High Potency Ginseng Combination

High Potency Ginseng Combination is a formulation designed for the relief of stress and exhaustion. It contains herbs recognised to improve tolerance to psychological and physiological stress, minimising the effects of stress on the body. This combination of the five ginsengs—Siberian, Indian, Korean, American and Tienchi (notoginseng)—may assist physical and mental performance under stress, reduce fatigue and stress-associated mood changes, and also enhance the immune response.

HERBS THAT MAY ASSIST

Eleutherococcus senticosus	(Siberian ginseng) root
Withania somnifera	(Indian ginseng) root
Panax ginseng	(Korean ginseng) root, white
Panax notoginseng	(Tienchi ginseng) root
Panax quinquefolius (formerly *P. quinquefolium)*	(American ginseng) root

CLINICAL APPLICATIONS

Key Applications

- Chronic stress
- Stress-associated fatigue
- To enhance cognitive function under stress
- Stress-associated anxiety or depressive symptoms
- Immune depression associated with chronic stress

BACKGROUND/TECHNICAL INFORMATION

***Eleutherococcus senticosis* (Siberian ginseng)** root is traditionally used as an adaptogen, immunomodulator and tonic; used to prevent colds and flu and to increase energy and vitality, particularly with fatigue and stress.[1,2]

***Withania somnifera* (Indian ginseng)** root is also traditionally used as a tonic and adaptogen, with the additional properties of being a mildly sedative, anti-inflammatory, immunomodulatory, and anti-anaemic.[3]

***Panax ginseng* (Korean ginseng)** root, again, is adaptogenic, tonic and immunomodulatory, as well as being used as a cardiotonic, and for enhancing cognitive ability.[4]

***Panax quinquefolius* (American Ginseng)** possesses similar beneficial effects to *Panax ginseng*. For example, *P. quinquefolius* has been widely used in traditional medicine for its

antioxidant and antifatigue properties.[5] American ginseng is used as an adaptogen, for increasing resistance to environmental stress, as a general tonic, stimulant, diuretic, and digestive aid. It has also been used for many other applications, including anaemia, diabetes, insomnia, for stimulating immune function, improving stamina and preventing the effects of ageing.[6]

***Panax notoginseng* (Tienchi ginseng)** root, also known as *Panax pseudoginseng*, has the traditionally recognised properties of being anti-inflammatory, antihaemorrhagic, and cardioprotective.[7] It has also been described as being antihypertensive, neuroprotective and haemostatic, antioxidant, hypolipidaemic, hepatoprotective, and renoprotective.[8]

RESEARCH

ADAPTOGENIC / ANTISTRESS

The stress response involves the complex interaction between the elements of the hypothalamic-pituitary-adrenal (HPA) axis. The process of adaptation may help to prevent the extreme responses which can occur with severe acute or prolonged stimulation, and which may result in nervous exhaustion and fatigue. One of the features of this is gradual loss of adrenal function, which may be reflected by adrenal hypertrophy. Gastric ulceration is another consequence of chronic stress. Adaptogens may help this process of adaptation, and enhance recovery, through attenuation of the HPA axis response.

Panax quinquefolius and *Panax ginseng* have shown potent adaptogenic activity in animal models of chronic stress. Administered daily from prior to commencement of the stress, they significantly reversed the chronic stress-induced changes which included increases in gastric ulcer incidence, adrenal gland weight, and plasma CK (creatinine kinase) and AST (aspartate transaminase) enzyme levels,* and plasma corticosterone.[9,10] The effects of *P. quinquefolius* on countering the elevations in plasma corticosterone have been found to occur with both acute and chronic stress models. [11]

Withania has also been found to be adaptogenic in a model of chronic stress, attenuating hyperglycaemia, glucose intolerance, and increases in plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression.[12]

Withania has been found to be protective of the physiological-stress induced behavioural and biochemical alterations in mice that result from sleep disruption[13] and from toxin administration.[14] These studies found significant antioxidant benefits, confirmed by another study which also showed efficacy in preventing stress-induced gastric ulceration.[15]

In an animal model of psychological stress, ginseng total saponins and ginsenosides Rg3 and Rb1 have been found to reduce brain markers of stress, indicating a possible neuroprotective role.[16]

Possible mechanisms:

Major constituents of *P. quinquefolius, P. ginseng and P. notoginseng,* the ginsenosides, have been shown to have corticosteroid-like effects, binding to the glucocorticoid receptor. These steroidal saponins may partly explain the attenuating effects of Panax on elevated corticosterone in both acute and chronic stress models.[17]

Another mechanism for the effects of these ginsengs has been suggested following other studies of the saponin fraction. Ginseng saponins have been found to attenuate the increase in plasma

* Elevations of these enzymes reflect tissue damage

corticosterone levels induced both by stress and by injection of adrenocorticotropic hormone (ACTH)—suggesting the mechanism of inhibition of corticosterone is through blockade of ACTH action at the adrenal gland.[18]

Panax ginseng saponins and their metabolites, particularly the protopanaxatriol-type, have been found effective in reducing the adrenal secretion of catecholamines stimulated by acetylcholine (which simulated an adrenal stress response *in vitro)*.[19]

STRESS AND FATIGUE

Siberian ginseng has the potential to improve chronic fatigue of a moderate severity. In a randomised double-blind placebo-controlled trial of subjects with a history at least 6 months of chronic fatigue of unknown cause, the equivalent of 2-4 g of dry root or placebo were administered via capsules daily for two months, after which all subjects were given Siberian ginseng. In the subgroup of 45 individuals with moderate fatigue there was a statistically significant improvement in fatigue levels over placebo (p=0.04), and when the placebo group was given the treatment in month 3 and 4 they achieved the same level of improvement, still being blind to their initial treatment. This study indicates the potential for Siberian ginseng to improve moderate fatigue.[20]

Panax ginseng has shown antistress and antifatigue effects in studies in mice. It was found to protect against various forms of stress, including heat stress, and in other tests increased endurance and resistance to fatigue.[21]

Animal models of swimming stress have confirmed the traditional uses of Siberian ginseng in reducing the effects of stress and fatigue by significantly prolonging activity.[22] Withania has similarly shown benefits in increasing tolerance to stress in this same model.[23,24]

COGNITIVE PERFORMANCE

Panax ginseng has been found to have beneficial effects on cognitive performance. In two double-blind, placebo-controlled, balanced-crossover design studies, healthy young adults completed a battery of cognitively demanding tasks. The results showed that *Panax ginseng* extract significantly enhanced performance of a mental arithmetic task and ameliorated the increase in subjective feelings of mental fatigue experienced by participants during the later stages of the task. Accuracy was also improved.[25,26]

MOOD

Prolonged stress is associated with alterations in brain neurotransmitters including the monoamines noradrenaline, dopamine and serotonin. Dysfunction of these monoamines due to prolonged stressful conditions has been associated with a wide range of central and peripheral disorders like anxiety, depression, drug abuse, obsessive compulsive disorder, eating and sleeping disorders, hyperglycaemia, and decreased immune response.[11]

In an animal model, *P. quinquefolius* root was evaluated for its effects in acute immobilisation stress and in chronic unpredictable stress (different stressors for 7 days). In both stress models, pretreatment with American ginseng significantly restored the induced changes in the levels of noradrenaline, dopamine and serotonin in different regions of the brain.[11]

Glycowithanolides from withania have been found in rat models to exhibit anxiolytic effects comparable to that produced by benzodiazepines, and reducing brain levels of anxiety markers; and also elicited antidepressant effects comparable to a tricyclic antidepressant.[27]

IMMUNE ENHANCEMENT

Multiple immune effects have been found for the ingredients of *High Potency Ginseng Combination,* including anti-arthritic effects and antiviral effects in humans.

In a randomised controlled trial of 84 patients with rheumatoid arthritis, the administration of saponins from notoginseng were found to result in significant clinical improvement. In addition to routine therapy, notoginseng saponins resulted in significantly greater improvements in joint swelling, tenderness, pain, morning stiffness, and in serological tests of inflammation, and markers of disease activity.[28] Extracts of notoginseng have also shown anti-inflammatory effects in a collagen-induced arthritis model, delaying the onset and progression of arthritis.[29]

A polysaccharide-rich *P. quinquefolius* extract, which *in vitro* has been shown to enhance production of interferon-γ (IFN-γ) and IL-2 (major cytokines involved in antiviral immune defence), has been shown to have beneficial effects with respect to viral upper respiratory tract infections. In a double-blind randomised placebo-controlled trial this particular extract, taken over a period of 4 months, was found to reduce the incidence of colds, the severity of symptoms and the duration of colds.[30]

In vitro studies have confirmed anti-inflammatory and immunomodulatory effects of *P. notoginseng*. Dendritic cells (DCs) are a type of antigen-presenting cell that play a central role in the regulation of both inflammation and adaptive immunity. One of the receptor types on DCs are the toll-like receptors (TLRs), which when stimulated lead to up-regulation of inflammatory mediators such as the pro-inflammatory cytokines tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These studies show that notoginseng inhibits the production of specific inflammatory molecules and innate immune responsiveness by DCs following TLR activation.[31]

Other immune effects of the components of this formulation include the following:

- *P. ginseng* has shown immune enhancing activity in an animal model, increasing the production of IFN-γ and TNF-α. [32]
- Saponins (including ginsenoside Rb1, Re, and Rg1) [33] and polysaccharides[34] from *P. notoginseng* have shown immunostimulating activity *in vitro*.
- Ginsenoside Rg1 (*P. ginseng* and notoginseng), which has the property of increasing the activity of T helper cells, has been found in an animal model to assist in the prevention of disseminated candidiasis through a T helper type-1 cytokine response.[35]
- Eleutherococcus has also shown immunomodulatory effects, enhancing humoral and cell-mediated immunity in animal models.[36]
- Withania has been found to enhance depleted T cell numbers and enhance T helper-1 cytokine production in a chronically stressed animal model,[37] and, along with its major constituent withanolide-A, it has been shown to augment cell-mediated and humoral immunity, also through a T helper-1 mechanism.[38]
- Withaferin, a lactone found in withania root, has anti-inflammatory properties, potently inhibiting nuclear factor-κB activation by preventing the TNF-induced activation of inhibitory kappaB kinase beta.[39] Other *in vitro* and *in vivo* studies have shown anti-inflammatory effects of withania root.[40]
- Withania has also shown immunopotentiation, enhancing cell mediated immunity[41] and the response to vaccination in animals.[42]
- Animal models of swimming stress have found that Siberian ginseng as well as reducing fatigue, also protected immunity; inhibiting both elevations in corticosterone and reductions in natural killer cell activity.[22]

CAUTIONS/CONTRAINDICATIONS

Contraindications

- **Warfarin**: American ginseng can decrease the effectiveness of warfarin therapy. In healthy patients receiving warfarin 5 mg daily, American ginseng 1 g twice daily, was found to reduce the international normalised ratio (INR).[6] *Panax ginseng* also has a caution with warfarin.[4]
- **Pregnancy** – see below.
- **Oestrogen-sensitive disorders:** as *Panax notoginseng* has some oestrogenic activity,[8] people with endometrial or breast cancer and other oestrogen-sensitive conditions should avoid this product.

Cautions

- **Antidiabetes drugs:** both American ginseng[6] and Siberian ginseng[1] may lower blood glucose. Theoretically, concomitant use with antidiabetes drugs might enhance blood glucose lowering effects and possibly cause hypoglycaemia. Monitor blood glucose.
- **Monoamine oxidase inhibitors (MAOIs):** Theoretically, American and Korean ginsengs [and notoginseng] may interfere with MAOI therapy. There is one case report of insomnia, headache, and tremors with concomitant phenelzine (Nardil) and unspecified ginseng use. There is also one case report of hypomania with concomitant phenelzine (Nardil) and unspecified ginseng use.[4,6]
- **Traditional cautions** of not using Siberian ginseng in acute infection or fever,[1] and *Panax ginseng* in fever, excessive menstruation, nose bleeds, acute infections, and acute asthma.[4]
- **Avoid concurrent use with other stimulants**
- **Hypertension:** caution with Siberian[1] and Korean ginseng.[4]
- **Sedatives:** (withania) theoretical additive effects – monitor.[43]
- **Immunosuppressants**: theoretically withania may reduce the effectiveness.[43]
- **Thyroxine**: withania may enhance T4 – monitor.[43]
- **Sensitivity to solanaceae family:** (withania) caution.[43]
- **Peptic ulcer disease:** withania may cause gastric irritation – monitor.[43]
- **Drugs metabolised by CYP1A and CYP2D6:** *Panax ginseng* may inhibit activity of these enzymes. Theoretical risk of unknown clinical significance. Monitor.[44]

Surgery

Suspend use 1 week prior to major surgery.

Pregnancy and lactation

- **Not for use in pregnancy:** Ginsenoside Rb1, an active constituent of American, Korean and Tienchi ginseng, has been found to have teratogenic effects in animal models.[6] Withania is also contraindicated in pregnancy.
- Compatible with breastfeeding.

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