, joints, muscles and other connective tissues.[73]

Padma 28, a multicomponent herbal formulation based on Tibetan medicine was reported to have beneficial effects on several experimental models of inflammatory, autoimmune diabetes and autoimmune encephalomyelitis[74]. In humans, PADMA-28 attenuated the symptoms associated with atherosclerotic patients.[75]

Limbrel, a herbal composition of flavonoids, from *Scutellaria baicalensis* and *Acacia catechu* was developed as metabolic therapy for osteoarthritis[76]. Flavocoxid, a proprietary blend of natural flavonoid ingredients, was recognized as safe meeting Generally Recognized As Safe (GRAS) status[77]. This proprietary formulation alleviated osteoarthritis symptoms inhibited COX-2 and LOX pathways[77]. It is a unique form traditional NSAIDs or strict COX-2 inhibitors as Limbrel had a very low side-effect in patients who have taken this prescription product.[77]

## CONCLUSION

Several plants are promising as sources of anti-inflammatory drug targets. Inflammation is a pathological condition mediated through production of PGE2 from arachidonic acid (AA) generated by enzyme system PG synthetase, a complex enzyme including COX-2. Another group of compounds eliciting inflammatory condition are leukotrienes which are derived directly from AA by enzymatic action of lipoxygenase (LOX). The inflammatory response is controlled by the master regulator NFκB. Medicinal plants viz., *Andrographis paniculata*, *Biophytum sensitivum*, *Boswellia serrata*, *Butea monosperma*, *Embelia ribes*, *Terminalia chebula* and *Tribulus terrestries* have the reported ability to down regulate NFκB activation. *Acacia catechu*, *Alstonia scholaris*, *Artocarpus hirsutus*, *Bacopa monnieri* and *Myristica fragrans* have reported COX-2 inhibitory activity. Further *Acacia catechu*, *Alstonia scholaris*, *Bacopa monnieri* and *Garcinia indica* have LOX inhibitory activity. Thus validating traditional application could provide sources of new, effective and safe drugs.

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## REFERENCES

1. Malik NN, Khan Y. Personalized medicine: potential impact on the biopharmaceutical industry. Drug Discovery 2010; doi:10.1016/j.drudis.2010.08.019
2. Myers N, Mittermeier RA, Mittermeier CG, da Fonseca GAB, Kent J. Biodiversity hotspots for conservation priorities. Nature 2000; 403:853-58.

3. Gadgil M. Western Ghats: A Lifescape. J Indian Institute Sci. 1996; 76:495-04.
4. Daniel RJR. Taxonomic uncertainties and conservation assessment of the Western Ghats. Current Sci. 1997; 73:169-70.
5. Datta R, Nouguier C, Pascal JP, Ramesh BR. Endemic tree species of the Western Ghats (India), CD ROM, 1997; French Institute of Pondicherry, India.
6. Jean-Philippe P, Davidar P, Jean-Pierre P, Ramesh BR. Analysis of threatened endemic trees of the Western Ghats of India sheds new light on the Red Data Book of Indian Plants. Biodiversity and Conservation. 2002; 12:2091-06.
7. Ganeshaiah KN, Kathuria S, Shaanker UR. Floral resources of Karnataka: A geographic perspective. Current Sci. 2002; 83:810-13.
8. Ganeshaiah KN. Sasya Sahyadri - Distribution, Taxonomy and Diversity of Plants of Western Ghats, CD ROMs 2003; ATREE and University of Agricultural Sciences.
9. Gordon JR, Galli SJ. Mast cells as a source of both preformed and immunologically inducible TNF-alpha/cachectin. Nature 1990 346:274-76.
10. MacEwan DJ. TNF ligands and receptors---a matter of life and death. Brit J Pharmacol. 2002; 135:855-875.
11. Duff GW, Durum SK. Fever and immunoregulation: hyperthermia, interleukins 1 and 2, and T-cell proliferation. Yale Biol Med. 1982; 55:437-442.
12. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nature Immunol 2009; 10:241-47.
13. Oh-ishi S. Analysis of chemical mediators involved in acute inflammatory reaction with the rat pleurisy model. Nihon Yakurigaku Zasshi 1997; 110:59-68.
14. Dubois RN, Abramson SB, Crofford L, Gupta R, Simon LS, van de putte LBA, Lipsky PE Cyclooxygenase in biology and disease. FASEB J. 1998; 12:1063-73.
15. Muta T, Takeshige K. Essential roles of CD14 and lipopolysaccharide-binding protein for activation of toll-like receptor (TLR)2 as well as TLR4 reconstitution of TLR2- and TLR4-activation by distinguishable ligands in LPS preparations. Eur J Biochem. 2001; 268 16:4580-9.
16. Qin H, Wilson CA, Lee SJ, Zhao X, Benveniste EN. LPS induces CD40 gene expression through the activation of NF-kappaB and STAT-1alpha in macrophages and microglia. Blood 2005; 106:3114-22.
17. Hoareau L, Bencharif K, Rondeau P, Murumalla R, Ravanan P, Tallet F, Delarue P, Cesari M, Roche R, Festy F. Signaling pathways involved in LPS induced TNFalpha production in human adipocytes. J Inflammation 2010 7:1.
18. Nishikori M. Classical and alternative NF-kB activation pathways and their roles in lymphoid malignancies. J Clin Exp Hematopathol. 2005; 45:15-24.
19. Victor VM, Rocha M, Fuente M Dela. Immune cells: free radicals and antioxidants in sepsis. Int Immunopharmacol. 2004; 4:327-47.
20. Lewis, D.A. Anti-inflammatory drugs from plant and marine sources. Birkhause Verlag, Basel. Wiley and Sons. 1989. Chichester, England.
21. Barbosa-Filho JM, Piuvezam MR, Moura MD, Silva MS, Lima KVB, Leitão da-Cunha EV, Fechine IM, Takemura OS. Anti-inflammatory activities of alkaloids - a twenty-century review. Revista Brasileira de Ciências Farmacêuticas. 2006; 16:109-22.
22. Zhang W, Jones A, Doherty M. Paracetamol reduces pain in osteoarthritis but is less effective than NSAIDs. Evid Based Nurs 2005; 8:21 doi:10.1136/ebn.8.1.21.
23. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, Strom BL. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med. 2005; 142:157-64.
24. Shishodia S, Aggarwal BB. Guggulsterone inhibits NF-κB and IαBα kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. J Biol. Chem. 2004; 279:47148-58.
25. Khanna D, Sethi G, Ahn KS, Pandey MK, Ajaikumar B, Kunnumakkara, Sung B, Aggarwal A, Aggarwal BB. Natural products as a gold mine for arthritis treatment. Current Opin. Pharmacol. 2007; 7:344-51.
26. Safayhi H, Sailer ER, Ammon HP. Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-beta-boswellic acid. Mol. Pharmacol. 1995; 47:1212-16.
27. Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. Acetyl-11-ketobeta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-κ B and NF-κ B-regulated gene expression. J. Immunol. 2006; 176:3127-40.
28. Sheng-Chu K, Sheng-Chih C, Jin-Bin W, Che-Hing T, Jih-Pyang W Abriquinone derivatives useful in treatment of inflammation and allergic reactions. 1997; US patent 5,856,352.
29. Wang JP, Hsu MF, Chang LC, Kuo JS and Kuo SC. Inhibition of plasma extravasation by abruquinone A, a natural isoflavonequinone isolated from *Abrus precatorius*. Europ J Pharmacol. 1995; 273:73-81.
30. Vaidya ADB, Raut AA, Vaidya RA. *Abrus precatorius*, Gaertin — an Ayurvedic potent phytomedicine. J Assoc. Physician India. 2005; 53:739-740.
31. Burnett BP, Jia Q, Zhao Y, Levy RM. A medicinal extract of *Scutellaria baicalensis* and *Acacia catechu* acts as a dual inhibitor of cyclooxygenase and 5-lipoxygenase to reduce inflammation. J Med Food 2007; 10:442-51.
32. Jia Q, Nichols TC, Rhoden E, Waite S Isolation of a dual COX-2 and 5-lipoxygenase inhibitor from acacia 2002; US Patent no. 7108868.
33. Jia Q: Generating and screening a natural product library for cyclooxygenase & lipoxygenase dual inhibitors. Studies Nat Prod Chem 2003; 29:643-718.
34. Ismail S, Asad M Immunomodulatory activity of *Acacia catechu*. Indian J Physiol. Pharmacol. 2009; 53:25-33.
35. Arulmozi S, Mazumder PM, Ashok P, Narayanan LS. Pharmacological activities of *Alstonia scholaris* Linn. – a Review. Pharmacog. Rev. 2007; 1:163-70.
36. Shang JH, Cai XH, Feng T, Zhao YL, Wang JK, Zhang LY, Yan M, Luo XD Pharmacological evaluation of *Alstonia scholaris*: anti-inflammatory and analgesic effects. J Ethnopharmacol. 2010; 129:174-81.
37. Huang CJ, Wu MC. Differential effects of foods traditionally regarded as 'heating' and 'cooling' on prostaglandin E2 production by a macrophage cell line. J Biomed Sci 2002, 9:596-06.
38. Wen-Wan C, Bi-Fong L. Isolation and identification of bioactive compounds in *Andrographis paniculata* (*Chuanxinlian*). Chao and Lin Chinese Med. 2010, **5**:17.
39. Burgos RA, Seguel K, Perez M, Meneses A, Ortega M, Guarda MI, Loaiza A, Hancke JL. Andrographolide inhibits IFN-gamma and IL-2 cytokine production and protects against cell apoptosis. Planta Med. 2005; 71:429-34.
40. Habtemariam S. Andrographolide inhibits the tumor necrosis factor-alpha-induced upregulation of ICAM-1 expression and endothelial-monocyte adhesion. Phytotherapy Res. 1998; 12:37-40.
41. Chao W-W, Kuo Y-H, Lin B-F. Anti-inflammatory activity of new compounds from *Andrographis paniculata* by NF-κB transactivation inhibition. J Agri Food Chem. 2010; 58:2505-12.
42. Sato M, Fujiwara S, Tsuchiya H, Fujii T, Iimuna M, Tosa H, Ohkawa Y. Flavones with antibacterial activity against cariogenic bacteria. J Ethnopharmacol. 1996; 54:171-76.
43. Fang SC, Hsu CL, Yen GC. Anti-inflammatory effects of phenolic compounds isolated from the fruits of *Artocarpus heterophyllus*. J Agric. Food Chem. 2008a; 56:4463-68.
44. Fang SC, Hsu CL, Yu YS, Yen GC. Cytotoxic effects of new geranyl chalcone derivatives isolated from the leaves of *Artocarpus communis* in SW 872 human liposarcoma cells. J Agric Food Chem. 2008b; 56:8859-68.
45. Jagtap UB, Bapat VA. Artocarpus: A review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol. 2010; 129:142-66.
46. Rao YK, Fang, Shih-Hua, Tzeng, Yew-Min. Antiinflammatory activities of flavonoids and a triterpene caffeate isolated from *Bauhinia variegata*. Phytotherapy Res. 2008; 22:957-62.
47. Banerjee T, Valacchi G, Ziboh VA, van der VA. Inhibition of TNFα-induced cyclooxygenase-2 expression by amentoflavone through suppression of NF-κB activation in A549 cells. Mol. Cellular Biochem. 2002; 238:105-10.
48. Guruvayoorappan C, Kuttan G. Inhibition of tumor specific angiogenesis by amentoflavone. Biochemistry (Mosc). 2008; 73:209-18.
49. Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR, Ammon HPT. Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. J Pharmacol Exp Ther. 1992; 261:1143-46.
50. Sharma ML, Bani S, Singh GB. Anti-arthritic activity of boswellic acids in bovine serum albumin (BSA)-induced arthritis. Int J Immunopharmacol. 1989; 11:647-52.
51. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. Curr Med Chem. 2006; 13:3359-69.
52. Akram M, Akhtar N, Asif HM, Shah P A, Saeed T, Mahmood A, Malik NS. *Butea monosperma* Lam.: A review. J Med. Plants Res. 2011; 5:3994-96.
53. Rasheed Z, Akhtar N, Khan A, Khan KA, Haqqi TM. Butrin, isobutrin and butein from medicinal plant *Butea monosperma* selectively inhibit NF-κB in activated human mast cells: suppression of TNF-α, IL-6 and IL-8. J Pharmacol Exp Ther. 2010; 1:1-34.
54. Chitra M, Sukumar E, Suja V, Devi CS. Antitumor, anti-inflammatory and analgesic property of embelin, a plant product. Chemother. 1994; 40:109-13.

55. Ahn KS, Sethi G, Aggarwal BB. Embelin, an inhibitor of X chromosome-linked inhibitor-of-apoptosis protein, blocks Nuclear Factor-κB (NF-κB) signaling pathway leading to suppression of NF-kB-regulated antiapoptotic and metastatic gene products. Mol. Pharmacol. 2007; 71:209-19.
56. Krishnamurthy N, Lewis YS, Ravindranath B. On the structures of garcinol, isogarcinol and camboginol. Tetrahedron Lett. 1981; 22:793-96.
57. Sang S, Pan MH, Cheng X, Bai N, Stark RE, Rosen RT, Lin-Shiau SY, Lin JK, Ho CT. Chemical studies on antioxidant mechanism of garcinol: analysis of radical reaction products of garcinol and their antitumor activities. Tetrahedron 2001; 57:9931-38.
58. Sang S, Liao CH, Pan MH, Rosen RT, Lin-Shiau SY, Lin JK, Ho CT. Chemical studies on antioxidant mechanism of garcinol: analysis of radical reaction products of garcinol with peroxyl radicals and their antitumor activities. Tetrahedron 2002; 58:10095-02.
59. Koeberle A, Northoff H, Werz O. Identification of 5-lipoxygenase and microsomal prostaglandin E2 synthase-1 as functional targets of the anti-inflammatory and anti-carcinogenic garcinol. Biochem Pharmacol. 2009; 77:1513-21.
60. Liao CH, Ho CT, Lin JK. Effects of garcinol on free radical generation and NO production in embryonic rat cortical neurons and astrocytes. Biochem. Biophys. Res Commun. 2005; 329:1306-14.
61. Padhye S, Ahmad A, Oswal N, Sarkar FH. Emerging role of Garcinol, the antioxidant chalcone from *Garcinia indica* Choisy and its synthetic analogs. J Hematol. Oncol. 2009; 2:2-38.
62. Woo WS, Shin KH, Wagner H, and Lotter H. The structure of macelignan from *Myristica fragrans.* Phytochemistry 1987; 26**:**1542-43.
63. Jin DQ, Lim CS, Hwang JK, Ha I, Han JS. Anti-oxidant and anti-inflammatory activities of macelignan in murine hippocampal cell line and primary culture of rat microglial cells. Biochem. Biophys. Res Commun. 2005; 331:1264-69.
64. Im YB, Ha I, Kang KW, Lee K-W, Han H-K. Macelignan: a new modulator of P-glycoprotein in multidrug-resistant cancer cells. Nutr. Cancer, 61(4), 538-43.
65. Maurya R, Ray AB. Constituents of *Pterocarpus marsupium*. J Nat Prod. 1984; 47:179-81.
66. Hougee S, Faber J, Sanders A, de Jong RB, van den Berg WB, Garssen J, Hoijer MA, Smith HF. Selective COX-2 inhibition by a *Pterocarpus marsupium* extract characterized by pterostilbene, and its activity in healthy human volunteers. Planta Medica 2005; 71:387-92.
67. Devgun M, Nanda A, Ansari SH. *Pterocarpus marsupium* Roxb. - A Comprehensive review. Phcog Rev. 2009; 3:359-63.
68. Nadakarni AK, Indian Materia Medica Vol 1, 3rd edn, Popular Prakashan Bombay (1999); 965-1125.
69. Ramprasath VR, Shanthi P, Sachdanandam P. Effect of *Semecarpus anacardium* Linn. nut milk extract on rat neutrophils functions in adjuvant arthritis. Cell Biochem. Funct. 2006; 24:333-40.
70. Majumdar SH, Chakraborthy GS, Kulkarni KS. Medicinal potentials of *Semecarpus anacardium* nut- a review. J Herbal Medicine Toxicol. 2008; 2:9-13.
71. Chattopadhyay RR, Bhattacharyya SK. *Terminalia chebula*: an update. Pharmacogn. Rev. 2007; 1:151-56.
72. Reddy DB, Reddy TC, Jyotsna G, Sharan S, Priya N, Lakshmipathi V, Reddanna P. Chebulagic acid, a COX-LOX dual inhibitor isolated from the fruits of *Terminalia chebula* Retz., induces apoptosis in COLO-205 cell line. J Ethnopharmacol. 2009; 30:506-12.
73. Lampronti I, Khan MTH, Borgatti M, Bianchi N, Gambari R. Inhibitory effects of Bangladeshi medicinal plant extracts on interactions between transcription factors and target DNA sequences. eCAM. 2007; 5:303-12.
74. A synergistic herbal composition for treatment of rheumatic and musculo-skeletal disorders (RMSDS) World patent WO/2009/010992.
75. Barak V, Kalickman I, Halperin T, Birkenfeld S, Ginsburg I. PADMA-28, a Tibetan herbal preparation is an inhibitor of inflammatory cytokine production. Eur Cytokine Netw. 2004; 15:203-9.
76. Moeslinger T, Friedl R, Volf I, Brunner M, Koller E, Spieckermann PG. Inhibition of inducible nitric oxide synthesis by the herbal preparation Padma 28 in macrophage cell line. Canadian J Physiol. Pharmacol. 2000; 78:861-66.
77. Burnett BP, Jia Q, Zhao Y, Levy RM. A medicinal extract of *Scutellaria baicalensis* and *Acacia catechu* acts as a dual inhibitor of cyclooxygenase and 5-lipoxygenase to reduce inflammation. J Med Food 2007; 10; 442-51.
78. Jia Q, Timothy CN, Eric ER, Scott W. Isolation of dual COX-2 and 5-lipoxygenase inhibitor from Acacia. US patent 2006/0269627 A1.
79. Janaki S, Vijayasekaran V, Viswanathan S, Balakrishna K. Anti-inflammatory activity of *Aglaia roxburghiana* var. *beddomei* extract and triterpenes roxburghiadiol A and B. J. Ethnopharmacol. 1999; 67:45-51
80. Viji V, Helen A. Inhibition of lipoxygenases and cyclooxygenase-2 enzymes by extracts isolated from *Bacopa monniera* (L.) Wettst. J Ethnopharmacol. 2008; 118:305-11.
81. Gupta SK, Agarwal R, Srivastava S, Agarwal P, Agrawal SS, Saxena R, Galpalli N. The Anti-inflammatory effects of *Curcuma longa* and *Berberis aristata* in endotoxin-induced uveitis in rabbits. Invest. Ophthalmol. Visual Sci. 2008; 49:4036-40.
82. Gokaraju G, Raju G, Raju GR, Trimurtulu G, Vendateswarlu S. Synergistic anti-inflammatory and antioxidant dietary supplement compositions. 2010 US Patent No. 20100098676.
83. Hong CH, Hur SK, Oh O-Jin, Kim SS, Nam KA, Kook SL. Evaluation of natural products on inhibition of inducible cyclooxygenase (COX-2) and nitric oxide synthase (iNOS) in cultured mouse macrophage cells. J Ethnopharmacol. 2002; 83:153-59.
84. Gupta, Shyam K. Antiaging cosmetic delivery systems. 2008. US Patent 7320797.
85. Se-Kyung O, Cho KR, Azizol AK, Ng TL. Use of asiatic acid or asiaticoside for treatment of cancer . 2004; US Patent 20040097463.
86. Won-Gil S, Hyun-Ock P, Gi-Su O, Kyu-Yun C, Tae-Oh K, Young-Gab Yun, Na-Young Kim, Hun-Taeg C. Inhibitory effects of methanol extract of *Cyperus rotundus* rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7cells. J Ethnopharmacol. 2001; 76:59-64.
87. Wagner H, Fessler B. *In vitro* 5-Lipoxygenase inhibition by *Eclipta alba* extracts and the coumestan derivative wedelolactone. Planta Medica. 1986; 52:374-77.
88. Patel MA, Patel PK, Patel MB. Aqueous extracts of *Ficus benghalensis* Linn. bark for inflammatory bowel disease. J Young Pharmacol. 2010; 2:130-36.
89. Khan H, Khan MA, Hussan I. Enzyme inhibition activities of the extracts from rhizomes of *Gloriosa superba* Linn. (*Colchicaceae*). J Enzyme Inhib. Medical Chem. 2007; 22:722-25.
90. Jensen, Jarakae C, Palu, Kehaati A. Preventative and treatment effects of *Morinda citrifolia* on osteoarthritis and its related conditions. 2002; US patent 7033624.
91. Rawson B, Matthias-Heinrich K, Paulu, Zhou AK, Bing-Nan W, Jensen BJ, Claude J Methods of manufacture of *Morinda citrifolia* based compositions for treatment of anti-inflammatory diseases through inhibition of COX-1, COX-2, interleukin-1, interleukin-6, TNF-α, HLE, and iNOS. 2009; WIPO patent application WO/2009/099840
92. Kiemer AK, Hartung T, Huber C, Vollmarm AM. *Phyllanthus amarus* has anti-inflammatory potential by inhibition of iNOS, COX-2, and cytokines via the NF-kappa B pathway. J Hepatol. 2003; 38:289-97.
93. Deshkar N, Tillo S, Pande V. A comprehensive review of *Rubia cordifolia* Linn. Pharmacogn Rev. 2008; 2:124-34.
94. Sutradhar RK, Rahman AM, Ahmad M, Bachar SC, Saha A, Guha SK. Bioactive alkaloid from *Sida cordifolia* Linn. with analgesic and anti-Inflammatory activities. Iran J Pharmacol. Ther. 2006; 5:175-78.
95. Kumaraswamy MV, Satish S. Free radical scavenging activity and lipoxygenase inhibition of *Woodfordia fructicosa* Kurz and *Betula utilis* Wall. African J Biotechnology. 2008; 7:2013-16.