Botanicals to Support Cellular Defense, Immune, and Lymph Systems

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Discussion

This paper discusses the therapeutic synergy and clinical applications of *Artemisia annua* concentrated herbal extract in combination with its bioactive compound artemisinin and other powerful botanicals such as Red Clover, Burdock, and Celandine. The focused activity of artemisinin combined with the whole herb extract, which offers abundant flavonoids, is found to create a synergistic influence greater than either one alone.[1-3] Currently, artemisinin and several of its derivatives are used in combination with other compounds to combat malaria. Because of its inherent mode of action, artemisinin and its derivative compounds are widely studied for their promising use as antiproliferative agents, which are found to effect numerous cancer cell lines.[4] Through understanding how artemisinin combats malarial parasites, researchers discovered its impact on tumor cells. This activity largely relates to the iron-dependent bioactivation of the endoperoxide bridge component of artemisinin.[4]

The focused action of artemisinin and *A. annua* in combination with alterative herbs act to improve cellular nutrition and lymphatic drainage. Alteratives are traditionally used in herbal formulas to help stimulate a positive change in dysfunctional metabolic or tissue function, especially in chronic conditions. The alteratives Red Clover and Burdock were valued by Eclectic physicians for their ability to improve cellular and lymphatic drainage, which is essential to facilitate the body's natural healing process.

Alterative herbs often work through promoting healthy liver function. Celandine also exerts direct action on the hepatic system. These supportive herbs – Red Clover, Burdock, and Celandine – together provide tonification to the lymph, liver, and gall bladder systems where they help clear conditions of chronic stasis. This facilitates restoration of healthy function especially when combined with adaptogenic or other appropriate nutritional and herbal formulations.

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Artemesinin and *Artemisia annua* Whole Herb Extract

Artemisia annua is an aromatic, annual herb that grows worldwide. With a sweet aroma, it was known as Sweet Annie in Europe. Often combined with other herbs to dispel worms, European herbalists also knew it as Sweet Wormwood, distinct from other herbs known simply as Wormwood. In Chinese medicine *A. annua* is known as Qing Hao, in reference to its blue-green color (qing) and tall growth (hao). It is historically valued as a powerful medicine, very bitter and cold in nature, used for infections and pathogenic disease conditions.[5,6]

Qing Hao first appeared in a Chinese herbal medicine book over 2000 years ago. It was used to relieve hemorrhoids and to treat fevers. The ancient method of preparation was to pound the leaves, picked in spring or summer, in a mortar and pestle to express the juice.[6] Artemisia is traditionally used in Chinese medicine to treat malaria and relieve its alternating fever and chills. Known as a cooling agent, it is used to treat very specific types of heat conditions known as deficiency heat; most often expressing with night sweats along with fever. As such, it is most often combined in formulas with herbs appropriate to the person and their condition.[5,6]

Researchers study whole plant extracts because they are polypharmacies in themselves containing many compounds

including secondary metabolites that are formed primarily as part of the plants defense system.[1-3] Over 600 bioactive compounds have been identified in *A. annua*, which is especially high in sesquiterponoids and flavonoids.[7] Flavonoids in *A. annua* include artemetin, kaempferol, luteolin, myricetin, quercetin, and rutin and are found to exert antimalarial activity. Flavonoids are also known to offer a high degree of biological activity including immunomodulatory influence that can benefit those with chronic diseases.[2]

Artemisinin and Malaria

A. annua is the only known source of artemisinin (ART), which is considered a frontline medicine for the treatment of malaria. ART is found effective against multi-drug resistant strains of the *Plasmodium* parasites and also exerts a broad range of action throughout all stages of its life cycle. This helps eliminate the parasite and reduce the spread of the disease.[4,7]

Since the amount of artemisinin varies widely in plants, depending on where they are grown and in what conditions, standardized extracts of ART are utilized. ART is a highly-oxygenated sesquiterpene compound that contains an endoperoxide bridge found to be an essential component for its antimalarial activity.[4,7,8]

ART is found to selectively act on parasite-infected erythrocytes. Studies report that iron is the key factor that allows ART to bind to parasite macromolecules. ART is also found effective against other parasites, including Toxoplasma and Babesia, that contain little hematin.[4] Unrelated to the endoperoxide component, studies finds that ART accumulates within lipids and causes cellular membrane damage to the parasite.[4]

Bioactivation of Artemisinin

Plasmodium species metabolize hemoglobin into an insoluble compound (hemozoin) that is non-toxic to the parasite. In this process, an abundance of heme iron accumulates within the parasite due to release of soluble heme during the degradation of hemoglobin.[4] Heme, a ubiquitous molecule with multiple key functions, provides oxygen transport, electron transfer, and regulates transcription. Present in sub-molecular levels in most cells, heme is potentially toxic in its free form due to its high redox activity.

Redox-active heme is found to activate ART *in vitro*. The endoperoxide bride in ART accepts an electron from heme, which activates a progression of biochemical events.[9] Because of its inherent ability to interact with heme, ART and its derivative compounds are widely studied for their potential not only as antiparasitic agents, but also as antiproliferative agents. Tumor cells are found to maintain a high intracellular concentration of iron. This is because tumor cells have the ability to synthesize greater amounts of heme, which supports the dysfunctional cells' ability to sustain proliferation.[4,9,10,13,14]

In multiple studies, ART compounds demonstrate the ability to effect numerous cancer cell lines through multiple pathways.[3,4,9-14] ART and its derivatives are found to exert selective cytotoxic activity against cancer cells in vivo and in vitro[13], which is largely attributed to the endoperoxide bridge in the ART molecule. Intracellular heme is thought to act as the mediator for this cytotoxic response.[4,9,10,13]

ART compounds exert a wide range of action selectively against tumor cells. ART and its derivative compounds are found to inhibit tumor cell growth and angiogenesis both *in vivo* and *in vitro*.[3,10,11] ART compounds are found to inhibit cell growth through promoting cell cycle arrest and modulating nuclear receptor responsiveness.[12] They demonstrate the ability to decrease cell proliferation, induce apoptosis, and inhibit angiogenesis.[3,4,10-12] ART and its derivatives are also found to influence numerous cell-signaling pathways both in vitro and in animal models.[3,12]

Scientists continue to investigate ART's pathways and mechanisms of action.[4,10,13,14] ART and other sesquiterpene lactones are found to inhibit activation of NF-kB (nuclear factor-kB), which is a key activator protein in the development and progression of cancer.[15] ART and some of its derivative compounds are also found to inhibit certain viruses including human cytomegalovirus, some members of the Herpesviridae family, and others.[8]

Burdock Seed (*Articum lappa*)

Burdock seeds are used in traditional Chinese medicine to clear heat and inflammation.[16] Arctigenin and arctiin, lignans in Burdock seeds, are studied for their numerous bioactive influence. Arctigenin is found to posses antioxidant, anti-inflammatory, anti-proliferative, antitumor, and antiviral activity.[16-20] Arctigenin inhibited activation of pro-inflammatory cytokines including TNF (tumor necrosis factor), IL-6, and overexpression of NO (nitric oxide) – the latter through down-regulating iNOS (inducible nitric oxide synthase) pathways.[16,17] Studies suggest that arctigen has the ability to modulate immune response.[16] It is also found to inhibit NF-kB pathways.[20]

Red Clover Aerial Parts (*Trifolium pratense*)

Red Clover, a member of the Legume family, is traditionally used in many cultures for multiple purposes. This powerful alterative herb is highly

valued in European herbal traditions and by the American Eclectic physicians to support healthy function of the lymph and blood.[21,22,23] Red Clover flowers, a rich source of isoflavones, also contain minerals (calcium, chromium, magnesium, phosphorus, and potassium), and vitamins (niacin, thiamine, and vitamin C).[24]

Celandine Whole Herb (*Chelidonium majus*)

Celandine grows wild throughout Europe, parts of Asia, and in North America. Used widely in traditional medicines, Celandine is well-known for its ability to treat a diverse range of issues including ulcers, oral infections, and lung conditions. It is best known for its benefits in liver disorders. Extracts of the leaves, flowers, and root are traditionally used to stimulate bile production and pancreatic digestive enzymes. Traditional herbalists use Celandine for dyspepsia, liver diseases, biliary disorders, and irritable bowel syndromes.[25,26]

Celandine contains numerous alkaloids including many isoquinoline alkaloids. Over 70 compounds are noted including alkaloids, flavonoids, saponins, vitamins (including A and C), minerals, and sterols.[26] Celandine contains isoquinoline alkaloids, including berberine, which are known for their anti-inflammatory activity.[25]

Studies find that the plant extract demonstrates a wide variety of activity including anti-inflammatory, antimicrobial, immunomodulatory, antitumor, cytotoxic, and hepatoprotective.[25,26] An *in vivo* study found the crude extract significantly prevented liver damage from carbon tetrachloride and other compounds.[26] Celandine extract and its compounds are found to reduce levels of inflammatory compounds and pathways including TNF, IL-6, COX-2, and others. It demonstrates a modulatory effect on T-cells and enhances production of regulatory T-cells, which helps reduce inflammation.[25,26]

Black Pepper Fruit (*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 help circulate other compounds throughout the body.

Piperine is a powerful and highly-researched compound. The pungent alkaloid piperine gives pepper its pungent quality.[27] One way that piperine is thought to enhance bioavailability is through influencing the cellular biomembrane and intestinal enzymes.[28-30]

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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