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Review Article

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# Formulations of dietary supplements and herbal extracts for relaxation and anxiolytic action: Relarian™

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## Summary

Dietary supplements are widely used for desired effects on memory, insomnia, mood and anxiety. This review focuses on supplements which have anxiolytic or mild relaxation properties and enhance mood. For example, Kava *(Piper methysticum)* is reported to have anaxiolytic actions and to reduce tension through skeletal muscle relaxation. Dried passion flower (genus Passiflora) is reported to reduce insomnia and hysteria. Skullcap (genus *Scutellaria*), hops (*Humulus lupulus*), lemon balm (*Melissa officinalis*) and Valerian (*Valeriana officinalis*) root are all herbs reported as anaxiolytic calming agents. Further, extracts of Magnolia and Phellondendron bark are mild sedatives. Supplements such as γ-aminobutyric acid (GABA), theanine, tryptophan and 5-hydroxytryptophan (5-HTP) are reported to promote relaxation. In general, these supplements appear to act as GABA receptor agonists or to boost GABA levels, although Kava inhibits both norephinephrine uptake and sodium and potassium channels and 5-HTP may act through elevation of serotonin. While questions remain in the literature regarding the medicinal value of these supplements in treating mood and anxiety disorders, based on cellular and animal studies as well as human clinical trials the literature supports a role for these preparations as useful alternatives in the management of the stress and anxiety of everyday life.

**key words:** **anxiolytic • dietary supplement • valerian • theanine • GABA • 5-HTP**

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## Background

The use of dietary supplements to support health is very popular and ranges from the use of antioxidants to reduce the risk of cancer and cardiovascular disease to the use of probiotics to maintain a balanced body flora [1–4]. Dietary supplements are also used for basic nutritional purposes and to address age related degenerative neurological and cardiovascular conditions such as Alzheimer's and Parkinson's diseases and atherosclerosis [5–9]. In addition, there are also numerous studies which support the popular use of dietary supplements to affect neurochemistry associated with improved mental focus, mood, behavior and energy levels [9–13].

The neuropharmacology of dietary supplements has primarily focused on use and discovery of natural antidepressants, anxiolytics and sedatives or sleep aids [14–20]. For example, in humans, at doses of 400–900 mg daily of either whole valerian (*Valeriana officinalis*) or aqueous root extracts have demonstrated anxiolytic effects, decreased restlessness, reduced somatic arousal and improved sleep [21–32]. In some of these studies the anxiolytic and stress relieving properties of valerian were observed when combined with hops (*Humulus lupulus*) [23,24] or lemon balm (*Melissa officinalis*) [30,32]. Kava (*Piper methysticum*) has also been shown to reduce anxiety and promote relaxation in humans [33] although potential hepatotoxicity have been associated with Kava supplementation [34,35] and subsequently banned in the United Kingdom. Extracts from herbs traditionally used for anxiolytic properties such as skullcap (genus *Scutellaria*), hops (*Humulus lupulus*), lemon balm (*Melissa officinalis*) have also been shown to reduce anxiety, relieve stress and improve sleep in humans in placebo controlled studies [23,24,32,36–38]. L theanine (delta-glutamylethylamide) is a Green Tea (*Camellia sinensis*)-derived amino acid which has been shown to cause relaxation in human studies [39]. Further, in placebo controlled studies in humans, L-theanine has been shown to modify alpha-band oscillatory brain activity during a visuo-spatial attention task demonstrating the L-theanine enhances focus and periods of attention to tasks [40–42]. The seeds from the woody shrub *Griffonia simplicifolia* are rich in 5-HTP, an amino acid dietary supplement which can elevate the levels of the neurotransmitter, serotonin in humans [43,44]. Serotonin levels are associated with good mood while low serotonin levels are associated with depression [45–48]. Moreover, supplementation with 5-HTP and its precursor, tryptophan, have been shown to elevate brain serotonin levels and enhance mood and a sense of well being [43–48]. St. John's wort (*Hypericum perforatum*) which has been traditionally used to control depression, has been shown in human clinical trials to be effective in the treatment of dysthymia [49]. Dried passion flower (genus *Passiflora*) has been traditionally used to reduce anxiety and insomnia and there are numerous studies in mice and rats which demonstrate a reduced anxiety and stress with passion flower treatment, however, only one human study shows that treatment with passion flower can serve as an anxiolytic in humans [50]. Further, extracts of Magnolia and Phellondendron bark have been shown to be anxiolytic in humans in one clinical study which recommends it use in premenopausal women [51]. Lastly, γ-aminobutyric acid (GABA), which is a neurotransmitter found in the human body and is found in herbs and natural product extracts and is also easily synthesized, is used as a popular supplement to reduce anxiety and stress. GABA is the chief inhibitory neurotransmitter and works to regulate neuronal excitability and thereby serves as a " brake" on the neural circuitry during stress. It is the brain's natural stress reliever. Low GABA levels in the brain are associated with depression, restlessness, anxiety, insomnia and a poor mood state. [52–57]. Because of the central role of GABA in controlling stress and anxiety, most research has focused on the development of drugs to boost GABA levels and the literature is awash in drugs which report to increase GABA or serve as a GABA agonist with remarkable medicinal values ranging from mood stabilizers to the treatment of depression and anxiety [58]. However, there are clinical studies which have focused on the use of GABA as a dietary supplement to relieve stress and anxiety in nonclinical settings [59–62]. Further, GABA supplementation has been shown in EEGs to increase relaxation-associated human brain alpha-wave production [unpublished data 63].

## The GABA Pathway

GABA (g-aminobutyric acid) is an inhibitory neurotransmitter of the central nervous system that reduces nerve impulse transmission between neurons through the hyperpolarization of postsynaptic membranes and the reduction of neurotransmitter release into the synapse through presynaptic G-protein coupled receptor inhibition of voltage-gated Ca++ mechanisms [64–66]. In order to mediate these two inhibiting effects, GABA binds at two distinct receptors. GABA-mediated fast synaptic inhibition due to the hyperpolarization of the postsynaptic membrane is the result of binding to the GABAA receptor which is a postsynaptic ligand-gated chloride and bicarbonate ion channel [64–66]. GABA-mediated inhibition of neurotransmitter release is the result of binding to the presynaptic GABAB G-protein coupled receptor. Postsynaptic GABAB receptors can also mediate a slow inhibitory effect through activation of potassium channels. In this regard, the inhibitory effect of GABA on the postsynaptic GABAA and GABAB receptors depend on both the resting- and Cl reversal-potential of the membrane [64–65]. Inhibitory sysnapses that use GABA are the most abundant synapse in the human brain. Therefore, the role GABA plays in inhibiting over excitation in the brain and thereby controlling anxiety and stress has been an area of significant interest and research.

In the search for anxiolytics and a means to control stress both GABA itself, and also synthetic drugs which agonize the GABA receptors, have been investigated for their ability to control anxiety, stress and mood [19,58,59,63]. For example, drugs that agonize the GABA receptors (GABAergic) include benzodiazepines, barbiturates, neuroactive steroids, anticonvutants, gabapentin and gamma hydroxybutyric and have been used to control anxiety, relieve pain, manage drug and alchohol addiction and to treat both depression and schizophrenia [19,58,59,63]. Indeed, low levels of GABA in the central nervous system are associated with anxiety, depression and insomnia [52–57] and the GABAergic benzodiazepines which include Xanax, Valium, Ambien and a host of others, have been successfully used to bolster GABA signaling and treat these conditions. Gabapentin, a GABA analogue has been shown to increase brain GABA levels and to successfully treat panic dissorders in humans [67].

In addition, GABA itself can cross the blood-brain barrier [68], and supplementation with GABA has been shown to increase brain alpha waves and serve as an anxiolytic agent [19]. While addiction and toxicity can be associated with the GABAergic drugs, GABA itself does not have any significant side effects [63]. Therefore, in addition to GABA supplementation, and in order to avoid the addictive qualities of synthetic drugs, there has been a great deal of both popular and scientific interest in the identification of natural supplements which will increase GABA signaling and serve as anxiolytic relaxants and sedatives.

Extracts from GABAergic anxiolytic herbs and plants have been shown to modify the GABA signaling pathway through GABAa receptor binding and elevation of GABAa receptor expression and GABA release *in vitro*. For example, crude methanol extracts of both the Noni fruit (*Morinda citrifolia*) and the female ginsing root (*Angelica sinensis*) exhibit competitive binding to the GABAa receptor *in vitro* [69,70]. Further, naturally occurring flavinoids isolated from Skullcap (*Scutellaria baicalensis*) have been shown to compete with benzodiazepine for binding to GABAa receptors expressed in *Xenopus* oocytes [71]. *In vitro* studies with rat brainstem preparations have shown that the kavalactones in extracts from Kava (*Piper methysticum*) compete with the GABAa agonist muscimol and also significantly reduce the discharge rate in the neurons of the nucleus tractus solitarius [72]. Not only have plant extracts been shown to bind to GABAa receptors, methanol extracts from the Arillus Longanae fruit has been shown to increase GAGAa receptor expression levels in cultured cerebellar granule cells [73]. Alternatively, hyperforin, a constituent of St. John's Wort (*Hypericum perforatum*) increases the release of GABA from cultured rat cortical synaptosomes [74] and maintains elevated synaptic GABA levels by inhibiting GABA reuptake [75]. Similarly, aqueous extracts of German chamomile (*Matricaria recutita*) and hops (*Humulus lupulus*) increase GABA levels in rat brain homogenate by inhibiting GABA transaminase while gotu kola (*Centella asiatica*) and valerian root (*Valeriana officiaonalis*) increase rat brain homogenate GABA levels through the activation of glutamic acid decarboxylase [76]. Valerian root and the valerenic acid extract of this root has been shown to compete with the GABAa agonist muscimol for benzodiazepine sites in rat brainstem preparations [77]. Further, valerenic acid both potentiates and inhibits GABAa receptors expressed in *Xenopus* oocytes [78] and using the voltage clamp technique has been shown to activate chloride currents associated with GABAa receptor binding [79]. The binding sites on GABAa for the valerian components, valerenic acid and valerenol have been mapped through point mutation recombinants to the beta2 and beta3 subunit [80]. Not only was valerenic acid and valerenol binging to GABAa abolished with these point mutations (N265M), in mice expressing these point mutations, the anxiolytic of valerian in the elevated plus maze and light/dark choice test was absent compared to wild-type mice [80]. Valerian root components also increase synaptic GABA levels by increasing GABA realease and decreasing reuptake in cultured slices of rat hippocampus [81]. Moreover, valerian extracts protect cultured rat hippocampal neurons from the toxicity of amyloid beta peptides [82].

Extracts from GABAergic herbs and plants have also been shown to have anxiolytic and calming effects in whole animal studies and in humans. For example, Asian dogbane (*Apocynum venetum*), cinnamon (*Cinnamomum cassia*), passion flower (*Passiflora incarnate*) and the rhizome of *Gastrodia elata* all bind to GABAa receptors and increase the time treated mice spent in the open arm of the elevated plus maze [83–86]. Valerian root extracts have also been shown to be anxiolytic in the elevated plus maze test in both rats and mice [80,87,88]. In humans, GABAergic herb and plant extracts have been shown to be anxiolytic in several double-blind and placebo controlled studies. The valepotiate extract of valerian root has been shown to be as effective as diazepam in the psychic factor of the Hamilton-anxiety scale [89] and the valerian extract LI 156 has been found to be as effective as oxazepam in overcoming insomnia [90]. Again, in double blind placebo controlled studies, in combination with lemon balm (*Melissa Officinalis*), valerian was show to be an effective anxiolytic through reduction of the defined intensity stressor simulation and decrements in performance on the stroop task module [38]. *Valerian wallichii* has also been on trial for relief of stress disorders and has been observed to attenuate stress and anxiety Hamilton's brief psychiatric rating scale [31]. Valerian has also demonstrated improved Epworth sleepiness scale scores in people with restless leg syndrome [91]. The Japanese green tea (*Camellia sinesis*) amino acid, theanine, has also been shown to have calming effects anti-stress in humans as evidenced by increase alpha wave activity in electroencephalographs [92–94]. Further, theanine has been shown to increase brain GABA levels in rat brain [95,96] and improve memory and cognitive function [95,97]. While the precise mechanisms through which theanine effects central nervous system function, sthe observation that the neuroptotective effect of theanine on memory loss from cerebral ischemia and infarct in rats and mice [98,99] can be prevented with the GABAa receptor agonist, bicuculine, suggests that theanine either acts as a GABAergic compound or through the GABA signaling pathway [100].

## SEROTONIN

Serotonin is a monoamine neurotransmitter and is found predominantly in the gut, however is also synthesized in the central nervous system where it plays a role in regulating mood, memory and various other functions [101]. Serotonin binds to pre- and postsynaptic receptors in neurons of the prefrontal cortex and amygdala [102–109]. Serotonin signaling through the postsynaptic receptors is critical in the control of obsessive compulsive disorders, panic disorders and social anxiety disorder in humans [102–107]. The strength and persistence of the serotonin signal once released is under the control of the presynaptic high-affinity serotonin transporter (SERT, 5-HTT) which clears serotonin from the synapse, thereby controlling activity of serotonin at the postsynaptic membrane. Indeed, polymorphism in the SERT/5-HTT gene has been associated with susceptibility to stress related diseases, anxiety and social anxiety disorder [102–107]. This observation has been supported in SERT knockout mice which have been found to show impaired stress-coping and fear [110] and insensitivity to antidepressants that target SERT [111]. Moreover, transgenic mice which over express SERT/5-HTT exhibit reduced anxiety associated behaviors [112]. Further, drugs which selectively bind to SERT, known as selective serotonin uptake

inhibitors (SSRIs), have been found to be effective in treating anxiety, panic and compulsive behavior in humans by elevating synaptic serotonin levels [113–115].

Serotonin is synthesized in the presynaptic neurons by tryptophan hydroxylase which converts tryptophan to 5-hydroxytryptophan (5-HTP) which is then converted to serotonin by aromatic L-amino acid decarboxylase. While an increase in synaptic serotonin can be achieved with SSRIs, either increasing serotonin synthesis, or identifying postsynaptic serotonin receptor agonist are additional anxiolytic strategies. In this regard, dietary supplementation with tryptophan and 5-HTP, which crosses the blood-brain barrier, increases brain serotonin levels in experimental animals and produces anxiolytic effects [116]. For example, dietary supplement of excitable horses with tryptophan was shown to have a calmative effect [117]. Further, dietary supplement of aged rats with the Chinese herb, yokukansan (YKS) was shown to increase serotonin and dopamine levels in the prefrontal cortex and provide the anxiolytic effect of increasing the frequency in the open arm of the elevated-plus maze [118]. Repeated administration of YKS has also been shown to overcome dimethoxyiodoamphetamine (DOI) induced reduction in the 5-HT2A postsynaptic serotonin receptor in mice [119]. Similarly, a combination of magnolia bark and ginger root polysacchrides and essential oils has been show to elevate murie prefrontal cortex serotonin levels [120]. *Rhodiola Rosea* supplementation has been shown to increase total hypothalamic serotonin in rats and work as an anxiolytic in humans as assessed by reduction the Hamilton anxiety rating score [121,122]. Lastly, 5-HTP increases in brain serotonin levels has also been promoted with the Chinese herb, Xiaobuxin-Tang [123]. In humans, tryptophan has been found to improve risky decision making under uncertain circumstances [124] and folic acid supplementation in healthy men has been shown to increase circulating serotonin levels [125]. Lastly, the serotonin enhancing herb, Rhodiola Rosea has been shown to have anxiolytic effect in humans [122]. While these studies in animals and humans have focused on boosting brain serotonin levels, dietary supplements also act at the postsynaptic membrane.

Dietary and herbal agonists of postsynaptic serotonin receptor binding sites (5-HT1A-1B, 5-HT2A-C and 5-HT3-7) also increase the serotonergic pathway. For example, black cohash (*Cimicfuga racemosa*) methanolic extracts contains the 5-HT7 binding molecule, N(omega)-methylserotonin, which stimulates postsynaptic cAMP and is consistent with the known serotonergic activity of black cohash [126]. In addition, a methanolic extract if the *Angelica sinensis* Diels root has been shown to contain four compounds (one phenolic ester and three phthalides) which compete for binding of $3^{[H]}$ LSD to human 5-HT7 serotonin receptor expressed in CHO cells [127]. Hyperforin from St. John's Wort (*Hypericum perforatum*) has also been shown to act on the H-T1A and 5HT2A postsynaptic serotonin receptors [128] and, as noted above, YKS provided protection from DOI-induced reductions 5-HT2A [119].

## Formulations on the Market

Medicines that act through the dopanminergic, GABAergic and serotonergic pathways have demonstrated tremendous value to treating anxiety disorders, clinical depression, schizophrenia and other neurological diseases such as epilepsy. However, due to the potential side-effects and risks associated with the use of these drugs, there is a great deal of popular and medical interest in the use of dietary supplements and nutraceuticals in order to manage normal "everyday" stress and anxiety. While these natural approaches may also have medical value, they are also of benefit to the general population because they are more available and accessible. Currently, there are several all-natural non-prescription products available which can be used to cope with stress and anxiety. For example, valerian root, 5-HTP, theanine and GABA are all available in capsule form. Proprietary formulations of multiple nutraceutical compounds and extracts can also be found in pill form such as Proloftin™ which contains phosphatidyl serine, L-theanine, magnolia bark, rhodiola and beta-sitosterol. Relora™, a patented proprietary blend of standardized extracts of magnolia officinalis and phellodendron amurense is also available in pill form. Seditol™, is a proprietary blend of a patented extract from *Magnolia officinalis* and *Ziziphus spinosa* which is a pill that can be taken for relaxation. One formulation named Good-Night-Rx™ contains 19 relaxation herbs and nutraceuticals including GABA, taurine, hops (*Humulus lupulus*), Valerian (*valeriana officinalis*) root, Kava kava (*Piper methysticum*) root, Bupleurum (*Bupleurum chinense*), chamomile (*Matricaria recutita*) flower, lemon balm flower (*Melissa officinalis*), magnolia (*Magnolia officinalis*) bark, passion flower (*Passiflora incarnata*), peony (*Peony officinalis*) root, jujube extract (*Zyzyphus jujube*) seed, 5-HTP from *Griffonia simplicifolia* seed, Ashwagandha (*Withania somnifera*) root, lavender (*Lavendula augustifolia*), peppermint (*Mentha piperita*) leaf, reishi mushroom (*Ganoderma lucidum*), sage (*Saliva officinalis*) root, and melatonin, which includes nearly all investigated supplements for relaxation presented in this review article and additional molecules such as melatonin which has been shown to cause drowsiness and induce sleep [129]. In addition to pills, various teas and herbal powders are available for mixing into drinks such as chamomile and Kava kava. More recently numerous relaxation beverages have appeared on the market containing various relaxation nutraceuticals such as valerian, theanine, GABA, 5-HTP and the sleep-aid melatonin. Relarian™ is a blend of aqueous valerian root extract, theanine, 5-HTP and GABA and is available in MiniChill™, a 2.0 oz volume "shot" which does not contain the sleep aid melatonin. In a recent unpublished subjective self-report pilot study, of 61 people who tested Relarian™ in the MiniChill™ drink, 52 reported feeling relaxed with 39 of these also describing an increase in focus during the execution of tasks. Five were not sure if they felt more relaxed or not and four stated that they did not feel any different after consuming the Relarian™. Of the 61, only one reported feeling drowsy.

## Conclusions

Due to the popularity of natural supplementation to ease everyday stress, a wide range of products are available on the market. The consumer is cautioned to distinguish between sleep aids and anxiolytic effects. Melatonin and other supplements may produce drowsiness, however, activation of the serotonergic and gabanergic pathways ™ appear to be science-supported safe ways to relieve stress and anxiety.

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