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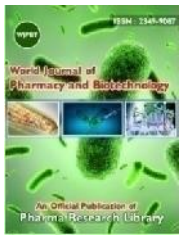

**Review Article** **Open Access**

# The Emerging Role of Plant Derived Therapeutic Compounds for Targeting Inflammatory and Oxidative Stress Related Pathways

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**A B S T R A C T**

Medicinal plants are extensively used in folk medicine for treatment of acute and chronic inflammatory diseases. The secondary metabolites, which are present in medicinal plants such as flavonoids, terpenoids, xanthones and coumarins, are responsible for anti-inflammatory activities by targeting arachidonic acid dependent and independent pathway. Based on the *invitro* and *invivo* anti-inflammatory studies ethanopharmacologists screened the various medicinal plants for their anti-inflammatory activities. The selected medicinal plants further subjected to activity guided fractionation. The bioactive fractions were further subjected to structural elucidation studies for characterization of bioactive compounds.

**Keywords:** Anti-inflammatory agents, cyclooxygenase (COX-2), Nuclear factor kappa B (NF-κB), phytocompounds, Reactive oxygen species (ROS), antioxidants, activity guided fractionation,

**A R T I C L E I N F O**

**CONTENTS**



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## 1. Introduction

**Inflammation:** Chronic diseases such as arthritis, cardiovascular diseases and cancer are related to chronic inflammation, the activation of pro inflammatory arachidonic acid dependent, independent pathways along with free radical generation promotes the incidence of these inflammatory diseases Inflammation is an important biological response of living organisms against infectious and noninfectious agents and tissue injuries which is clinically characterized by fundamental signs of redness, swelling, warmth, pain and loss of function [1]. Inflammation leads to renovation of tissue structure and function. The mechanism of inflammatory cascades can be studied under Arachidonic acid dependent and Arachidonic acid independent pathways. Arachidonic acid dependent pathways are mediated by cyclooxygenase (COX-2), lipoxygenase (5-LOX) and phospholipase$A_2$ ($PLA_2$) inflammatory enzymatic system as shown in figure 1. In contrast the second mechanism of inflammation involves a network of inflammatory cytokines responsible for the activation of many inflammatory mediator genes. Nuclear factor kappa B (NF-κB) is considered as an important transcriptional factor that can control the inflammatory response. NF-κB has a role in promoting several proinflammatory intermediaries such as induced nitric oxide, TNF-α, IL-1β and $PGE_2$ [2]. In arachidonic acid dependent mechanism, prostaglandins ($PGE_2$) play a crucial role in the induction of inflammatory response, their biosynthesis are significantly heightened in inflamed tissues, [3]. Prostaglandins (PGE-2) or thrombaxanes (TXA2) are collectively termed as eicosanoids, these are the bioactive inflammatory mediators formed from 20 carbon polyunsaturated fatty acids stored in plasma membrane by the sequential action of PGG/H synthase or cyclooxygenases [4]. The arachidonate 5-lipoxygenase catalyzes oxidation of arachidonate at the 5-position to yield the 5-hydroperoxy eicosa tetraenoic acid (5-HPETE), then HPETE converted to leukotriene A4 (LTA 4). The inflammatory products from both pathways are considered to be important mediators in the control of inflammation.

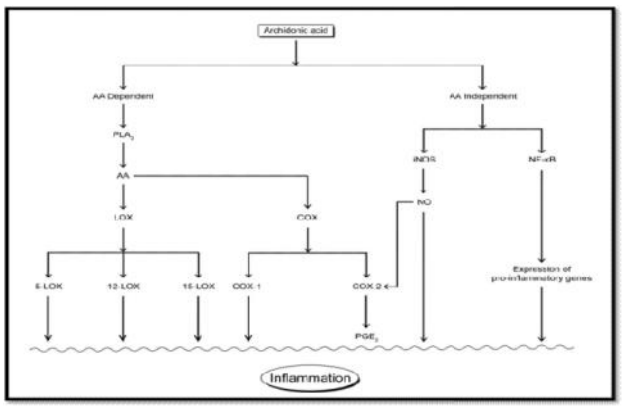


**Figure 1:** Arachidonic acid dependent and independent pathways of inflammation (Modified from Issa*et al.,* 2006)

Cyclooxygenase is a key enzyme involved in the synthesis of inflammatory mediators. COX exists in two major isoforms COX-1 and COX-2. All these isoforms distributed in different tissue and express in physiological and pathological conditions. Lipoxygenases are a heterogeneous family of lipid peroxidating enzymes exists in different isoforms such as 5-LOX, 12-LOX and 15-LOX produce their respective inflammatory mediators 5-HETE, 12-HETE and 15-HETE. COX/LOX dual pathways are believed to be promising targets for the development of anti-inflammatory agents without any side effects. In arachidonic independent pathway, transcription factors NF-κB coregulates the transcription of COX-2 and iNOS. NO synthesized by iNOS activates soluble guanylate cyclase (SGC) and the resulting increase in cGMP induced up regulation of COX-2 expression in inflammatory cells. Nitric oxide stimulates COX-2 expression through MAPKinase pathway. TNF-α and IL-1β are most important proinflammatory cytokines produced by tissue macrophages, Mast cells, endothelial and epithelial cells which mediates acute and chronic inflammation. TNF-α and IL-1β induce expression of cell adhesion molecules, and nitric oxide which are capable of activating NF-κB and PI3K pathways [5]. Improvement of new anti-inflammatory drugs specially developed for treating inflammatory diseases such as rheumatism, asthma, inflammatory bowel diseases is in progress Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) have multiple roles within the circulatory system. At lower concentrations ROS and RNS are important signaling molecules, whereas in higher concentrations both participate in the alternation of molecular and cellular mechanism from a basal state to an activated state resulting in increased inflammatory signaling pathways [6].

Oxidative stress is described as an imbalance between antioxidant and pro oxidant species. Oxidative stress is associated with cardiovascular diseases, atherosclerosis, hypertension and diabetes mellitus [7]. Reactive oxygen species (ROS) including hydrogen peroxide (H2O2), hydroxyl radical, superoxide anion and RNS, Peroxy nitrate (ONOO-) contribute pro-oxidant/antioxidant imbalance. O2-, H2O2, and ONOO- are three of the key pro-oxidants contribute to oxidative stress. In inflammatory conditions, both ROS and RNS are considered to be toxic in their upregulated state due to lower activity of antioxidant system. Multiple sources of reactive oxygen species (ROS) have been identified in vascular cells, these include pro-oxidases like NADPH oxidase, xanthine oxidase [8]. Uncoupled NOS are thought to be the main contributors to intracellular O2-. Both enzymatic and non-enzymatic systems contribute free radical scavenging within the cell thus protecting from radical induced inflammation and cancer. Many man-made antioxidant agents have been developed to cure oxidative stress related diseases.

However, the aspects including side effects, high cost, and lack of availability associated with synthetic antioxidants made scientists to focus on natural antioxidants. Natural antioxidants got prominence, as they are free from side effects. [9]. Plant derived antioxidants such as ascorbic acid, rutin and quercetin play a protective role by scavenging the generated free radicals hence they are highly beneficial to cure the diseases caused by oxidative stress.

Anti-inflammatory drugs are generally prescribed for the healing of chronic inflammatory diseases, neurological diseases and cancer [10]. Anti-inflammatory drugs are classified into steroidal and nonsteroidal anti-inflammatory drugs (NSAIDS). Cortisol and hydrocotisol are a group of glucocorticoids used as most potent anti-inflammatory drugs to treat inflammatory diseases. Glucocorticoids directly repress the NF-κB and AP-1 transcription factors responsible for genes encoding proinflammatory enzymes and cytokine mediators. The clinical use of glucocorticoids is associated with several deleterious side effects i.e. hypertension, hyperglycemia, water and electrolyte imbalance, osteoporosis and exhibit nonspecific reactions in their mechanism [11].

Nonsteroidal anti-inflammatory drugs (NSAIDS) are a group of anti-inflammatory drugs used to treat inflammatory symptoms such as swelling, pain and fever. NSAIDs inhibit cyclooxygenases, which catalyze the oxygenation of arachidonic acid to form prostaglandin G2 during the formation of prostaglandins and thrombaxanes. Cyclooxygenase enzymes are present in mammalian cells as isoforms COX-1 and COX-2 [12]. COX-1 is a constitutive enzyme, which maintains homeostasis of renal system and gastrointestinal tract, whereas COX-2 is an inducible enzyme induced by inflammatory conditions. Nonspecific inhibition of both COX-1and COX-2 by NSAIDS results in adverse side effects like gastrointestinal toxicity and myocardial infarctions. Hence great effort has been devoted in developing natural COX-2 selective NSAIDS as effective anti-inflammatory drugs from medicinal plants that get rid of the side effects associated with the usage of NSAIDS.

## 2. Development of anti-inflammatory & antioxidant agents

Adverse side effects coupled with both steroidal and nonsteroidal anti-inflammatory drugs focused on the development of novel anti-inflammatory and antioxidant agents which are free from side effects. A number of phyto-compounds with specific activity have been identified, screened and developed to treat the inflammatory and oxidative stress associated diseases by targeting both oxidative and proinflammatory pathways. The phyto-constituents having potential anti-inflammatory and antioxidant activities include curcumin from turmeric genistein from soyabeans, withanolides from *withania somnifera* and silymarin from *artichoke*. The novel anti-inflammatory compounds are developed based on inhibition studies of NF-κB activation, proinflammatory enzymes such as COX-2, $PLA_2$, 5-LOX, proinflammatory cytokines and mediators which include TNF-α, IL-1β, IL-6 and nitric oxide [13]

## 3. Plant-derived anti-inflammatory agents

Plants occupy premier position in human history as an ultimate source of phytocompounds having high therapeutic value. It is found that 40% of all medicines derived from natural sources and out of them 25% are from plant sources. Plant-derived compounds are significant therapeutic agents which are used to cure both acute and chronic inflammatory diseases.

**Plant-derived anti-inflammatory compounds that act on Arachidonic acid- induced nitric oxide and nuclear factor kappa B (NF-κB) mediated pathways**

Cellular and molecular mechanisms involved in inflammatory response are promising targets for the discovery and development of anti-inflammatory drugs to cure inflammatory diseases. Key inflammatory mediators such as $PGE_2$, LTA4, TNF-α and iNOS whose production pathways have been the selective targets for improvement of novel anti-inflammatory drugs.

**Plant-derived inhibitors affecting prostanoid formation**

Boswellic acid is a potent phytoconstituent of *Boswellia serrate* the secondary metabolites from the resin of boswellic acid are acetyl beta boswellic acid, it is proved as potent anti-inflammatory compound by inhibition of COX-2/LOX dual pathways. Curcumin is a naturally occurring anti-inflammatory agent, isolated from *turmeric* used for controlling various inflammatory disorders and wound healing. Based on *in vivo* and *in vitro* studies, circumin found to inhibit the inflammatory macrophage activation, inhibition of cyclooxygenase and lipoxygenase metabolic pathways. Resveratrol is a polyphenolic compound isolated from the roots of white hellebore (*Veratrum grandi florum*). It inhibits both COX-2/5-LOX dual pathways and proinflammatory cytokine TNF-α. Quercetin is isolated from *Allium cepha* acts as most potent anti-inflammatory agent by targeting Arachidonic acid dependent pathways (COX and LOX) and independent pathways such as TNF-α, IL-1β and IL-6.

**Plant-derived inhibitors affecting nitric oxide production**

Baicalin and wogonin are present in *Scuttellaria baicalensis Georgi* belongs to the family Lamiaceae. The anti-inflammatory potential of baicalin is due to its antioxidant property and ability to inhibit LPS induced NO production, iNOS gene expression and increases in TNF-α levels in RAW 264.7 cells

**Plant-derived inhibitors affecting NF-κB signaling pathway**

Avicins are a family of triterpenoid saponins separated from *Acacia victoria Bentham* belongs to the family leguminosae. They inhibit the COX-2 expression by inhibiting NF-κB pathway. Parthenolide is a sesquiterpene lactone isolated from *Tanacetum parthenium* which is commonly used in folk medicine as a remedy for treating inflammatory diseases. The anti-inflammatory potential of parthenolide is due to its ability to inhibit NF-κB pathway Silymarin is a bioactive flavonoid isolated from *Silybum*

*marianum* belongs to the family asteraceae, whose potent anti-inflammatory activity is due to the ability of inhibiting NF-κB pathway.

**Plant-derived inhibitors affecting the proinflammatory cytokine formation**

Nobiletin is a polymethoxy flavonoid isolated from citrus fruits. Nobiletin is considered as potent inhibitors of $PGE_2$ and proinflammatory mediators. Pycnogenol is a phenolic compound purified from the bark of *Pinus maritime Mill* belongs to the family pinaceae. Pycnogenol is an effective anti-inflammatory compound which is highly capable of reducing the synthesis of IL-1β and appearance of IL-1β mRNA in LPS stimulated RAW 264.7 cells [14]. Ginsenosides are terpenes isolated from *Panaxginseng* C.A.Meyer belong to the family araliaceae.

## 4. Plant-derived antioxidant agents

Antioxidant secondary metabolites of medicinal plants can minimize the generation of reactive oxygen species and alleviate the inflammatory diseases caused by oxidative stress The phenolic and flavonoid constituents of metabolites contribute to the antioxidant activities of medicinal plants. Antioxidants like flavonoids, polyphenolic compounds and phenolics derived from plant sources significantly prevent oxidative stress conditions caused by free radicals such as reactive nitrogen and oxygen species. Reactive oxygen species are originated from NADPH oxidase, myeloperoxidase of neutrophils and xanthine oxidase of endothelial cells [15]. Some of the antioxidants from medicinal plants induce antioxidant enzymes, which deplete oxidants in inflammatory cells.

Glycyrrhizin is triterpenoid saponin isolated from the bark of *Glycyrrhiza glabra* (Fabaceae), is a potent antioxidant. Silymarin is a flavonoid isolated from flower buds of *Cynara cardunculus var. scolymus* (Asteraceae), is a potent antioxidant. Eugenol is a constituent of the phenyl propanoids group of chemical compounds extracted from the leaf of *Ocimum sanctum* Linn (Lamiaceae), shows potent antioxidant activity [16]. Bakuchiol is a meroterpene isolated from the seed of *Psoralea corylifolia* Linn (Fabaceae), used as an antioxidant. Santalol is an organic compound comes under sesquiterpene category isolated from the bark of *Santalum album* Linn (Santalaceae), shows antioxidant activity *Withania somnifera* (Solonaceae) roots contain oxygenated ergostane type steroids known as withanolides are potent antioxidant compounds. Ascorbic acid commonly known as vitamin C is obtained from fruit of *Emblica officinalis* (Euphorbiaceae) is a well-known potent antioxidant. Curcumin is a diaryl heptanoid obtained from the leaf of *Curcuma domestica Valeton (*Zingiberaceae), is a potent antioxidant Carotenoids are organic compounds present in chloroplasts and chromoplasts obtained from roots of *Daucus carota* (Apiaceae) are potent antioxidants. Fenchone is a monoterpene obtained from fruit oil of *Foeniculum vulgare* Mill (Apiaceae) shows antioxidant activity.

## 5. Conclusion

Based on the Inhibitory activities of plant derived bio active compounds Ethanopharmacologists develops potential anti-inflammatory and antioxidant drugs for curing both inflammatory and oxidative stress related diseases. The present research continuous to focus on the assessment and development of non toxic anti-inflammatory and anti oxidant compounds from the medicinal plants by *invitro* and *invivo* activity guided fractionation.

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