

Botanicals that Mediate Chronic Inflammation and Modulate Immune Response

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Discussion

INFLAMMATORY RESPONSE

Our body's protective inflammatory response is mediated by the immune system to promote healing and recovery. This response involves a complex and multi-layered series of actions and interactions at the cellular and other levels of our physiology.

Many compounds are found to both promote inflammation and to support its resolution. For decades, researchers and clinicians have focused on addressing inflammatory conditions through the use of compounds to target specific inflammatory pathways, such as the well-known COX-2. The downside of a mono-target approach is the degree of adverse side effects. Hence, there is currently a huge amount of research on plant medicines because they have the inherent ability to work on multiple pathways to modulate cellular and physiological functions.

Researchers find that many of the botanicals, which have successfully and safely been used for inflammatory conditions for thousands of years, contain a wide array of natural compounds that also exert a normalizing influence. For this reason, the modulatory influence of herbs can be especially beneficial to calm inflammation while supporting normal cellular functions.

The activation and resolution of inflammation is a complex process that is triggered by external or internal events. Acute inflammation is resolved in a short period of time. When inflammation persists, there may be dysfunction of the immune response resulting in disruption of normal functioning of the cells, organs and tissues of the body. Chronic inflammation, caused by multiple factors, is widely recognized as being a major causative factor in most chronic disease conditions including autoimmune, neuro-degenerative, cardiovascular, cancer, arthritis and many more.¹⁻³

Some of the key players involved in the inflammatory process play a dual role in the body. Many compounds that promote

the inflammatory process also play a role in the resolution of inflammation, healthy function and homeostasis.¹⁻⁵ These include enzymes (such as the cyclooxygenase), lipids (the prostaglandins) and proteins (the cytokines and others). This discussion is necessarily highly simplified due to the vast amount of research and information now available. Further research is intriguing and offers many insights.

The oxygenation of free, unbound arachidonic acid via two main pathways is the start of the pro-inflammatory cascade. The enzyme cyclooxygenase (COX) helps convert arachidonic acid to prostaglandins (PGs) which further produce other compounds. The two main COX enzymes of interest to researchers and clinicians are known as COX-1 and COX-2. The former is naturally produced in the body, is implicated in the inflammatory process and is also found to play a role in homeostasis and health, such as in the gastric mucosa and in the kidneys. COX-2, mostly produced in response to inflammation, induces the inflammatory cascade, though in some cases COX-2 and its products are found to help resolve inflammation.⁴⁻⁶

PGs, key players in the inflammatory process, are naturally present in human tissue and play diverse roles including regulation of essential physiological processes. These include blood clotting, bone metabolism, nerve growth, kidney function, blood vessel tone and immune responses.⁴ COX-2 is also implicated in protective functions. For example, it is an important modulator of brain health, known for its role in neural response, development, imprinting and adaptation.⁴ However, chronic activation of COX-2 energizes an inflammatory cascade which provokes numerous disease processes.⁴ Hence, research and clinical efforts over the last decades have been focused on compounds that inhibit the COX enzymes and its products, including the pro-inflammatory PGs. The desirable inhibition of COX-2 with mono-targeting agents often causes concurrent inhibition of COX-1 with resulting dysfunction in tissues where it plays a

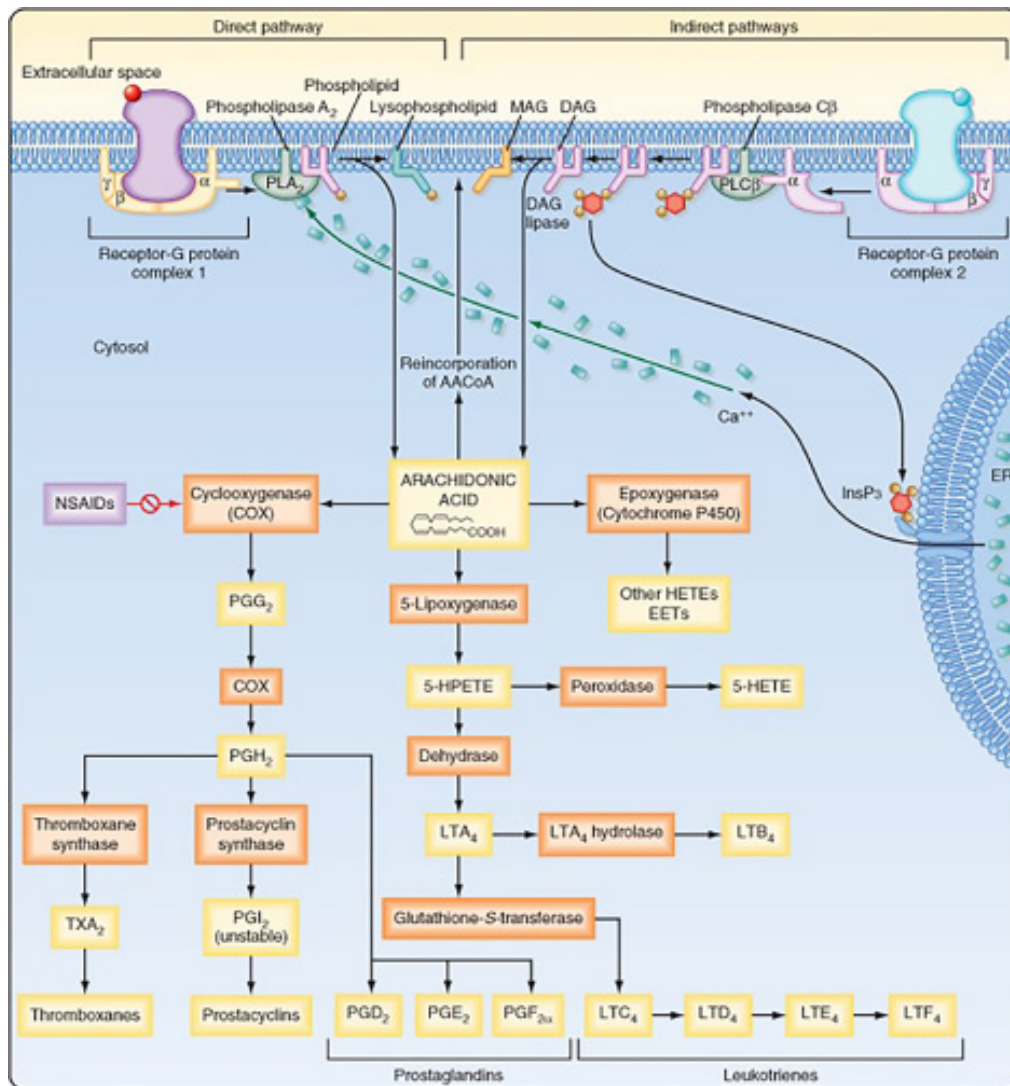
modulatory role, such as in the gastric mucosa.^{4,5} Similarly, PGs are implicated in both promotion and resolution of inflammation.

Research indicates they can respond contextually to either promote inflammation, enhance resolution of inflammation or support homeostasis. PGs can act to support homeostasis in the body including intracellular cell-signaling pathways.³ Increased PGs are found in both acute and inflammatory conditions. PGs mediate a complex array of biological processes including cytokine production. Specialized cytokine proteins modulate the inflammatory response. Cytokines such as IL-1 and IL-6 (interleukin 1 and 6) and TNF (tumor necrosis factor) provoke an inflammatory response that involves multiple response mechanisms, complex interactions and cell-signaling processes. Many pathways become dysregulated or dysfunctional.^{2,7,8}

There are numerous other factors involved with the promotion

of inflammation. An inflammatory cascade and series of compounds is elicited from the activity of the 5-LOX (lipoxygenase) enzyme, which also plays a major role in the inflammatory process.⁵ The transcription protein NF- κ B (nuclear factor kappa-beta), another key player in the inflammatory response, also regulates gene expression and influences cell health.² NF- κ B is a protein that promotes expression of pro-inflammatory factors⁸ and is linked to expression of multiple disorders including arthritis and cellular disturbances.^{9,10}

A great deal of research is focused on the role and efficacy of botanicals to mediate chronic inflammation and to support the return of dysregulated biochemical pathways to normal and thus restore homeostasis and health.^{2,8} These herbs are found to both inhibit and modulate formation of inflammatory compounds to prevent continuation of the inflammatory cascade and help support a return to healthy homeostasis.



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BOTANICALS THAT MULTI-TASK INFLAMMATION PATHWAYS

BOTANICAL	NF- κ B	COX-2	LOX-5/12	IL-6	TNF- α	AP-1	PG2
Andrographis (<i>Andrographis paniculata</i>)	X			X	X		
Chinese Skullcap (<i>Scutellaria baicalensis</i>)	X	X	X	X	X		X
Feverfew (<i>Tanacetum parthenium</i>)	X	X	X	X	X	X	X
Ginger (<i>Zingiber officinale</i>)	X	X		X	X		X
Indian Frankincense (<i>Boswellia serrata</i>)	X	X	X		X		
Magnolia Bark (<i>Magnolia officinalis</i>)	X	X					

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Botanicals that Mediate Chronic Inflammation and Modulate Immune Response



Frankincense (*Boswellia serrata*)

Frankincense is revered as a sacred plant and potent medicine in many cultures. Both Ayurvedic and Chinese medicines use it to invigorate and move the blood to promote health and dredge out the system. It is traditionally used in Ayurvedic medicine to alleviate both rheumatoid and osteoarthritis. Studies with *Boswellia* extract confirm these benefits.^{11,12}

Frankincense contains gum-like resinous constituents known as boswellic acids which exhibit powerful anti-inflammatory, analgesic and health-promoting activity. Boswellic acids are the key compounds from Frankincense that are studied including one known as AKBA (acetyl-11-keto-beta-boswellic acid).

Boswellia extract is found to benefit those with inflammatory bowel conditions.¹³ Boswellic acid extracts are found to down-regulate multiple inflammatory pathways including 5-LOX, COX-2 and NF- κ B. LOX acts as a biological fuel for cellular dysfunction by stimulating EGF (epidermal growth factor), VEGF (vascular endothelial growth factor) and other growth factors.¹⁴⁻¹⁶ They are also found to induce apoptosis, modulate cell-signaling^{15,17,18} and to exert immuno-modulatory influence.¹⁹⁻²¹

Boswellia crosses the blood-brain barrier and exhibits neuro-

protective qualities. Widely studied for its possible benefits to brain conditions, including brain injury, it is reported to reduce cerebral edema²²⁻²⁶ and to inhibit neuro-degeneration of the hippocampus.²⁷ Studies find *Boswellia* beneficial for learning and memory disorders.²⁸



Feverfew (*Tanacetum parthenium*)

A member of the Aster family, Feverfew is native to the Balkan Peninsula but is grown around the world. Feverfew is traditionally used to prevent migraine headaches.²⁹ Its name comes from the Latin word *febrifugia*, meaning “fever-reducer.” The ancient Greeks and early Europeans used Feverfew for multiple disorders including psoriasis, rheumatism, colic and inflammation. The ancient Greek physician Dioscorides used Feverfew for all “hot” conditions.³⁰

Feverfew contains many compounds including flavonoids, volatile oils and sesquiterpene lactones. Parthenolide is perhaps the most studied of the sesquiterpene lactones, valued for its anti-inflammatory properties.³¹ Studies show that parthenolide interferes with the inflammatory actions of arachidonic acid, histamine and NF- κ B.^{32,33} NF- κ B, a transcription factor, is a stimulator protein that can activate growth genes, promoting uncontrolled cellular growth.³⁴ Parthenolide is found to inhibit the 5-LOX and COX pathways

and to help prevent conversion of arachadonic acid to prostaglandins.²⁸

Feverfew inhibits pro-inflammatory, cytokine-mediated cell-signaling and inhibits prostaglandin synthesis through various pathways. It is thought to benefit migraines through multiple pathways including inhibition of prostaglandin synthesis and by decreasing spasm of vascular smooth muscles.³⁰

Magnolia (*Magnolia officinalis*)



The highly-aromatic Magnolia bark is a primary herb in Chinese medicine, used for both respiratory and digestive benefits. It is traditionally revered to help calm respiratory allergies including asthma. Magnolia bark is rich in many biologically-active compounds including alkaloids, coumarins, flavonoids, lignans and terpenoids.³⁶

One of Magnolia bark's main constituents is honokiol – a polyphenolic compound that exhibits powerful antioxidative and anti-inflammatory activity. Honokiol is also studied for its neuro-protective influence as it is found to calm oxidative and inflammatory processes in neurons and microglial cells.³⁶

Modern research finds that Magnolia bark extract strongly inhibits various inflammatory responses including COX-2, prostaglandin and TNF-alpha formation, and NF- κ B and IL (interleukin) factors.³⁷⁻⁴⁰ Magnolia bark extract is reported to protect against endothelial injury.^{41,42}

Andrographis (*Andrographis paniculata*)



This herb is highly regarded as a powerful agent to alleviate inflammatory and infectious diseases in both Chinese and Ayurvedic medicines. Chinese medicine describes Andrographis as a very bitter and cold tonic capable of removing “pathogenic heat” from the blood – meaning it was often used to treat serious conditions. Andrographis is anti-pyretic and anti-inflammatory. Traditional medicine reveres it as an antibacterial, antifungal, antiviral and choleric with adaptogenic properties. It is also considered to be both hepato-protective and a liver tonic.

Found to be high in flavonoids and diterpenoids, Andrographis exerts powerful anti-inflammatory influence. It is able to modulate both the humoral and cellular adaptive immune system. It inhibits NO (nitric oxide) and prostaglandin production⁴³⁻⁴⁷ along with COX-2 protein expression.^{45,48}

Modern studies verify its hepato-protective benefits and find that it also exerts the ability to normalize glucose levels, perhaps explained by its ability to increase antioxidant enzyme activity. Andrographis extract is found to reduce lipid peroxide activity and inhibit formation of oxygen-derived free radicals.^{47,49} It also enhances SOD (superoxide dismutase), an

enzyme involved with antioxidant activity.^{47,49}

Chinese Skullcap (*Scutellaria baicalensis*)



This yellow root, known as Huang Qin (Yellow Gold) in Chinese medicine, is one of the “Three Yellows” of Chinese medicine that are used to alleviate inflammatory and infectious conditions. Chinese Skullcap root is a rich source of over 35 flavonoids. The flavonoid baicalen shows impressive anti-inflammatory and antioxidant qualities. It is found to inhibit LOX and IL expression and to prevent COX-2 gene expression and prostaglandin synthesis.

Chinese Skullcap is anti-microbial, anti-pyretic and anti-inflammatory. Extract of Chinese Skullcap is found to inhibit multiple inflammatory pathways including cytokine, NF- κ B and VEGF production.⁵⁰⁻⁵⁴ It is also found to inhibit angiogenesis⁵⁵ and to promote normal cell-cycle function.⁵⁶



Ginger (*Zingiber officinale*)

This world-renowned and well-loved herb has been used as cooking spice, herbal remedy and revered medicine for centuries. It is a daily household remedy for digestive upset, sore throat, colds and flu. Known as a valuable anti-nausea remedy it is also a digestive carminative. Ginger aids circulation and is used to warm the system during cold weather. Herbalists also use Ginger to enhance the effectiveness of other herbs in a formula by supporting digestion and circulating the herbs. Its active ingredients are its many volatile oils.^{57,58}

Ginger has a thermogenic and diaphoretic effect. It demonstrates powerful antioxidant⁵⁹⁻⁶¹ and anti-inflammatory activity. It inhibits expression of COX-2, activation of NF- κ B^{62,63} and is found to modulate lipid peroxidation.⁶⁴ Ginger influences prostaglandin metabolism, is a potent inhibitor of thromboxane synthesis and is found to significantly inhibit platelet aggregation and inflammation.⁶⁵⁻⁶⁷



Bromelain (*Ananas comusus*)

Bromelain, a proteolytic enzyme, is a component of pineapple commonly used as a digestive aid. It demonstrates anti-edematous, anti-inflammatory and fibrinolytic activities. It is also an immuno-modulator and modulates cytokines.^{68,69} Bromelain is well-absorbed orally, and therapeutic effects are enhanced with higher doses.⁷⁰



Black Pepper (*Piper nigrum*)

Black Pepper is widely known for its ability to enhance the bioavailability of herbs and nutrients. In Chinese and Ayurvedic medicine it is added to

formulas for its ability to “move” other compounds to carry them throughout the body.

Piperine is a powerful and highly-researched compound in *Piper nigrum*. One possible way that piperine is thought to enhance bioavailability is through influencing the cellular biomembrane and intestinal enzymes.⁷¹⁻⁷³

Piperine is found to reduce levels of pro-inflammatory mediators including COX-2, IL factors and TNF-alpha. It also supports healthy glutathione and SOD (super oxide dismutase) levels.^{74,75} It is found to inhibit VEGF and to modulate cytokine and growth factor responses.⁷⁶ Piperine is known to be antioxidative, anti-mutagenic, antibacterial and hepato-protective.^{72,77}

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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Frankincense

Feverfew

Herbs:135-142.

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