

Tryp•to•ZEN™ Comparison

Hydrolyzed Bioactive Milk Peptide

Independent Research Compilation

A COMPARATIVE REVIEW OF NATURAL STRESS RELIEF SUPPLEMENTS

Stress Affects Your Health

Stress has become an important health concern in modern society. It is both additive and cumulative in its negative effects on individuals and organizations. Stress is a worldwide phenomenon and the costs, when not translated in hours lost at work, are paid back in compromised health.

Early signs of stress include headaches, mood and sleep disturbances, difficulty concentrating, upset stomach as well as deteriorating relationships with family and friends.

Stress is directly linked to the six leading causes of death in the U.S.: heart disease, cancer, lung ailments, accidents, cirrhosis of the liver and suicide. Moreover, many psychiatrists believe that the majority of back problems - one of the most common adult ailments in the United States - are related to stress.

The Global Burden of Disease study, conducted by researchers at Harvard University, Cambridge, Massachusetts, found mental disorders, including suicide, ranked second only to cardiovascular conditions as social burdens for developed nations.

It is not surprising that people living in modern societies are searching for solutions to reduce the impact of stress in their lives, and the popularity of prescription drugs, even with the long list of their side effects, is increasing fast.

Is there such a thing as a safe and effective natural option to stress relief? We believe so.

In the following article, the author reviews and compares the natural alternative options available to help reduce stress and summarizes the clinical data available on the subject.

Did you know?

- *Stress is directly linked to the six leading causes of death in the U.S.: heart disease, cancer, lung ailments, accidents, cirrhosis of the liver and suicide.*
- *The majority of back problems are related to stress.*
- *Nearly one in four full-time working mothers with children under 13 say they feel stressed almost every day.*

Coping with Stress

Stress is an unavoidable part of life. It can result from many things, both physical and psychological. It can arise from a welcome event such as the birth of a child or a difficult situation such as divorce. Stress can be either chronic or acute and manifests itself in many different ways, depending on the individual.

While stress is often viewed as a psychological problem, it has very real physical effects. The body responds to stress by triggering a chain reaction of physiological changes: increased secretion of adrenaline, elevation of blood pressure, acceleration of the heartbeat, greater tension in

muscles, release of fats and sugars, rise in cholesterol levels as well as increased production of adrenocorticotrophic hormone (ACTH) followed by the release of the hormones cortisone and cortisol.

The increased production of adrenal hormones is responsible for a number of symptoms associated with stress. The consequences of hormone imbalances can be exacerbated by hormone deficiencies.

The result, especially with prolonged or recurrent stress, is that the body becomes deficient in many nutrients causing a number of stress related health disorders.

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“Prolonged or recurrent stress depletes the body’s energy reserve and can eventually lead to emotional burnout and complete exhaustion. This can be avoided by learning to manage stress in a way that helps the body adjust better and maintain a higher energy level.”

Proper nutrition and dietary supplements that include B-vitamins, minerals, essential fatty acids and amino acids combined with exercise, relaxation and the proper attitude are all part of a stress management program.

Some supplements on the market offer promises of relaxation and well-being but it is not always clear how they work and how safe they are.

For instance, Kava Kava, a botanical traditionally used in the Pacific Islands to relieve anxiety, has been studied in humans and has demonstrated significant results, but recent reports suggest problems with its safety. This has raised concerns in the minds of consumers and reduced its popularity.

The purposes of this article is to presents facts and, in the light of what we know about stress, identify natural safe and effective solutions to stress relief.

The Physiology of Stress

Increased secretion of adrenaline

Elevation of blood pressure

Acceleration of heartbeat

Greater tension in muscles

Release of fats and sugars

Rise in cholesterol levels

Increased production of ACTH

Release of cortisone and cortisol

depressants are similarly effective. Randomized trials have varied significantly with regard to participants, settings and interventions, as well as in the preparations of hypericum that have been used (Linde and Mulrow, 2001).

Side effects reported for SJW are generally mild. Gastrointestinal symptoms and fatigue have been reported. The most predictable side effect seems to be photosensitization. However, photosensitization is generally mild and transient and is usually associated with higher than normal doses. Animal studies indicate low toxicity for SJW (Fugh-Berman and Cott, 1999).

SJW appears to be reasonably safe when taken alone. However, it may interfere with the effectiveness of other medications, including treatments for HIV infections, oral

contraceptives, immunosuppressants, blood thinners as well as chemotherapy and asthma drugs (National Institute of Mental Health, 2001).

The major problem concerning hypericum is the availability of standardized hypericum preparations. The potential active ingredient content in preparations may vary considerably. Hypericum extracts are standardized to the hypericin content, which itself is not responsible for the antidepressant activity. Compositions of the other components of the extract are not evaluated and thus may vary between extracts. The standard dosage of SJW is 300 mg, 3 times a day of an extract standardized to contain 0.3% hypericin. A few new products are standardized to hyperforin content (usually 2 to 3%). Furthermore, it is difficult to separate high quality from low quality preparations.

L-Theanine



L - theanine, or ψ -glutamylethylamide, is a unique amino acid found in the leaves of green tea (*Camellia sinensis*). L-theanine constitutes between 1 – 2 % of the dry weight of tea leaves.

L-theanine is quite different from the polyphenol and catechin antioxidants found in green tea. In fact, the tea plant converts L-theanine into catechins through the natural production of polyphenols.

To obtain adequate quantities efficiently, Taiyo Kagaku Company of Japan synthesizes L-theanine with a patented enzymatic technology. This technology produces a 99% pure amino acid that is called Suntheanine™ (Juneja et al., 1999).

Laboratory studies indicate that L-theanine counters the excitation effect of caffeine measured by EEG in rats. L-theanine increases the level of gamma-amino-butyric acid (GABA), while caffeine decreases it (Kakuda et al., 2000). L-theanine also appears to increase levels of dopamine, another brain chemical with mood-enhancing effects, which can reduce blood pressure (Yokogoshi et al., 1998a). Also L-theanine has been shown to reduce the level of brain serotonin in rats by decreasing its synthesis and increasing its degradation (Yokogoshi et al., 1998b).

The principal aspect of L-theanine activity is its ability to increase the brain’s output of α -waves. The generation of α -waves is considered an index of relaxation.

A clinical trial studied the relaxation effect of L-theanine in eight female subjects that included four high-anxiety and four low-anxiety university students. This study showed that 200 mg of Suntheanine™ dissolved in 100 ml of water, compared to water alone, given once a week for a two month period, resulted in the generation of α -waves 30 minutes after oral administration. The emission intensity of α -waves was significantly greater in the high-anxiety group than the one observed in the low-anxiety group (Juneja et al., 1999).

Clinical studies show that L-theanine is effective at a dosage of 200 mg per day (equivalent to the amount in 2-4 cups of green tea). L-theanine reaches its maximum levels in the blood between 30 minutes and two hours after ingestion. No adverse side effects are associated with L-theanine consumption. However, the anti-stress effect of L-theanine requires more scientific support with well-controlled studies involving a greater number of subjects to prove that it is more efficient than placebo in reducing stress.

At present, the mechanism of action of L-theanine is not well characterized. Comparisons between L-theanine and other anxiolytic drugs or alternative therapies are still not available.

Conclusion

Among the supplements reviewed in this paper, only Tryp•to•ZEN, L-theanine and Relora directly address the stress problematic. Though also promoted for anxiety, 5-HTP and SJW are currently used for their anti-depressant properties. *Rhodiola* has been studied for its “adaptogenic” properties, or in other words, its resistance effect on adverse physical, chemical or biological stressors. Thus *Rhodiola* addresses a larger number of nonspecific conditions.

This review also reveals that herbal compounds may present promising anti-stress and mood enhancing properties, but their adulteration and lack of standardization generally makes it difficult to ascertain safe clinical use. In addition, plant extracts are very rich in different bioactive compounds possessing a large spectrum of activities. For the majority of the plant extracts reviewed in this article, the compound carrying the anxiolytic effect has not been well identified.

Compared to herbal remedies, the Tryp•to•ZEN bioactive compound is standardized and its properties are well characterized.

Herbal remedies reviewed in this article are considered to be safe. However, they may induce moderate side effects such as photosensitization (SJW), mild diarrhea and slight sedation (Relora) as well as insomnia and irritability (*Rhodiola*). 5-HTP and L-tryptophan

induce more severe side effects such as mild nausea, heartburn, flatulence, feelings of fullness, and rumbling sensations. No adverse effects have been noted with the use of L-theanine.

Tryp•to•ZEN induces no side effects, as it has been demonstrated in pre-clinical and clinical studies.

It is difficult demonstrate a true drug activity in clinical trials due to the high placebo response observed in the field of anxiety and depression disorders. Consequently, it is important to prove successfully that alternative therapies are more efficient than placebo in reducing stress or depression in well-controlled clinical trials.

In general, herbal remedies require higher quality clinical evidence in order to demonstrate their efficacy compared to placebo in reducing stress. There is also a lack of conclusive scientific evidence on L-theanine. To date, clinical trials on 5-HTP have not been conclusive and its validity as an antidepressant is questionable.

Tryp•to•ZEN has been shown to be very effective in reducing stress responses and stress symptoms compared to placebo in well-controlled clinical trials. Tryp•to•ZEN appears to be the most promising solution for limiting the detrimental effects of everyday stress.

Compared to herbal remedies, the Tryp•to•ZEN™ bioactive compound is standardized and its properties are well characterized.

Relora®



Magnolia officinalis



Phellodendron amurense

Relora is a proprietary blend of patent-pending extracts from *Magnolia officinalis* and *Phellodendron amurense*, standardized to 1.5% Honokiol (3.75 mg) and 0.1 % Berberine (0.25 mg).

Magnolia bark is a traditional Chinese medicine used for treating “stagnation of qi” (low energy) as well as a variety of syndromes such as digestive disturbances caused by emotional distress.

Magnolia bark is rich in two biphenol compounds (magnolol and honokiol) which are thought to contribute to the primary anti-stress and cortisol-lowering effects of the plant (Kuribara et al., 2000).

Berberine is an alkaloid present in a number of clinically important medicinal plants. Berberine has been shown to exhibit anti-inflammatory, immunostimulatory and anti-microbial activity against a variety of bacteria, fungi, and viruses. Several clinical trials suggest that berberine may act as an anti-arrhythmic agent in cardiac muscle (Birdsall and Kelly, 1997).

Numerous animal studies have demonstrated that honokiol acts as a central nervous system depressant in high doses, but as a non-sedating anxiolytic (anti-anxiety and anti-stress) agent in lower doses.

When compared to pharmaceutical agents such as Valium (diazepam), honokiol appears to be as effective in its anti-anxiety activity, yet not nearly as powerful in its sedative ability (Kuribara et al., 1999).

The plant extracts in Relora have been shown to be an effective non-sedating anti-stress product in animal tests.

The first formulation of Relora was tested in fifty subjects for two weeks. The recommended dosage was 200 mg of Relora

three times daily (the new dosage for Relora is 750 mg daily). In this test, Relora helped control stress-related symptoms, such as irritability, emotional ups and downs, restlessness, tense muscles, poor sleep and difficulty concentrating. 24% of subjects reported drowsiness.

A second trial was undertaken to measure cortisol and DHEA levels in patients with mild to moderate stress. A two-week regimen of Relora caused a significant increase in salivary DHEA (227%) and a significant decrease in morning salivary cortisol levels (37%). Cortisol and DHEA levels returned to normal in all subjects during the course of the study.

A third trial of 49 subjects achieved results similar to the ones observed in the first trial with regard to relaxation and restful sleep. In addition, Relora reduced stress-related snacking on sweets such as ice cream, cake, pie, and cookies.

No significant toxicity or adverse effects have been associated with traditional use of magnolia bark, but high doses can cause drowsiness. An acute toxicity study in

rat observation revealed mild diarrhea and slight sedation in female rats.

Relora contains a broad spectrum of biologically active compounds and it is therefore difficult to control every component in the plants. Preparations may differ considerably in their content of potentially active ingredients.

Relora is standardized to the honokiol and berberine content, but only honokiol itself is believed to act as an anxiolytic agent. More placebo controlled studies are necessary to demonstrate that Relora is more efficient than placebo in reducing stress.

Comparisons between Relora and other alternative therapies are still not available.

“Relora is a combination of two plants extracts, *Magnolia officinalis* and *Phellodendron amurense*, containing a broad spectrum of biological active compounds. Consequently, it is difficult to control every component in the plants.”

Rhodiola Rosea

Rhodiola rosea is a popular plant in traditional medical systems in Eastern Europe and Asia. It has a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue and preventing high altitude sickness.

Twenty-eight compounds have been isolated from the roots and above-ground parts of *Rhodiola rosea*. Salidroside (rhodiololide), salidroside-like glycoside compounds (rhodiolin, rosin, rosavin, rosarin and rosiridin) and p-tyrosol are thought to be the most critical plant constituents needed for therapeutic activity, though the active component has not yet been identified.

The constituent currently selected for the standardization of extracts is rosavin (Kelly, 2001), but there is insufficient information to support this choice.

There are three randomized, double-blind, placebo-controlled trials of the standardized extract of *Rhodiola rosea* root (SHR-5) containing 3.6% rosavin, 1.6% salidroside and less than 0.1% p-tyrosol.

Darbinyan et al. evaluated the effect of chronic administration of 170 mg of *Rhodiola rosea* root on the mental performance and fatigue of 56 healthy male and female physicians (aged 24-35) on night duty for a period of 14 days.

A statistically significant improvement in the Fatigue Index was observed during the first two-week period in the SHR-5 group and the improved mental performance reverted toward baseline values during the washout period. Administration of SHR-5 for the final two weeks of the six-week night duty period did not offset declines in mental performance (Darbinyan et al., 2000).

Spasov et al. investigated the effects of SHR-5 on male medical students during an exam period. Forty students were randomized to receive either 50 mg SHR-5 or placebo twice daily for a period of 20 days. The students receiving the standardized extract of *Rhodiola rosea* demonstrated significant improvements in physical fitness, psychomotor function, mental performance, general well-being, mental fatigue, sleep patterns, a reduced need for sleep, greater mood stability and a greater motivation to study (Spasov et al., 2000).

The therapeutic dosage of *Rhodiola rosea* has not been well characterized in pre-clinical and clinical studies. Because of this, it seems prudent to keep doses at a moderate level both in terms of the quantity and duration of supplementation. Irritability and insomnia may be a risk with high doses of *Rhodiola*.

More studies are required to clarify the mechanism of *Rhodiola*'s anti-fatigue and mental performance enhancing action.



Rhodiola Rosea

The constituent currently selected for the standardization of extracts is rosavin but there is insufficient information to support this choice.

5-Hydroxytryptophan and L-Tryptophan

5-Hydroxytryptophan (5-HTP) is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan. Produced commercially by extraction from the seeds of the African plant, *Griffonia simplicifolia*, 5-HTP has been used clinically for over 30 years.

The clinical efficacy of 5-HTP is due to its ability to increase production of serotonin (5-hydroxytryptamine) in the brain. In the central nervous system (CNS), serotonin intervenes in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behavior and pain sensation.

5-HTP is the intermediate metabolite of L-tryptophan in the production of serotonin. 5-HTP easily crosses the blood-brain barrier, not requiring the presence of a transport molecule.

L-tryptophan on the other hand, requires use of a transport molecule to gain access to the CNS (Birdsall, 1998).

Since L-tryptophan shares this transport molecule with several other amino acids, the presence of these competing amino acids can inhibit L-tryptophan transport into the brain.



Griffonia simplicifolia

5-Hydroxytryptophan and L-Tryptophan (cont.)

“The authors concluded that the available evidence suggests that these substances were better than placebo at alleviating depression. However, the evidence was of insufficient quality to be conclusive.”

A meta-analysis published by the Cochrane library (Shaw et al., 2002) evaluated 108 trials, of which only two trials involving a total of 64 patients were of sufficient quality to meet inclusion criteria. The authors concluded that the available evidence suggests that these substances were better than placebo at alleviating depression. However, the evidence was of insufficient quality to be conclusive.

Some adverse effects are associated with 5-HTP use in the treatment of depression. These side effects include mild nausea, heartburn, flatulence, feelings of fullness, and rumbling sensations. The most significant safety concern related to 5-HTP and L-tryptophan supplements is the remote possibility for contamination with a compound (“Peak X”)

linked to a disorder known as eosinophilic myalgia syndrome (EMS).

The FDA issued a “talk paper” in 1998 which seemed to confirm the presence of “Peak X” at low levels in several commercially available brands of 5-HTP, raising the possibility that EMS could strike those taking 5-HTP supplements. However, the FDA has not taken action, such as removing 5-HTP from the market or issuing any precautions against using 5-HTP.

Three to five weeks of supplementation with 5-HTP are needed before the effects of the product are seen. L-tryptophan presents no advantages compared to 5-HTP for treating depression. L-tryptophan and 5-HTP induce several side effects and may be contaminated.

St. Johns Wort



Hypericum perforatum

Usually known as St. John's Wort (SJW), extracts of the plant *Hypericum Perforatum*, have been used as an antidepressant for over 2,000 years. In Germany, SJW is licensed and prescribed under medical supervision for anxiety, depression and sleep disorders (Maidment, 2000; Miller, 1998).

Hypericum extracts contain at least ten constituents or groups of components that may contribute to its pharmacological effects. These include naphthodianthrone (hypericin and pseudohypericin), flavonoids (quercetin), hyperforin xanthenes, proanthocyanidins, carotenoids and bioflavonoids. Extracts are usually standardized to the substance hypericin though there is no evidence that hypericin itself has any antidepressant action (Maidment, 2000).

The exact mechanism of action of the antidepressant effect is still unclear. Early research suggested that SJW works like the oldest class of antidepressants, the monoamine oxidase (MAO) inhibitors. However, later research has been unable to confirm this (Bladt and Wagner, 1994). More recent research suggests that SJW may

inhibit the reuptake of serotonin, norepinephrine and dopamine. Hyperforin has been identified as the reuptake inhibiting constituent of hypericum extract (Müller et al., 1998). Nonetheless, there may be other active components in SJW.

A meta-analysis published by the Cochrane library (Linde and Mulrow, 2001) evaluated 27 trials involving 2,291 patients. Seventeen trials were placebo-controlled and ten trials compared hypericum with other antidepressant or sedative drugs, mostly tricyclic and MAO inhibitor-based antidepressants. The daily doses of extract applied varied from 350 mg to 1800 mg. Available evidence from randomized trials suggests hypericum is superior to placebo in the treatment of mild to moderately severe depressive disorders and that it has fewer short-term side effects than older antidepressants.

Comparisons between hypericum and newer antidepressants as selective serotonin reuptake inhibitors are still not available. There is insufficient evidence to determine whether hypericum and standard anti-

Tryp•to•ZEN™

Tryp•to•ZEN™ is a milk casein trypsin hydrolysate which has been tested for its anxiolytic effect. Using molecular separation technology, a peptide having specific anxiolytic-like activity was isolated from the hydrolysate. The first generation of Tryp•to•ZEN contains 2.5 mg of a bioactive compound called δs_1 -casozepine that binds to the benzodiazepine site of the GABA_A receptors *in vitro*. These findings indicate that δs_1 -casozepine is effective via GABA_A receptors (Miclo et al., 2001). GABA is the predominant inhibitory neurotransmitter in the central nervous system.

The anti-stress properties of Tryp•to•ZEN were tested in pre-clinical studies on rats, as well as in clinical studies on humans (Lefranc,

2001) and its activity was compared to those of diazepam and placebo.

The results of the animal tests showed that Tryp•to•ZEN was as effective as diazepam on the global anxiety score. Effects were observed 30 minutes after administration (Lefranc et al., 2001). Moreover, Tryp•to•ZEN did not produce any subsequent behavioral, neurological or toxicological effects nor did it cause dependency, amnesia or tolerance effects.

Four clinical studies, involving more than 180 volunteers, were also conducted. All studies were double-blind placebo controlled. One study also followed a crossover design. The main results of the first three studies are summarized as follows:

Grenoble 24 subjects 15 days	Volunteers with high anxiety level that were given Tryp•to•ZEN had a smaller increase in their global anxiety state score compared to those who were given the placebo.
Necker Hospital (Paris) 42 subjects 2 days	During the stress test, subjects that were given Tryp•to•ZEN had a significantly smaller increase in their SBP and DBP than the ones from the Control group. The plasmatic cortisol concentration of the subjects that were given Tryp•to•ZEN decreased significantly while it remained stable for the subjects from the Control group.
CRSSA (La Tronche) 63 subjects 30 days	The mean blood pressure (MBP) test reactivity was lower at day 11 and 31 in subjects taking Tryp•to•ZEN compared to the ones that were taking the placebo. The MBP test reactivity of high stress responders was particularly significantly lower at day 11 and 31 in the group that was given Tryp•to•ZEN and that effect remained significant at day 43 after the washout period.

A double-blind placebo-controlled and crossover designed study was carried on 63 female volunteers showing at least one symptom of stress.

A significantly greater positive evolution of stress symptoms was demonstrated in the Tryp•to•ZEN group compared to the placebo group in five areas of health problems: digestive, cardiovascular, intellectual, emotional and social.

Tryp•to•ZEN had a greater effect on subjects having a high stress intensity score at the beginning of the study.

These previous studies strongly established the efficacy of Tryp•to•ZEN compared to placebo in treating the effects of stress.

Tryp•to•ZEN produces a noticeable effect in as little as one hour and optimal results can be observed after ten days of treatment.

These results also suggest that Tryp•to•ZEN reduces the intensity of the physiological reactions triggered by stress. In other words, it helps the body adjust better and become more equipped to deal with stressful situations.

Tryp•to•ZEN has been proven to have excellent biological activity and efficacy (both in animal and in human studies) with no side effects.

Helps the body adjust to stress better

- Proven efficacy
- Controlled process
- No dependency
- No toxicity
- No memory loss
- No drowsiness

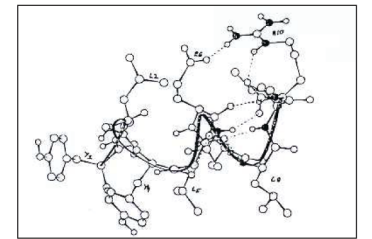


Image of α_1 -casein decapeptide



Using the CDB test model, it was demonstrated that Tryp•to•ZEN was more efficient in reducing stress responses than St. John's Wort or Kava Kava, whose effects were similar to the effect of the placebo. Moreover, it was shown that Tryp•to•ZEN was also more efficient than L-theanine at reducing stress. L-theanine, at 100 mg/kg, showed a similar response than Tryp•to•ZEN at only 15 mg/kg.