Stressed by Wall Street woes? Explore natural actives that help to boost your resilience…

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INTRODUCTION

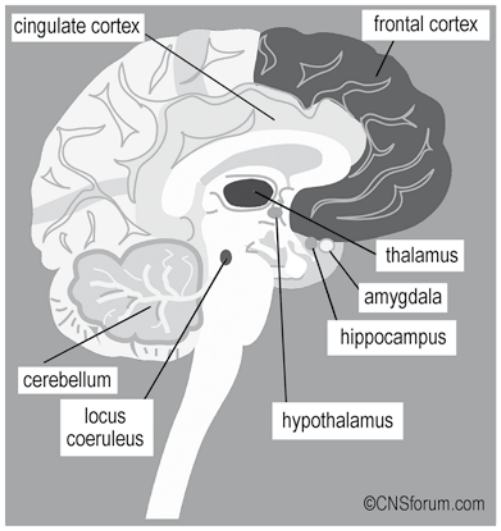
In the 1950's endocrinologist Hans Selye described stress as "the consequence of the failure to adapt to change, specifically the inability to respond appropriately to emotional or physical threats to the organism, whether actual or imagined" (1). It is a logical inference, therefore, that coping with stress involves approaches that boost an individual's adaptability to change. Nature provides a number of phytonutrients that function as relaxants, "adaptogens" or "revitalizers", with a positive influence on the symptoms of stress including anxiety, insomnia, depression and irritability.

The resultant "fight-or-flight" response by the autonomous nervous system culminates in cardiovascular, respiratory, gastrointestinal, renal, and endocrine effects. The hypothalamic-pituitary-adrenal axis (HPA), a major part of the neuroendocrine system is also activated by release of CRH and AVP. Adrenocorticotropic hormone (ACTH) is released from the pituitary gland into the general bloodstream. This results in secretion of cortisol and other glucocorticoids that carry the stress response to various body tissues and organs, and ultimately contribute to the termination of the response via feedback inhibition. Stress significantly affects the body's immune response as well and compromises resistance to microbial infection and other environmental stressors.

STRESS AND ADAPTOGENS

Several plants inherently harbor "adaptogenic" properties, and the substances enabling these properties have been termed "Adaptogens". Adaptogens are well established in the traditional systems of medicine. For example, *Charaka Samhita* (1000 B.C.), a renowned Ayurvedic text,

Figure 1.



The neurobiology and biochemistry of stress have been researched extensively, leading to a fairly comprehensive understanding of the effects of stress in humans. Nerve centers in the brain, and the autonomous nervous system, trigger the release of messenger hormones that then effect the stress response. In response to a stressor, corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) are secreted into the hypophyseal portal system and activate neurons of the paraventricular nuclei (PVN) of the hypothalamus. The locus ceruleus and other noradrenergic cell groups of the adrenal medulla and pons, collectively known as the LC/NE system, also become active, and use brain epinephrine to execute autonomic and neuroendocrine responses, serving as a global warning system.

describes phytonutrients that are adaptogens, designating them as "vitalizers". These phytonutrients appear to increase the SNIR (State of Non-specifically Increased Resistance) of the human body, protecting the organism against stresses of a diverse nature.
An ideal "Adaptogen" should possess the following qualities:

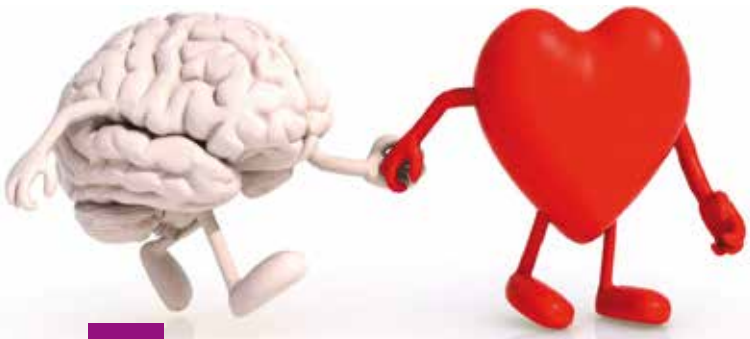
- Be relatively innocuous and cause minimal disorder in the human body.
- The action should be non-specific. For example, it should increase resistance to adverse influences of several kinds including those of physical, chemical and biological nature.

RELAXING HERBS

Central nervous system effects including anxiolytic, sedative, anticonvulsant, local anesthetic, spasmolytic, and analgesic activities are reported for a number of herbs used in traditional and folk medicine. A well known herbal ingredient in this context is kava kava *(Piper methysticum)* which came under regulatory scrutiny in 2002 on account of adverse reports (2). However, supplement manufacturers now use a variety of safer, clinically validated alternatives that do not have such side effects. These herbs with a long history of traditional use provide the anxiolytic and other relaxing effects of kava kava without the adverse side effects that led to its withdrawal. Some of these are described in this paper.

The brain's principal inhibitory neurotransmitter, gamma-amino-butyric acid (GABA), along with serotonin and norepinephrine, is one of several neurotransmitters that appear to be involved in the pathogenesis of anxiety and mood disorders. Some of the proposed mechanisms of action of herbs that support the management of stress are as follows (3-6):

- GABA-binding, reported to be a mechanism for sedative or anxiolytic effects;
- Modulation of serotonin reuptake or noradrenaline reuptake;
- Anticonvulsant effect that may be mediated by Na^+ channel receptor sites, a common target of anti-epileptic drugs;
- Direct influence on limbic system, with greatest effect on hippocampus and amygdala.



HERBS FOR STRESS MANAGEMENT SUPPORT

1. ASHWAGANDHA

The roots of *Withania somnifera* (Ashwagandha) are used extensively in Ayurveda, the classical Indian system of medicine, and the herb is categorized as a rasayana, used to promote physical and mental health, to provide resistance against disease and adverse environmental factors and to arrest the aging process (adaptogenic functions). Ashwagandha has been traditionally used to stabilize mood in patients with behavioural disturbances.

Bioactives isolated from the root of *W. somnifera* have been shown to be effective in attenuating experimentally induced stress responses including anxiety, depression, analgesia, thermic change, gastric ulceration, convulsions and adrenocortical activation in experimental animals. These findings support the reference to Ashwagandha as "Indian Ginseng".

One study investigated the anxiolytic and antidepressant actions of the bioactive glycowithanolides (WSG), isolated from Ashwagandha roots, in rats. WSG (20 and 50 mg/kg) was administered orally once daily for five days and the results were compared to those elicited by the benzodiazepine lorazepam for anxiolytic studies, and by the tricyclic anti-depressant, imipramine, for the antidepressant investigations. Both these standard drugs were administered once, 30 min prior to the tests.

WSG induced an anxiolytic effect, comparable to that produced by lorazepam, in the standard tests. Further, both WSG and lorazepam, reduced rat brain levels of biochemical markers of clinical anxiety, when the levels were increased following administration of the anxiogenic agent. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioral despair' and 'learned helplessness' tests. The investigations support the use of Ashwagandha as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda (7).

From a global perspective, depression is the most common mental health problem reported. There is also much controversy surrounding the current regularly prescribed anti-depressants, with regard to safety and side effects. Ashwagandha has historically been prescribed in Indian traditional medicine for its "sedative" and "tranquilizing" effects. Clinical studies with Ashwagandha in combination with other herbs, have established its beneficial role in supporting the management of depression.

2. BACOPA MONNIERA

Bacopa monniera Wettst (syn. *Herpestis monniera*), commonly known as Indian water hyssop, or Brahmi, belonging to the family Scrophulariaceae. Brahmi has been used by Ayurvedic medical practitioners in India for

almost 3000 years. The earliest chronicled mention is in the treatise the *Charaka Samhita* (100 AD), where Brahmi is recommended in formulations for the management of a range of mental conditions including anxiety, poor cognition and lack of concentration. According to *Charaka*, Brahmi acts as an effective brain tonic, boosting one's capabilities to think and reason.

The anti-anxiety effects of *B. monniera* (Brahmi, active principles saponins – bacosides) and its beneficial role in memory and cognition are well documented. Preclinical and clinical studies reveal that treatment with *B. monniera* extract lowered the stress related increased secretion of adrenal hormones.

In human studies, patients receiving a regimen of treatment with Brahmi syrup at a dose of 30 ml per day in two divided doses (the total daily dose provided 12 g of dry, crude *B. monniera*) for a period of one months, reported no untoward side effects (8). Anticonvulsant effects of the standardized extract of the herb are documented in studies on epileptic patients. The extract is documented to improve learning and memory functions and is beneficial in improving attention span and intellectual functions in children (9).

3. NEEM

The Neem tree *(Azadirachta indica)* is traditionally labeled as "The Village Pharmacy" in India, on account of its multifaceted healthful properties. Its properties range from immunomodulatory and anti-inflammatory effects, to antimicrobial and pesticidal attributes. The leaves and seeds of Neem yield limonoids with wide biological applications. These have antibacterial, antiviral, insect repellant, anti-protozoal and anti-helmenthic properties.

An animal model study was conducted to evaluate the effects of stress and its modulation by Neem extract and other adaptogens. Gamma glutamyl transpeptidase (GGT) activity in different tissues of the lymphoid system in rats, was used as a marker. Restrain stress (RS) suppressed the GGT activity in different tissues of lymphoid system viz. the lymphocyte, the spleen, the thymus and the macrophage, and the maximum effect was seen in the spleen. Chlordiazepoxide, a prototype anti-stress agent, which did not alter GGT activity *per se,* reversed the effect of RS on this enzyme activity in tissues of lymphoid system studied. *A. indica* extract stimulated the GGT activity and nearly normalized RS induced suppression of GGT in the lymphoid system thereby confirming the adaptogenic and immunomodulatory effects of Neem (10).

4. MELISSA OFFICINALIS

Lemon balm (*Melissa officinalis*), is a perennial herb in the mint family Lamiaceae, native to southern Europe and the Mediterranean region. Lemon balm is used as a flavoring agent foods and herbal teas, often in combination with other herbs mint or spearmint.

A lyophilized hydroalcoholic extract of *M. officinalis* L. (Lamiaceae) has been evaluated for behavioral effects in mice. According to the traditional use of *M. officinalis*, sedative properties have been confirmed for low doses by the decrease of behavioral parameters measured in a non-familiar environment test (staircase test) and in a familiar environment test (two compartment test). With high doses, a peripheral analgesic activity was obtained by reducing the acetic acid-induced pain (writhing test); moreover, the plant extract induced the sleep in mice after treatment with pentobarbital, and potentiated the sleep induced by pentobarbital (11).

A human study further validated the calming effects of lemon balm (12). In this double-blind, placebo-controlled, randomized, balanced crossover experiment, 18 healthy volunteers received two separate single doses of a standardized *M. officinalis* extract (300 mg, 600 mg) and a placebo, on separate days separated by a 7-day washout period. Modulation of mood was assessed during pre-dose

and 1-hour postdose completions of a 20-minute version of the Defined Intensity Stressor Simulation (DISS) battery. Cognitive performance on the four concurrent tasks of the battery was also assessed. The 600 mg dose of Melissa reversed the negative mood effects of the DISS, with significantly increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of the 300 mg dose.

5. VALERIAN

Valerian has a history of use as a medicinal herb, and was used in ancient Greece and Rome. Hippocrates described its properties, and Galen later prescribed it as a remedy for insomnia.

In a clinical study, both kava kava and valerian were found to moderate the effects of psychological stress induced under laboratory conditions in a group of healthy volunteers (13).

Another study compared the effects of kava kava and valerian in stress induced insomnia. In this pilot study, 24 patients suffering from stress-induced insomnia were treated for 6 weeks with kava 120 mg daily. This was followed by 2 weeks off treatment and then, 5 having dropped out, 19 received valerian 600 mg daily for another 6 weeks. Stress was measured in three areas: social, personal and life-events; insomnia in three areas also: time to fall asleep, hours slept and waking mood. Total stress severity was significantly relieved by both compounds ($p < 0.01$) with no significant differences between them; as was also insomnia ($p<0.01$) (14).

A randomized clinical trial compared the efficacy and tolerability of valerian and of and oxazepam in non-organic and non-psychiatric insomniacs. The study showed no differences in the efficacy for valerian and oxazepam. 75 patients were randomly allocated either to the index group (Valerian extract) or control group (oxazepam). The patients took study medication daily over a period of 28 days 30 min before going to bed. In both groups sleep quality improved significantly ($p<0.001$), but no statistically significant difference could be found between groups ($p=0.70$) (15).

Melissa–valerian combinations have been equated to benzodiazepine by researchers (16).

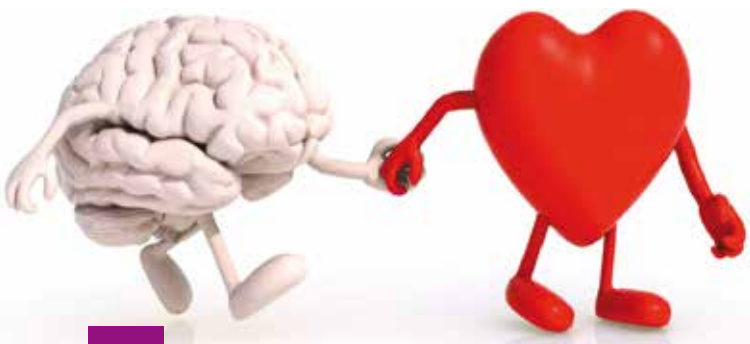
6. L-THEANINE

Theanine is a unique amino acid found in tea. Laboratory studies have established its beneficial role in mental relaxation. Theanine was found to act as a neurotransmitter in the brain and to decrease blood pressure significantly in hypertensive rats. Weak electric pulses called brain waves are generally generated on the surface of the animal brain. Four types of brain waves are generated, viz α, β, δ, θ, depending upon the mental state of the subject. The α-waves are an index of relaxation. In human volunteers, α-waves were generated on the occipital and parietal regions of the brain surface within 40 min after the oral administration of theanine (50-200 mg), signifying relaxation without causing drowsiness (17).

7. MUCUNA PRURIENS

Mucuna pruriens, from the botanical family Fabaceae, commonly known as velvet bean or cowitch is a plant indigenous to India. Ayurvedic practitioners have used the seeds for centuries, in the management of Parkinson's disease and nervous debility. The herb has also been used in formulations to control depression and improve mental alertness (18). The long record of safe and effective use prompted detailed research into the phytochemistry and pharmacological effects of this plant. The endocarp of the beans was found to contain about 5% levodopa (L-dihydroxy-phenyl-alanine, L-DOPA), which is used in conventional medical practice in the treatment of Parkinson's disease (19) and its beneficial effects were demonstrated in a clinical study.

The herb is used in combination with Ashwagandha in the management of depression. In one clinical trial (18), twenty-five patients diagnosed with either endogenous or reactive (neurotic) type depression volunteered to participate in an evaluation of Ashwagandha and *M. pruriens* (Kapikacchu) in relieving depressive symptoms. Basal and post-treatment assessments were made for severity of depression and anxiety, symptoms profile, sleep disturbance, and appetite. Patients consumed one pill containing 6 g of powdered *M. pruriens* (Kapikacchu)



in the morning and one pill containing 6 g of powdered *Withania somnifera* (Ashwagandha) in the evening for two months. At the end of 2 months all twenty-five patients had completed the study. Significant improvements were reported in the symptoms profile, anxiety, and depression scores were observed (Figure 2).

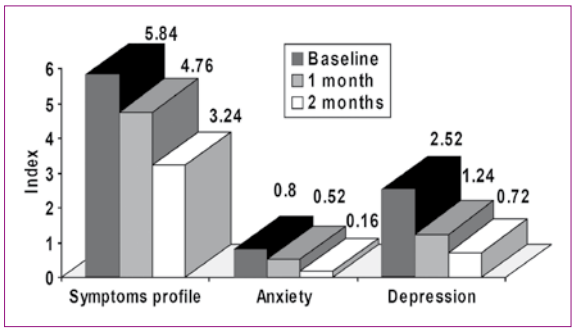


Figure 2. Symptoms profile, anxiety, and depression scores in patients receiving a formulation containing Ashwagandha and Mucuna pruriens *(18).*

Most patients reported improved appetite and sleep patterns, as well as an overall feeling of well-being. Evaluations of the overall efficacy indicated that 48% of the patients were free of any symptoms of depression, 36% were improved, and only 8% of the subjects reported no improvement in symptoms. No side effects were reported. Evaluation of the possible toxic side effects indicated that there were no significant changes in liver enzyme functions. However, in several patients there was a reduction in fasting and post-prandial blood sugar levels, suggesting a hypoglycemic effect of the herbal preparation.

8. PASSIFLORA EXTRACT (CHRYSIN)

Chrysin is chemically 5,7-Dihydroxy-2-phenyl-4H-1-benzopyran-4-one (5,7-dihydroxyflavone). The compound has been isolated from Passiflora plants such as *Passiflora coerulea* (used as a sedative in folklore medicine) (20) and *P. incarnata*. *P. incarnata* (maracuja "passion flower") is well known in traditional medicine for its diverse biological effects (21). The anti-anxiety effects of chrysin (1 mg/kg dose level) were studied in mice (22). It was found that mice treated with chrysin showed anti-anxiety effects comparable to those produced by the known drug diazepam. No associated sedation or muscle relaxation was observed in the chrysin-treated mice. The authors of this study concluded that chrysin is a partial antagonist of the central BDZ (benzodiazepine) receptors and thereby functions as an anxiolytic agent.

One group of researchers reported that chrysin is a ligand for both central and peripherial BDZ receptors. When administered to mice by the intracerebroventricular route, chrysin was able to prevent the expression of tonic-clonic seizures induced by a known convulsant, pentylenetertrazol. Chrysin was also shown to exert a muscle relaxant action under these conditions (20).

CONCLUSIONS

This paper presents an overview of some herbs that support stress management. Dietary interventions including probiotics, mineral supplements such as selenium and magnesium, amino acids, and other nutrients also benefit stress management.

Contact Sabinsa Corporation for further information, and formulation guidelines.

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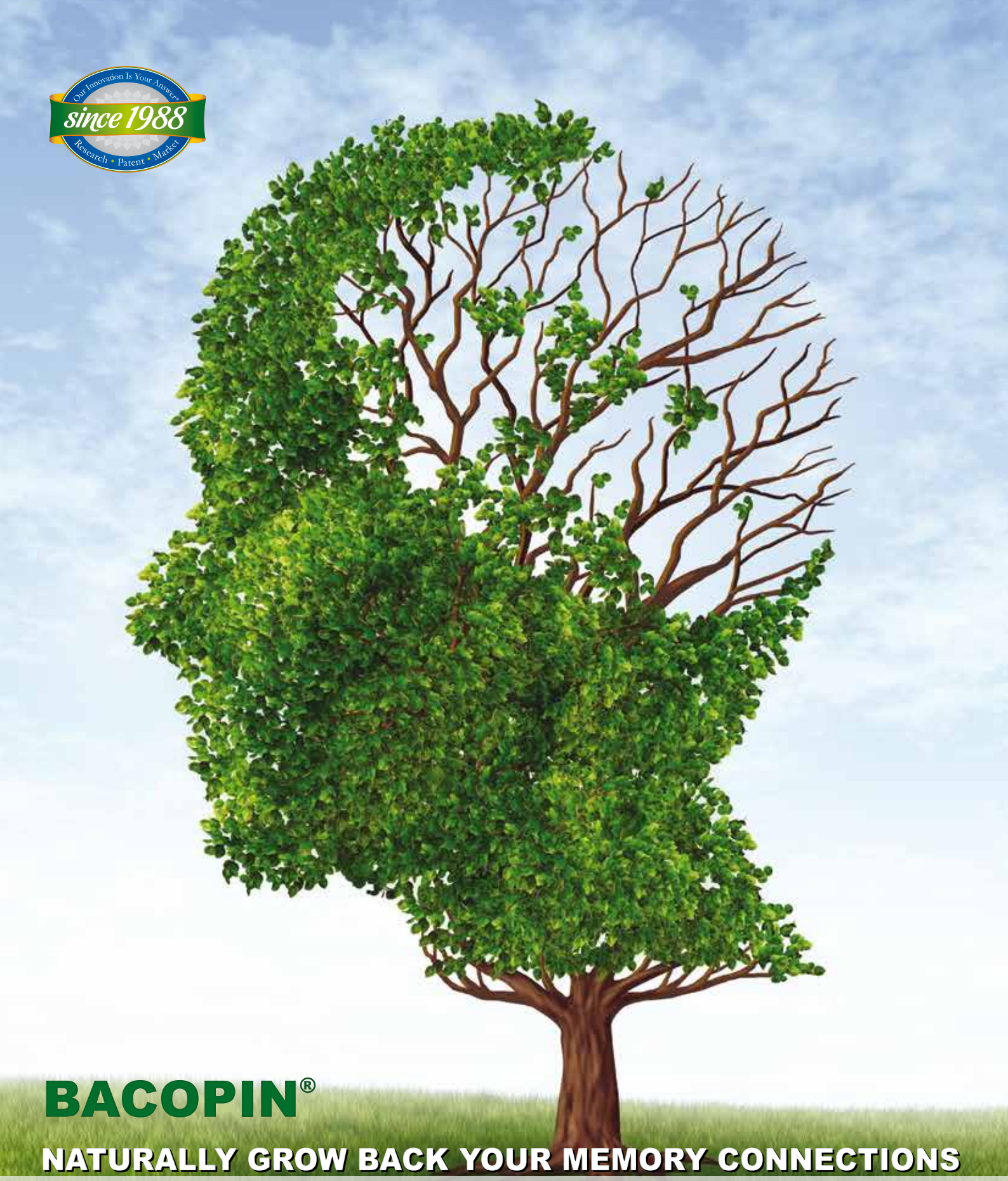

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