MOOD+

All-Natural Mood Support*

amare®

TECHNICAL DATA SHEET

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MOOD+

A comprehensive blend of research-backed premium herbs for mood support. Reduces tension and nervousness; Improves disposition and overall well-being.*

KEY INGREDIENTS

Zembrin® *(Sceletium tortuosum)* - also known as Kanna, Sceletium tortuosum was traditionally used by the San and Khoi peoples of Southern Africa as an analgesic (pain reliever), sedative, tonic (energy/stamina) and mood elevator. The traditionally prepared dried plant material is chewed, smoked, or powdered and inhaled as a snuff. It is also used as a tea or tincture. It was typically used in cognitively stressing situations such as hunting or coping in which its "adaptogenic" (stress-balancing) properties are readily apparent. Lower daily doses are known to have a subtle effect providing a sense of serenity and at the same time an elevated sense of alertness and awareness, while larger doses lead to a transient euphoria. Zembrin delivers a wide range of positive health benefits, including elevated mood and mental clarity; improved focus and memory; increased energy and motivation; lower stress hormone levels; and decreased everyday anxiety. Kanna is known to influence the amygdala of the brain (a brain region central in emotional processing) and is known to also have inhibitory effects on both the serotonin transporter as well as an enzyme known as phosphodiesterase 4 (PDE4); both of these proteins existing in the amygdala. Kanna contains a family of alkaloids (mesembrine, mesembrenone, mesembrenol, and mesembranol) confirmed to have dual effects on inhibiting serotonin reuptake and PDE4. These mechanisms are thought to be responsible for the dramatic mood-elevating and anti-stress benefits.*

Venetron® *(Apocynum venetum)* - commonly known as Rafuma, is a small shrub, the leaves of which make a tea that is particularly popular in China and has been used in TCM for thousands of years (Luo Bu Ma Ye). Commonly called dogbane in both TCM and in the Uighur traditional medicine of the western China plateau near Tibet, Rafuma is used to soothe the nerves, calm the liver and dissipate heat. The first recorded use was in the Ming Dynasty in the 15th century ancient Chinese herbal book Jiu-Huang Ben-Cao. The Compendium of Materia Medica, which also was written in the 15th century, states that the herb eliminates "dampness" (water retention) through diuresis. In modern times, A. venetum is known as Luobuma in China, and the Chinese Pharmacopoeia recommends it for a wide range of what we in Western society would view as "anti-stress" and "mood-elevating" effects – including calming the liver, soothing nerves, and clearing heat (inflammation). It is also listed in ancient texts for treating neurasthenia (anxiety/depression), palpitation, insomnia, edema with frequent urination, and hypertension. Apocynum venetum is said to have cardioprotective, diuretic, and sedative and anti-anxiety properties that can help reduce blood pressure. Its mechanism of action appears to be via GABA and serotonin pathways with primary bioactive compounds including quercetin and hyperoside.*

Sensoril® Ashwagandha *(Withania somnifera)* - also referred to as Indian ginseng, and has been used in Ayurvedic medicine for centuries. Traditionally considered within the "rasayana" (vitalizer) group of medicinal

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plants that stabilize and revitalize systemic functions. The Ayurvedic system of medicine uses ashwagandha to promote stress relief, health and longevity by potentiating the immune system, arresting premature aging, restoring homeostasis, and increasing resistance to adverse environmental factors, collectively known as an "adaptogenic" anti-stress effects. Sensoril ashwagandha delivers a range of natural bioactive constituents, including various glycowithanolides, alkaloids like withanine, somniferine, tropine, as well as steroidal lactones. These compounds help the body by balancing hormones that cause stress and are disrupted by stress.*

Relora® *(Magnolia officinalis and Phellodendron amurense bark)* - a combination of two herbs that are each important parts of traditional Chinese herbal medicine, although only occasionally in this particular combination. One herb is derived from a type of magnolia bark (Hou Po), the other from a species of phellodendron (Huang Bai). Magnolia/Hou Po is an aromatic herb that "transforms dampness" – what Western scientists and medical professionals would refer to as a generalized anti-anxiety effect with resolution of psychological pain. It was first described in 100AD for "promoting movement of Qi" (life force) and resolving stagnation (burnout). Phellodendron/Huang Bai is an herb that "clears heat and drains dampness" – referring to what Western scientists and medical professionals might refer to as inflammation and physical pain. The unique and patented Relora combination has been shown to calm anxiety and reduce stress without inducing drowsiness or sleepiness, while also maintaining healthy cortisol and DHEA production.*

Rosemary - common medicinal uses for rosemary has involved improving memory, where this common culinary herb also has a very stimulating effect on the mind. In addition, rosemary helps to nourish the "2nd brain" in the gut where it helps control the growth of many pathogenic bacteria without killing the good microflora (beneficial bacteria and yeast) in your body.*

Tulsi Leaf - *(Holy Basil)* - is known as an adaptogenic herb. It helps the body to better adapt to stress by modulating the production of stress hormones like cortisol and adrenaline.*

Oregano - has extremely high levels of free-radical-fighting antioxidants , agents that protect the body. Good for bacterial, viral, and fungal infections. Aids in digestion. Helps reduce pain and inflammation.*

Clove - according to traditional herbalists, the health benefits of clove oil can be attributed to its antimicrobial, antifungal, antiseptic, antiviral, aphrodisiac and stimulating properties. Boosts immunity, has a stimulating effect on the mind and removes mental exhaustion and fatigue.*

Sage - improves brain function, and reduces inflammation throughout the body – with a unique ability among culinary herbs to stimulate brain function to improve memory and concentration.*

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CLINICAL STUDIES

J Ethnopharmacol. 2016 Jan 11;177:140-7.

Electropharmacogram of Sceletium tortuosum extract based on spectral local field power in conscious freely moving rats.

Dimpfel W, Schombert L, Gericke N.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

The endemic succulent South African plant, Sceletium tortuosum (L.) N.E. Br. (synonym Mesembryanthemum tortuosum L.), of the family Mesembryathemaceae, has an ancient oral tradition history of use by San and Khoikhoi people as an integral part of the indigenous culture and materia medica. A special standardized extract of Sceletium tortuosum (Zembrin®) has been developed and tested pre-clinically in rats, and clinically in healthy subjects.

AIM OF THE STUDY:

The present investigation aimed at the construction of electropharmacograms of Zembrin® in the presence of three dosages (2.5, 5.0 and 10.0 mg/kg), and comparative electropharmacograms and discriminatory analyses for other herbal extracts, citicoline and rolipram.

MATERIAL AND METHODS:

Seventeen adult Fischer rats were each implanted with a set consisting of four bipolar concentric steel electrodes fixed by dental cement and three screws driven into the scalp. After two weeks of recovery from surgery the animals were adapted to oral administration by gavage and to experimental conditions (45 min pre-drug period and 5h of recording after a rest of 5 min for calming down). Data were transmitted wirelessly and processed using a Fast Fourier Transformation (FFT). Spectral power was evaluated for 8 frequency ranges, namely delta, theta, alpha1, alpha2, beta1a, beta1b, beta2 and gamma power.

RESULTS:

Zembrin® dose dependently attenuated all frequency ranges, to varying degrees. The most prominent was the statistically significant reduction in alpha2 and beta1a waves, correlated with activation of the dopaminergic and glutamatergic transmitter systems respectively. This feature is common to all synthetic and herbal stimulants tested to date. The second strongest effects were reduction in both the delta and the theta frequency ranges, correlated with changes in the cholinergic and norepinephrine systems respectively, a pattern seen in preparations prescribed for neurodegenerative diseases. Theta wave reduction in common with the delta, alpha2 and beta1 attenuation has been noted for analgesic drugs. Attenuation of alpha1 waves emerged during the highest dosage in all brain areas, a feature seen in all antidepressants.

DISCUSSION:

The electropharmacogram of Zembrin® was compared to the electropharmacograms of herbal extracts archived in our database. Extracts of Oenothera biennis and Cimicifuga racemosa gave a very similar electropharmacograms to that of Zembrin®, and extracts of Ginkgo biloba and Rhodiola rosea gave rather similar electropharmacograms to Zembrin®. Linear discriminant analysis confirmed these similarities and demonstrated that all three dosages of Zembrin® plotted in close neighbourhood to

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each other. Citocoline, a synthetic compound originally developed for cognitive enhancement, had a similar electropharmacogram to Zembrin®. Similarity to the electropharmacograms of the synthetic phosphodiesterase-4 inhibitor, rolipram, suggests Zembrin® has antidepressant and cognitive function enhancing potential.

CONCLUSION:

The combined results from the electropharmacograms and comparative discriminatory analyses suggest that Zembrin® has dose dependent activity, with potential applications as a cognitive function enhancer, as an antidepressant, and as an analgesic.

Evid Based Complement Alternat Med. 2014;2014:682014.

Proof-of-Concept Randomized Controlled Study of Cognition Effects of the Proprietary Extract Sceletium tortuosum (Zembrin) Targeting Phosphodiesterase-4 in Cognitively Healthy Subjects: Implications for Alzheimer's Dementia.

Chiu S, Gericke N, Farina-Woodbury M, Badmaev V, Raheb H, Terpstra K, Antongiorgi J, Bureau Y, Cernovsky Z, Hou J, Sanchez V, Williams M, Copen J, Husni M, Goble L.

Abstract

Introduction. Converging evidence suggests that PDE-4 (phosphodiesterase subtype 4) plays a crucial role in regulating cognition via the PDE-4-cAMP cascade signaling involving phosphorylated cAMP response element binding protein (CREB). Objective. The primary endpoint was to examine the neurocognitive effects of extract Sceletium tortuosum (Zembrin) and to assess the safety and tolerability of Zembrin in cognitively healthy control subjects. Method. We chose the randomized double-blind placebo-controlled cross-over design in our study. We randomized normal healthy subjects (total n = 21) to receive either 25 mg capsule Zembrin or placebo capsule once daily for 3 weeks, in a randomized placebo-controlled 3-week cross-over design. We administered battery of neuropsychological tests: CNS Vital Signs and Hamilton depression rating scale (HAM-D) at baseline and regular intervals and monitored side effects with treatment emergent adverse events scale. Results. 21 subjects (mean age: 54.6 years ± 6.0 yrs; male/female ratio: 9/12) entered the study. Zembrin at 25 mg daily dosage significantly improved cognitive set flexibility ($P < 0.032$) and executive function ($P < 0.022$), compared with the placebo group. Positive changes in mood and sleep were found. Zembrin was well tolerated. Conclusion. The promising cognitive enhancing effects of Zembrin likely implicate the PDE-4-cAMP-CREB cascade, a novel drug target in the potential treatment of early Alzheimer's dementia.

Food Chem Toxicol. 2014 Dec;74:190-9.

A toxicological safety assessment of a standardized extract of Sceletium tortuosum (Zembrin®) in rats.

Murbach TS, Hirka G, Szakonyiné IP, Gericke N, Endres JR.

Abstract

A well-characterized standardized hydroethanolic extract of a traditionally recognized mak (mild) variety of Sceletium tortuosum, a South African plant with a long history of traditional ingestion, is marketed

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under the trade name Zembrin(®) as an ingredient for use in functional foods and dietary supplements. It is standardized to contain 0.35-0.45% total alkaloids (mesembrenone and mesembrenol ≥60%, and mesembrine <20%). A 14-day repeated oral toxicity study was conducted at 0, 250, 750, 2500, and 5000 mg/kg bw/day. A 90-day subchronic repeated oral toxicity study was conducted at 0, 100, 300, 450, and 600 mg/kg bw/day. Because S. tortuosum has a long history of human use for relieving stress and calming, a functional observation battery, including spontaneous locomotor activity measured using LabMaster ActiMot light-beam frames system, was employed. Several parameters, such as locomotion, rearing behavior, spatial parameters, and turning behavior were investigated in the final week of the study. No mortality or treatment-related adverse effects were observed in male or female Crl:(WI)BR Wistar rats in the 14- or 90-day studies. In the 14- and 90-day studies, the NOAELs were concluded as 5000 and 600 mg/kg bw/d, respectively, the highest dose groups tested.

Neuropsychopharmacology. 2013 Dec;38(13):2708-16.

Acute effects of Sceletium tortuosum (Zembrin), a dual 5-HT reuptake and PDE4 inhibitor, in the human amygdala and its connection to the hypothalamus.

Terburg D, Syal S, Rosenberger LA, Heany S, Phillips N, Gericke N, Stein DJ, van Honk J.

Abstract

The South African endemic plant Sceletium tortuosum has a long history of traditional use as a masticatory and medicine by San and Khoikhoi people and subsequently by European colonial farmers as a psychotropic in tincture form. Over the past decade, the plant has attracted increasing attention for its possible applications in promoting a sense of wellbeing and relieving stress in healthy individuals and for treating clinical anxiety and depression. The pharmacological actions of a standardized extract of the plant (Zembrin) have been reported to be dual PDE4 inhibition and 5-HT reuptake inhibition, a combination that has been argued to offer potential therapeutic advantages. Here we tested the acute effects of Zembrin administration in a pharmaco-fMRI study focused on anxiety-related activity in the amygdala and its connected neurocircuitry. In a double-blind, placebo-controlled, cross-over design, 16 healthy participants were scanned during performance in a perceptual-load and an emotion-matching task. Amygdala reactivity to fearful faces under low perceptual load conditions was attenuated after a single 25 mg dose of Zembrin. Follow-up connectivity analysis on the emotion-matching task showed that amygdala-hypothalamus coupling was also reduced. These results demonstrate, for the first time, the attenuating effects of S. tortuosum on the threat circuitry of the human brain and provide supporting evidence that the dual 5-HT reuptake inhibition and PDE4 inhibition of this extract might have anxiolytic potential by attenuating subcortical threat responsivity.

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J Altern Complement Med. 2013 Nov;19(11):898-904.

A randomized, double-blind, parallel-group, placebo-controlled trial of Extract Sceletium tortuosum (Zembrin) in healthy adults.

Nell H, Siebert M, Chellan P, Gericke N.

Abstract

OBJECTIVES:

The objective of the study was to evaluate the safety and tolerability of two doses (8 mg and 25 mg once daily) of a 2:1 standardized extract of the South African medicinal plant Sceletium tortuosum (L.) N.E. Br., trademarked Zembrin,(®) in healthy adult volunteers over a three-month period.

DESIGN:

This was a randomized, double-blind, parallel-group, placebo-controlled single center study.

SETTING:

Tiervlei Trial Centre, Karl Bremer Hospital, Bellville, Cape Town, South Africa.

PARTICIPANTS:

The study took place between February 2 and July 27, 2009. Thirty-seven healthy adults were recruited from the general population.

INTERVENTION:

Participants were randomized to receive either one of two doses of study medication, or an identical placebo, taken once daily for 3 months. Of the 37 subjects, 12, 12, and 13 subjects received 8 mg extract Sceletium tortuosum (Zembrin), 25 mg extract Sceletium tortuosum (Zembrin), and placebo treatment, respectively.

OUTCOME MEASURES:

No efficacy variables were assessed. The safety and tolerability variables comprised of vital signs, physical examination, 12-lead electrocardiogram (ECG), laboratory assessments (hematology, biochemistry, and urinalysis), and the recording of adverse events (AEs).

RESULTS:

There were no apparent differences between the three treatments with regard to vital signs, 12-lead ECG, body weight, and physical examination from screening to the end of the 3-month treatment period. No significant changes were observed in hematology or biochemistry parameters between initial screening and the end of the study. Both doses of extract Sceletium tortuosum (Zembrin) were well-tolerated. The most commonly reported AE was headache, followed by abdominal pain and upper respiratory tract infections, all with greater incidence in the placebo group than in the treatment groups. Unsolicited positive effects on well-being were noted in patient diaries by some participants taking extract Sceletium tortuosum (Zembrin), including improved coping with stress and sleep.

CONCLUSION:

Both doses of extract Sceletium tortuosum (Zembrin) (8 mg and 25 mg) were well tolerated when used by healthy human subjects once daily for 3 months.

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J Ethnopharmacol. 2011 Oct 11;137(3):1124-9.

Pharmacological actions of the South African medicinal and functional food plant Sceletium tortuosum and its principal alkaloids.

Harvey AL, Young LC, Viljoen AM, Gericke NP.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

The South African plant Sceletium tortuosum has been known for centuries for a variety of traditional uses, and, more recently, as a possible source of anti-anxiety or anti-depressant effects. A standardised extract Zembrin(®) was used to test for pharmacological activities that might be relevant to the ethnopharmacological uses, and three of the main alkaloids were also tested.

MATERIALS AND METHODS:

A standardised ethanolic extract was prepared from dried plant material, along with the purified alkaloids mesembrine, mesembrenone and mesembrenol. These were tested on a panel of receptors, enzymes and other drug targets, and for cytotoxic effects on mammalian cells.

RESULTS:

The extract was a potent blocker in 5-HT transporter binding assays (IC(50) 4.3 μg/ml) and had powerful inhibitory effects on phosphodiesterase 4 (PDE4) (IC(50) 8.5 μg/ml), but not other phosphodiesterases. There were no cytotoxic effects. Mesembrine was the most active alkaloid against the 5-HT transporter (K(i) 1.4 nM), while mesembrenone was active against the 5-HT transporter and PDE4 (IC(50)'s<1 μM).

CONCLUSIONS:

The activity of the Sceletium tortuosum extract on the 5-HT transporter and PDE4 may explain the clinical effects of preparations made from this plant. The activities relate to the presence of alkaloids, particularly mesembrine and mesembrenone.

J Ethnopharmacol. 2012 Sep 28;143(2):565-71.

Apocynum venetum leaf extract, an antihypertensive herb, inhibits rat aortic contraction induced by angiotensin II: a nitric oxide and superoxide connection.

Lau YS, Kwan CY, Ku TC, Hsieh WT, Wang HD, Nishibe S, Dharmani M, Mustafa MR.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

The leaves extract of Apocynum venetum (AVLE), also known as "luobuma", have long been used in traditional Chinese medicine to treat hypertension and depression in parts of China and it has been shown to possess anti-oxidant and anti-lipid peroxidation effects. AVLE (10 μg/ml) has been reported to have a long-lasting endothelium-dependent relaxant effect and this effect has been proposed to be due to its nitric oxide(NO)-releasing and superoxide anion(SOA)-scavenging properties.

AIM OF THE STUDY:

The present study seeks to evaluate the differential actions of AVLE extract between Ang II- and PE-induced vasoconstriction and the involvement of superoxide anions.

MATERIALS AND METHODS:

Single dose of Ang II (100 nM and 1 nM)- or PE (0.1 μM)-induced contraction were assessed in both

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endothelium-intact and -denuded aortic rings after pre-incubation of AVLE (10 µg/ml) for 15 min. The experiment was repeated in either the presence of NO synthase inhibitor, L-NAME (300 µM) or selective AT(1) receptor inhibitor, losartan (0.1 nM), or superoxide scavenger, tiron (1 mM) or a combination of L-NAME and AVLE. Superoxide production was measured by using enhanced-chemiluminescence assay.

RESULTS:

We have demonstrated that AVLE (10 µg/ml) effectively suppressed the Ang II-induced contraction (100 nM and 1 nM) of both endothelium-intact and -denuded rat aortic rings. In endothelium-intact rings, L-NAME, reversed AVLE-induced inhibition of Ang II-contraction. PE-induced contraction was significantly inhibited by AVLE in endothelium-intact rings, but not in endothelium-denuded rings. The inhibition by AVLE of PE-induced contraction was totally abolished in the presence of L-NAME. Ang II-induced SOA production concentration dependently with the optimal effect seen at 100 nM of Ang II, and AVLE (0.3, 1, 10 µg/ml) reduced this effect. SOA production in Ang II-stimulated rings was significantly higher than unstimulated control rings, while PE did not stimulate SOA production at all. SOA formation in the presence of Ang II was also inhibited in the presence of SOD (superoxide scavenger), DPI (NADPH inhibitor) and losartan (specific AT(1) receptor antagonist).

CONCLUSION:

These results collectively suggest that the ability of AVLE in inhibiting Ang II-induced contraction via its SOA scavenging properties and nitric oxide releasing effect may account for its usage as an antihypertensive treatment in traditional folk medicine.

J Ethnopharmacol. 2012 May 7;141(1):1-8.

Botany, traditional uses, phytochemistry and pharmacology of Apocynum venetum L. (Luobuma): A review.

Xie W, Zhang X, Wang T, Hu J.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Apocynum venetum L. (Apocynaceae, Luobuma) has a long history as a Chinese traditional medicine with uses to calm the liver, soothe the nerves, dissipate heat, and promote diuresis. Recently, Luobuma tea has been commercialized as a sedative and anti-aging supplement that has become increasingly popular in North American and East Asian health food markets.

AIMS OF THE REVIEW:

The aim of this review is to provide an up-to-date and comprehensive overview of the botany, chemical constituents, traditional uses, pharmacological activities and safety aspects of Apocynum venetum in order to assess its ethnopharmacological use and to explore its therapeutic potentials and future opportunities for research.

BACKGROUND AND METHODS:

The accessible literature on Apocynum venetum written in English, Chinese and Japanese were collected and analyzed. The literatures included ancient Chinese herbal classics, pharmacopoeias and articles that included in Pubmed, Web of Science, Google Scholar and Wanfang.

KEY FINDINGS:

Modern pharmacological studies demonstrated that Apocynum venetum possess wide pharmacological

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activities that include antihypertensive, cardiotonic, hepatoprotective, antioxidant, lipid-lowering, antidepressant and anxiolytic effects, which can be explained by the presence of various flavonoid compounds in this plant. The traditional (Lop Nor region) use of Apocynum venetum with tobacco as an agent to detoxify nicotine may receive interest as a possible therapeutic option to detoxify the body from smoking. Based on animal studies and clinical trials, Apocynum venetum causes no severe side effects, even in a stable daily dosage (50mg/person/day) for more than three years.

CONCLUSIONS:

Apocynum venetum potentially has therapeutic potential in the prevention and treatment for the cardiovascular and neurological diseases, especially for high blood pressure, high cholesterol, neurasthenia, depression and anxiety. Further investigations are needed to explore individual bioactive compounds responsible for these in vitro and in vivo pharmacological effects and the mode of actions. Further safety assessments and clinical trials should be performed before it can be integrated into medicinal practices.

Phytomedicine. 2012 Jan 15;19(2):145-9.

Antidepressant-like effect of hyperoside isolated from Apocynum venetum leaves: possible cellular mechanisms.

Zheng M, Liu C, Pan F, Shi D, Zhang Y.

Abstract

In the present work, we studied the possible cellular mechanisms of hyperoside isolated from Apocynum venetum leaves in corticosterone-induced neurotoxicity, using PC12 cells as a suitable in vitro model of depression. Cell viability was quantitated by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The release amount of lactic dehydrogenase (LDH) and intracellular Ca(2+) concentration were measured using kit and transcript abundances of brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB) were determined by real-time RT-PCR. The results of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and lactic dehydrogenase (LDH) assays showed that 2.5, 5 and 10 μg/ml hyperoside or 10 μM fluoxetine (FLU) protected PC12 cells from the lesion induced by a 48 h treatment with 10 μM corticosterone. Fura-2/AM (acetoxymethyl ester) assays showed that 2.5, 5 and 10 μg/ml hyperoside or 10 μM FLU attenuated the intracellular Ca(2+) overloading in PC12 cells induced by corticosterone. The transcript abundance of BDNF and CREB in PC12 cells was elevated upon hyperoside treatment. These results suggest that the possible cellular mechanisms of hyperoside antidepressant-like effect is a cytoprotective action related to elevation the expression of BDNF and CREB through the signal pathway AC-cAMP-CREB.

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J Ethnopharmacol. 2011 Jun 14;136(1):149-55.

Apocynum venetum leaf aqueous extract inhibits voltage-gated sodium channels of mouse neuroblastoma N2A cells.

Kuo CS, Kwan CY, Gong CL, Tsai MF, Nishibe S, Tatsuzaki J, Leung YM.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Apocynum venetum Linn. (Apocynaceae family), also called Luobuma, is a shrub which grows widely in the Xinjiang Autonomous Region of China. Its leaves are used in herbal tea for the treatment of hypertension, anxiety and depression. Animal studies have also shown that Apocynum venetum leaf extract (AVLE) also exerts anti-depressant and anti-anxiety activities. The effects of AVLE on neuronal tissues in vitro are not fully understood.

MATERIALS AND METHODS:

Using the whole-cell voltage-clamp method, we studied the effects of AVLE on ion channels in cultured mouse neuroblastoma N2A cells.

RESULTS:

AVLE inhibited voltage-gated inward Na(+) current in a reversible and concentration-dependent manner (half-inhibitory concentration was 18 μg/ml and maximum inhibition at 100 μg/ml). AVLE specifically promoted steady-state inactivation of Na(+) channels but did not affect voltage-dependence of activation. The inhibitory effect was not use-dependent and was not affected by 300μM L-NAME, suggesting that NO was not involved in the action of AVLE in neuronal cells. AVLE also had a mild inhibitory effect on voltage-gated K(+) channels, but did not affect ATP-sensitive K(+) channels.

CONCLUSIONS:

Since voltage-gated Na(+) and K(+) channels are associated with neuronal excitability and therefore affect neurotransmission, the modulation of neuronal ion channels by AVLE may exert neuropharmacological effects. In particular, the inhibition of voltage-gated Na(+) currents by AVLE may in part account for the psychopharmacological effects of this herbal remedy.

Cell Mol Neurobiol. 2011 Apr;31(3):421-8.

Protective effects of flavonoid extract from Apocynum venetum leaves against corticosterone-induced neurotoxicity in PC12 cells.

Zheng M, Liu C, Pan F, Shi D, Ma F, Zhang Y, Zhang Y.

Abstract

Depression is a major psychiatric disorder affecting nearly 21% of the world population and imposes a substantial health burden on society. Although significant progress has been made in depression research, the common molecular mechanism of antidepressants is still far from clearly understood. The neuroprotective effect of antidepressants has been proposed as a possible mechanism. Although Apocynum venetum (AV) L. (Apocynaceae) was previously shown to produce an antidepressant-like effect in the tail suspension test, the mechanisms underlying such antidepressant-like effect are yet to be understood. In this work, we studied the neuroprotective effect of AV leaf flavonoid extract in corticosterone-induced neurotoxicity, using PC12 cells as a suitable in vitro model of depression. Cell

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viability was quantitated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The release amount of lactic dehydrogenase (LDH) and intracellular Ca(2+) concentration were measured using kit, cell period change was tested by flow cytometry, and transcript abundances of brain-derived neurotrophic factor (BDNF) and microtubule-associated protein 4 (MAP4) were determined by real-time RT-PCR. The results showed that AV extract (25, 50, and 100 μg/ml) increased the A490 nm values, but decreased LDH release and Ca(2+) concentration, suppressed the apoptosis of PC12 cells and up-regulated BDNF and MAP4 transcript abundances compared with the corresponding corticosterone-treated group. These results suggest that the AV extract could generate a neuroprotective effect on corticosterone-induced neurotoxicity in PC12 cells, pointing to a possible action pathway by decreasing the Ca(2+) concentration and up-regulating BDNF and MAP4 genes.

J Med Invest. 2005 Nov;52 Suppl:249-51.

Approach to novel functional foods for stress control 5. Antioxidant activity profiles of antidepressant herbs and their active components.

Shirai M, Kawai Y, Yamanishi R, Terao J.

Abstract

Oxidative stress is frequently mentioned in relation to the neurodegenerative diseases. This study examined the effect of three herb extracts, Hypericum perforatum, Ginkgo biloba L. and Apocynum venetum L., and their components on lipid hydroperoxide-induced oxidative stress in PC-12 cells. Among them, the extract of Apocynum venetum and its components showed the remarkable inhibitory effect, indicating that this herb extract serves as a protective agent against lipid peroxidation-related oxidative stress in CNS. Oxidative stress may be associated with the progress of depression, as this extract has been proposed to be an effective antidepressant herb.

Biol Pharm Bull. 2001 Jul;24(7):848-51.

Antidepressant effects of apocynum venetum leaves in a forced swimming test.

Butterweck V, Nishibe S, Sasaki T, Uchida M.

Abstract

An extract of the leaves of Apocynum venetum L. (Apocynaceae) markedly shortened the immobility time of male rats in a forced swimming test (FST) in a dose range of 30-125 mg/kg, indicating a possible antidepressant activity. This effect was comparable to that of the tricyclic antidepressant imipramine (20 mg/kg). Neither imipramine (20 mg/kg) nor the Apocynum extract in various doses (30, 60, 125 mg/kg) produced any overt behavioural change or motor dysfunction in the open field test. This result confirms the assumption that the antidepressant effect of an Apocynum extract in the FST is specific. Further, it can be speculated that this effect might be related to hyperoside and isoquercitrin which are major flavonoids in the extract.

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Biogerontology. 2017 Aug;18(4):601-614.

Intermittent fasting combined with supplementation with Ayurvedic herbs reduces anxiety in middle aged female rats by anti-inflammatory pathways.

Singh H, Kaur T, Manchanda S, Kaur G.

Abstract

Intermittent fasting-dietary restriction (IF-DR) is an increasingly popular intervention to promote healthy aging and delay age associated decline in brain functions. Also, the use of herbal interventions is gaining attention due to their non-pharmacological approach to treat several abnormalities and promote general health with least side effects. The present study was aimed to investigate the synergistic effects of IF-DR regimen with herbal supplementation on anxiety-like behavior and neuroinflammation in middle aged female rats. We used dried leaf powder of Withania somnifera and dried stem powder of Tinospora cordifolia for our study. The rats were divided into three groups: (1) Control group fed ad libitum (AL); (2) rats deprived of food for full day and fed ad libitum on every alternate day (IF-DR); and (3) IF-DR and herbal extract (DRH) group in which rats were fed ad libitum with herbal extract supplemented diet, every alternate day. Post regimen, the rats were tested for anxiety-like behavior and further used for study of key inflammatory molecules (NFκB, Iba1, TNFα, IL-1β, IL-6) and glial marker (GFAP) in hippocampus and piriform cortex regions of brain. The study was further extended to explore the effect of DRH regimen on stress response protein (HSP70) and calcium dependent regulators of synaptic plasticity (CaMKIIα, Calcineurin). Our data demonstrated that DRH regimen reduced anxiety-like behavior in middle age female rats and associated neuroinflammation by ameliorating key inflammatory cytokines and modulated stress response. The present data may provide scientific validation for anxiolytic and anti-inflammatory potential of herbal intervention combined with short term IF-DR regimen.

Mol Cell Biochem. 2017 Mar;427(1-2):91-101.

Withania somnifera as a potential anxiolytic and immunomodulatory agent in acute sleep deprived female Wistar rats.

Kaur T, Singh H, Mishra R, Manchanda S, Gupta M, Saini V, Sharma A, Kaur G.

Abstract

Sleep is a profound regulator of cellular immunity, and the curtailment of sleep in present day lifestyle leads to disruption of neuro-immune-endocrine interactions. No therapeutic remedy is yet known for the amelioration of detrimental effects caused by sleep deprivation (SD). The current study was aimed to elucidate the effects of acute SD on immune function and its modulation by water extract from leaves of Withania somnifera (ASH-WEX). Three groups of animals, i.e. Vehicle-Undisturbed sleep (VUD), Vehicle-Sleep deprived (VSD) and ASH-WEX fed sleep deprived (WSD) rats were tested for their anxiety-like behaviour and further used for the study of inflammatory and apoptotic markers expression in piriform cortex and hippocampus regions of the brain. VSD animals showed high level of anxiety in elevated plus maze test, which was ameliorated in WSD group. The stress induced expression of inflammatory and immune response markers GFAP, TNFα, IL-6, OX-18 and OX-42 in VSD animals was found to be modulated by ASH-WEX. Further, the stress induced apoptosis was suppressed in WSD group as indicated by expression of NF-κB, AP-1, Bcl-xL and Cytochrome c. This study provides scientific validation to the anxiolytic, anti-inflammatory and anti-apoptotic properties of ASH-WEX, which may serve as an effective dietary supplement for management of SD induced stress and associated functional impairments.

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J Evid Based Complementary Altern Med. 2017 Jan;22(1):96-106.

Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial.

Choudhary D, Bhattacharyya S, Joshi K.

Abstract

Chronic stress has been associated with a number of illnesses, including obesity. Ashwagandha is a well-known adaptogen and known for reducing stress and anxiety in humans. The objective of this study was to evaluate the safety and efficacy of a standardized root extract of Ashwagandha through a double-blind, randomized, placebo-controlled trial. A total of 52 subjects under chronic stress received either Ashwagandha (300 mg) or placebo twice daily. Primary efficacy measures were Perceived Stress Scale and Food Cravings Questionnaire. Secondary efficacy measures were Oxford Happiness Questionnaire, Three-Factor Eating Questionnaire, serum cortisol, body weight, and body mass index. Each subject was assessed at the start and at 4 and 8 weeks. The treatment with Ashwagandha resulted in significant improvements in primary and secondary measures. Also, the extract was found to be safe and tolerable. The outcome of this study suggests that Ashwagandha root extract can be used for body weight management in adults under chronic stress.

Curr Pharm Des. 2016;22(5):535-40.

Unique Medicinal Properties of Withania somnifera: Phytochemical Constituents and Protein Component.

Dar PA, Singh LR, Kamal MA, Dar TA.

Abstract

Withania somnifera is an important medicinal herb that has been widely used for the treatment of different clinical conditions. The overall medicinal properties of Withania somnifera make it a viable therapeutic agent for addressing anxiety, cancer, microbial infection, immunomodulation, and neurodegenerative disorders. Biochemical constituents of Withania somnifera like withanolideA, withanolide D, withaferin A and withaniamides play an important role in its pharmacological properties. Proteins like Withania somnifera glycoprotein and withania lectin like-protein possess potent therapeutic properties like antimicrobial, anti-snake venom poison and antimicrobial. In this review, we have tried to present different pharmacological properties associated with different extract preparations, phytochemical constituents and protein component of Withania somnifera. Future insights in this direction have also been highlighted.

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J Ethnopharmacol. 2015 Aug 2;171:264-72.

Direct evidence for GABAergic activity of Withania somnifera on mammalian ionotropic GABAA and GABAρ receptors.

Candelario M, Cuellar E, Reyes-Ruiz JM, Darabedian N, Feimeng Z, Miledi R, Russo-Neustadt A, Limon A.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Withania somnifera (WS) has been traditionally used in Ayurvedic medicine as a remedy for debility, stress, nervous exhaustion, insomnia, loss of memory, and to enhance cognitive function. This study provides an empirical evidence to support the traditional use of WS to aid in mental process engaging GABAergic signaling.

AIM OF THE STUDY:

We evaluated the effect of aqueous WS root extract (aqWS), and its two main components, withaferin A and withanolide A, on the main inhibitory receptors in the central nervous system: ionotropic GABAA receptors.

MATERIALS AND METHODS:

The pharmacological activity of aqWS, withaferin A and withanolide A, was tested on native rat brain GABAA channels microtransplanted into Xenopus oocytes and GABAρ1 receptors heterologously expressed in oocytes. The GABAergic activity of aqWS compounds was evaluated by the two-electrode voltage-clamp method and the fingerprint of the extract was done by LC-MS.

RESULTS:

Concentration-dependent inward ion currents were elicited by aqWS in microtransplanted oocytes with an EC50 equivalent to 4.7 mg/mL and a Hill coefficient (nH) of 1.6. The GABAA receptor antagonist bicuculline blocked these currents. Our results show that aqWS activated inotropic GABAA channels but with lower efficacy compared to the endogenous agonist GABA. We also demonstrate for first time that aqWS is a potent agonist of GABAρ1 receptors. GABAρ1 receptors were 27 fold more sensitive to aqWS than GABAA receptors. Furthermore, aqWS activated GABAρ1 receptors eliciting maximum currents that were no significantly different to those produced by GABA (paired t-test; p=0.533). The differential activity on GABAA and GABA ρ1 receptors and the reported lack of significant GABA presence in WS root extract indicates that the GABAergic activity of aqWS is not mediated by GABA. WS main active components, witaferin A and withanolide A, were tested to determine if they were responsible for the activation of the GABA receptors. Neither compound activated GABAA nor GABAρ1 receptors, suggesting that other constituent/s in WS are responsible for GABAA receptor mediated responses.

CONCLUSIONS:

Our results provide evidence indicating that key constituents in WS may have an important role in the development of pharmacological treatments for neurological disorders associated with GABAergic signaling dysfunction such as general anxiety disorders, sleep disturbances, muscle spasms, and seizures. In addition, the differential activation of GABA receptor subtypes elucidates a potential mechanism by which WS accomplishes its reported adaptogenic properties.

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J Altern Complement Med. 2014 Dec;20(12):901-8.

An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera).

Pratte MA, Nanavati KB, Young V, Morley CP.

Abstract

OBJECTIVE:

To assess existing reported human trials of Withania somnifera (WS; common name, ashwagandha) for the treatment of anxiety.

DESIGN:

Systematic review of the literature, with searches conducted in PubMed, SCOPUS, CINAHL, and Google Scholar by a medical librarian. Additionally, the reference lists of studies identified in these databases were searched by a research assistant, and queries were conducted in the AYUSH Research Portal. Search terms included "ashwagandha," "Withania somnifera," and terms related to anxiety and stress. Inclusion criteria were human randomized controlled trials with a treatment arm that included WS as a remedy for anxiety or stress. The study team members applied inclusion criteria while screening the records by abstract review.

INTERVENTION:

Treatment with any regimen of WS.

OUTCOME MEASURES:

Number and results of studies identified in the review.

RESULTS:

Sixty-two abstracts were screened; five human trials met inclusion criteria. Three studies compared several dosage levels of WS extract with placebos using versions of the Hamilton Anxiety Scale, with two demonstrating significant benefit of WS versus placebo, and the third demonstrating beneficial effects that approached but did not achieve significance ($p=0.05$). A fourth study compared naturopathic care with WS versus psychotherapy by using Beck Anxiety Inventory (BAI) scores as an outcome; BAI scores decreased by 56.5% in the WS group and decreased 30.5% for psychotherapy ($p<0.0001$). A fifth study measured changes in Perceived Stress Scale (PSS) scores in WS group versus placebo; there was a 44.0% reduction in PSS scores in the WS group and a 5.5% reduction in the placebo group ($p<0.0001$). All studies exhibited unclear or high risk of bias, and heterogenous design and reporting prevented the possibility of meta-analysis.

CONCLUSIONS:

All five studies concluded that WS intervention resulted in greater score improvements (significantly in most cases) than placebo in outcomes on anxiety or stress scales. Current evidence should be received with caution because of an assortment of study methods and cases of potential bias.

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J Clin Psychiatry. 2013 Nov;74(11):1076-83.

Randomized placebo-controlled adjunctive study of an extract of withania somnifera for cognitive dysfunction in bipolar disorder.

Chengappa KN, Bowie CR, Schlicht PJ, Fleet D, Brar JS, Jindal R.

Abstract

OBJECTIVE:

Cognitive impairments contribute significantly to inadequate functional recovery following illness episodes in bipolar disorder, yet data on treatment interventions are sparse. We assessed the cognitive effects of a standardized extract of the medicinal herb Withania somnifera (WSE) in bipolar disorder.

METHOD:

Sixty euthymic subjects with DSM-IV bipolar disorder were enrolled in an 8-week, double-blind, placebo-controlled, randomized study of WSE (500 mg/d) as a procognitive agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder. Study enrollment and data analyses were completed between December 2008 and September 2012. Cognitive testing at baseline and 8 weeks assessed primary efficacy outcomes. Psychopathology and adverse events were monitored at scheduled visits.

RESULTS:

Fifty-three patients completed the study (WSE, n = 24; placebo, n = 29), and the 2 groups were matched in terms of demographic, illness, and treatment characteristics. Compared to placebo, WSE provided significant benefits for 3 cognitive tasks: digit span backward (P = .035), Flanker neutral response time (P = .033), and the social cognition response rating of the Penn Emotional Acuity Test (P = .045). The size of the WSE treatment effect for digit span backward was in the medium range (Cohen d = 0.51; 95% CI, 0.25-0.77). None of the other cognitive tasks showed significant between-group differences. Mood and anxiety scale scores remained stable, and adverse events were minor.

CONCLUSIONS:

Although results are preliminary, WSE appears to improve auditory-verbal working memory (digit span backward), a measure of reaction time, and a measure of social cognition in bipolar disorder. Given the paucity of data for improving cognitive capacity in bipolar disorder, WSE offers promise, appears to have a benign side-effects profile, and merits further study.

Indian J Psychol Med. 2012 Jul;34(3):255-62.

A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults.

Chandrasekhar K, Kapoor J, Anishetty S.

Abstract

CONTEXT:

Stress is a state of mental or emotional strain or tension, which can lead to underperformance and adverse clinical conditions. Adaptogens are herbs that help in combating stress. Ayurvedic classical texts, animal studies and clinical studies describe Ashwagandha as a safe and effective adaptogen.

AIMS:

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The aim of the study was to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots in reducing stress and anxiety and in improving the general well-being of adults who were under stress.

SETTINGS AND DESIGN:

Single center, prospective, double-blind, randomized, placebo-controlled trial.

MATERIALS AND METHODS:

A total of 64 subjects with a history of chronic stress were enrolled into the study after performing relevant clinical examinations and laboratory tests. These included a measurement of serum cortisol, and assessing their scores on standard stress-assessment questionnaires. They were randomized to either the placebo control group or the study drug treatment group, and were asked to take one capsule twice a day for a period of 60 days. In the study drug treatment group, each capsule contained 300 mg of high-concentration full-spectrum extract from the root of the Ashwagandha plant. During the treatment period (on Day 15, Day 30 and Day 45), a follow-up telephone call was made to all subjects to check for treatment compliance and to note any adverse reactions. Final safety and efficacy assessments were done on Day 60.

STATISTICAL ANALYSIS:

t-test, Mann-Whitney test.

RESULTS:

The treatment group that was given the high-concentration full-spectrum Ashwagandha root extract exhibited a significant reduction ($P<0.0001$) in scores on all the stress-assessment scales on Day 60, relative to the placebo group. The serum cortisol levels were substantially reduced ($P=0.0006$) in the Ashwagandha group, relative to the placebo group. The adverse effects were mild in nature and were comparable in both the groups. No serious adverse events were reported.

CONCLUSION:

The findings of this study suggest that a high-concentration full-spectrum Ashwagandha root extract safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life.

Asian Pac J Trop Med. 2012 May;5(5):380-4.

Influence of Withania somnifera on obsessive compulsive disorder in mice.

Kaurav BP, Wanjari MM, Chandekar A, Chauhan NS, Upmanyu N.

Abstract

OBJECTIVE:

To study the influence of methanolic and aqueous extract of Withania somnifera (W. somnifera) root on the marble-burying behavior of mice a well-accepted model of obsessive compulsive behavior.

METHODS:

Mice were divided in different groups (n = 6). Fluoxetine (5, 10, 15 mg/kg), (10, 25, 50, 100 mg/kg) and methanolic extract W. somnifera (MEWS) (10, 25, 50, 100 mg/kg) were administered i.p. 30 min. prior to the assessment of marble burying behavior and locomotor activity. The control group received vehicle of the extract.

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RESULTS:

Administration of aqueous extracts W. somnifera (AEWS) and MEWS (50 mg/kg) successively decreased the marble burying behavior activity without affecting motor activity. This effect of AEWS and MEWS was comparable to standard fluoxetine, ritanserin and parachlorophenylalanine.

CONCLUSIONS:

W. somnifera extract is effective in treating obsessive compulsive disorder.

PLoS One. 2009 Aug 31;4(8):e6628.

Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974.

Cooley K, Szczurko O, Perri D, Mills EJ, Bernhardt B, Zhou Q, Seely D.

Abstract

BACKGROUND:

Anxiety is a serious personal health condition and represents a substantial burden to overall quality of life. Additionally anxiety disorders represent a significant cost to the health care system as well as employers through benefits coverage and days missed due to incapacity. This study sought to explore the effectiveness of naturopathic care on anxiety symptoms using a randomized trial.

METHODS:

Employees with moderate to severe anxiety of longer than 6 weeks duration were randomized based on age and gender to receive naturopathic care (NC) (n = 41) or standardized psychotherapy intervention (PT) (n = 40) over a period of 12 weeks. Blinding of investigators and participants during randomization and allocation was maintained. Participants in the NC group received dietary counseling, deep breathing relaxation techniques, a standard multi-vitamin, and the herbal medicine, ashwagandha (Withania somnifera) (300 mg b.i.d. standardized to 1.5% with anolides, prepared from root). The PT intervention received psychotherapy, and matched deep breathing relaxation techniques, and placebo. The primary outcome measure was the Beck Anxiety Inventory (BAI) and secondary outcome measures included the Short Form 36 (SF-36), Fatigue Symptom Inventory (FSI), and Measure Yourself Medical Outcomes Profile (MY-MOP) to measure anxiety, mental health, and quality of life respectively. Participants were blinded to the placebo-controlled intervention.

RESULTS:

Seventy-five participants (93%) were followed for 8 or more weeks on the trial. Final BAI scores decreased by 56.5% ($p<0.0001$) in the NC group and 30.5% ($p<0.0001$) in the PT group. BAI group scores were significantly decreased in the NC group compared to PT group ($p = 0.003$). Significant differences between groups were also observed in mental health, concentration, fatigue, social functioning, vitality, and overall quality of life with the NC group exhibiting greater clinical benefit. No serious adverse reactions were observed in either group.

RELEVANCE:

Many patients seek alternatives and/or complementary care to conventional anxiety treatments. To date, no study has evaluated the potential of a naturopathic treatment protocol to effectively treat anxiety. Knowledge of the efficacy, safety or risk of natural health products, and naturopathic treatments is important for physicians and the public in order to make informed decisions.

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INTERPRETATION:

Both NC and PT led to significant improvements in patients' anxiety. Group comparison demonstrated a significant decrease in anxiety levels in the NC group over the PT group. Significant improvements in secondary quality of life measures were also observed in the NC group as compared to PT. The whole system of naturopathic care for anxiety needs to be investigated further including a closer examination of the individual components within the context of their additive effect.

Indian J Exp Biol. 2008 Jun;46(6):470-5.

Effect of Withania somnifera Dunal in ethanol-induced anxiolysis and withdrawal anxiety in rats.

Gupta GL, Rana AC.

Abstract

Withania somnifera (WS) or its psychotropic preparation is known to play a critical role in morphine, alcohol and benzodiazepines addiction. This study investigates the role of WS in acute ethanol and withdrawal from chronic ethanol consumption using elevated plus maze paradigm in rats. Acute administration of ethanol (1.5-2 g/kg, ip) triggered anxiolytic effect and withdrawal from prolonged ethanol (9% v/v ethanol, 15 days) consumption elicited enhanced behavioral despair (anxiety). Acute administration of WS (50 mg/kg, oral) potentiated the anxiolytic action of subeffective dose of ethanol (0.5 or 1 g/kg, ip). Moreover, the ethanol withdrawal anxiety was markedly antagonized in dose dependent manner by WS at 200 and 500 mg/kg or higher dose of ethanol (2.5 g/kg). However, co-administration of subeffective doses of WS (50 mg/kg, oral) and ethanol also attenuated withdrawal-induced anxiety due to chronic ethanol (9% v/v ethanol, 15 days) consumption. The results suggest the protective effect of WS in the management of ethanol withdrawal reactions.

Indian J Physiol Pharmacol. 2007 Oct-Dec;51(4):345-53.

Protective effect of Withania somnifera dunal root extract against protracted social isolation induced behavior in rats.

Gupta GL, Rana AC.

Abstract

This study investigated the effect of Withania somnifera Dunal (WS) root extract and diazepam in social isolation induced behavior such as anxiety and depression in rats. Rats were isolated for 6 weeks and the assessment of changed behavior were done on elevated plus maze (EPM) and forced swim test (FST). Isolation reared rats spent less time into the open arms on EPM and significantly increased immobility time in FST compared to group housed rats. WS (100, 200 or 500 mg/kg, oral) and diazepam (1 or 2 mg/kg, ip) dose dependently increased the time spent and entries into the open arms on EPM test and showed the anxiolytic activity. Subeffective dose of WS (50 mg/kg, oral) potentiated the anxiolytic action of diazepam (0.5, 1 or 2 mg/kg, ip). WS (100, 200 or 500 mg/kg, oral) also reduced the immobility time in FST, thus showed antidepressant effect in both group housed and social isolates. The investigations support the use of WS as a mood stabilizer in socially isolation behavior in Ayurveda.

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Phytomedicine. 2000 Dec;7(6):463-9.

Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: an experimental study.

Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S.

Abstract

The roots of Withania somnifera (WS) are used extensively in Ayurveda, the classical Indian system of medicine, and WS is categorized as a rasayana, which are used to promote physical and mental health, to provide defence against disease and adverse environmental factors and to arrest the aging process. WS has been used to stabilize mood in patients with behavioural disturbances. The present study investigated the anxiolytic and antidepressant actions of the bioactive glycowithanolides (WSG), isolated from WS roots, in rats. WSG (20 and 50 mg/kg) was administered orally once daily for 5 days and the results were compared by those elicited by the benzodiazepine lorazepam (0.5 mg/kg, i.p.) for anxiolytic studies, and by the tricyclic anti-depressant, imipramine (10 mg/kg, i.p.), 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 elevated plus-maze, social interaction and feeding latency in an unfamiliar environment, tests. Further, both WSG and lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioural despair' and 'learned helplessness' tests. The investigations support the use of WS as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda.

Indian J Psychiatry. 2000 Jul;42(3):295-301.

A double-blind, placebo-controlled evaluation of the anxiolytic efficacy of an ethanolic extract of withania somnifera.

Andrade C, Aswath A, Chaturvedi SK, Srinivasa M, Raguram R.

Abstract

A double-blind, placebo-controlled study was conducted to evaluate the efficacy an ethanolic extract of Aswagandha (Withania somnifera), in patients with ICD-10 anxiety disorders. The sample comprised 39 subjects, of whom 20 received the drug and 19 received placebo. The two groups were sociodemographically and clinically similar at baseline. At 2 and 6 weeks follow-up, data from approximately 85% of patients in each group were available for analysis. Statistical trends favouring the drug were observed at both time points. At 6 weeks, significantly more patients met a priori response criteria in the drug group (88.2%) as compared with the placebo group (50%). The drug was well-tolerated and did not occasion more adverse effects than did placebo. It is concluded that this ethanolic extract of Withania somnifera has useful anxiolytic potential and merits further investigation.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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J Int Soc Sports Nutr. 2013 Aug 7;10(1):37.

Effect of Magnolia officinalis and Phellodendron amurense (Relora®) on cortisol and psychological mood state in moderately stressed subjects.

Talbott SM, Talbott JA, Pugh M.

Abstract

BACKGROUND:

Magnolia (Magnolia officinalis) and Phellodendron (Phellodendron amurense) barks are medicinal plants commonly used as traditional remedies for reducing stress and anxiety. Modern dietary supplements are intended to induce relaxation and reduce stress as well as stress-related eating. Previous studies have shown the combination of Magnolia/Phellodendron (MP) to reduce both cortisol exposure and the perception of stress/anxiety, while improving weight loss in subjects with stress-related eating. Competitive athletes are "stressed" by their intense exercise regimens in addition to their normal activities of daily living and thus may benefit from a natural therapy intended to modulate baseline perceptions of stress and stress hormone exposure.

METHODS:

We assessed salivary cortisol exposure and psychological mood state in 56 subjects (35 men and 21 women) screened for moderate stress and supplemented with a standardized/patented MP combination (Relora®, Next Pharmaceuticals) or Placebo for 4 weeks.

RESULTS:

After 4 weeks of supplementation, salivary cortisol exposure was significantly ($p<0.05$) lower (-18%) in the Relora group compared to Placebo. Compared to Placebo, the Relora group had significantly better ($p<0.05$) mood state parameters, including lower indices of Overall Stress (-11%), Tension (-13%), Depression (-20%), Anger (-42%), Fatigue (-31%), and Confusion (-27%), and higher indices of Global Mood State (+11%) and Vigor (+18%).

CONCLUSION:

These results indicate that daily supplementation with a combination of Magnolia bark extract and Phellodendron bark extract (Relora®) reduces cortisol exposure and perceived daily stress, while improving a variety of mood state parameters, including lower fatigue and higher vigor. These results suggest an effective natural approach to modulating the detrimental health effects of chronic stress in moderately stressed adults. Future studies should examine the possible performance and recovery benefits of Relora supplementation in athletes overstressed by the physical and psychological demands of training and competition.

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Nutr J. 2008 Apr 21;7:11.

Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind, placebo-controlled clinical trial.

Kalman DS, Feldman S, Feldman R, Schwartz HI, Krieger DR, Garrison R.

Abstract

BACKGROUND:

Recent research has established correlations between stress, anxiety, insomnia and excess body weight and these correlations have significant implications for health. This study measured the effects of a proprietary blend of extracts of Magnolia officinalis and Phellodendron amurense (Relora) on anxiety, stress and sleep in healthy premenopausal women.

METHODS:

This randomized, parallel, placebo controlled clinical study was conducted with healthy, overweight (BMI 25 to 34.9), premenopausal female adults, between the ages of 20 and 50 years, who typically eat more in response to stressful situations and scores above the national mean for women on self-reporting anxiety. The intervention was Relora (250 mg capsules) or identical placebo 3 times daily for 6 weeks. Anxiety as measured by the Spielberger STATE-TRAIT questionnaires, salivary amylase and cortisol levels, Likert Scales/Visual Analog Scores for sleep quality and latency, appetite, and clinical markers of safety. The study was conducted by Miami Research Associates, a clinical research organization in Miami, FL.

RESULTS:

The intent-to-treat population consisted of 40 subjects with 26 participants completing the study. There were no significant adverse events. Relora was effective, in comparison to placebo, in reducing temporary, transitory anxiety as measured by the Spielberger STATE anxiety questionnaire. It was not effective in reducing long-standing feelings of anxiety or depression as measured using the Spielberger TRAIT questionnaire. Other assessments conducted in this study including salivary cortisol and amylase levels, appetite, body morphology and sleep quality/latency were not significantly changed by Relora in comparison to placebo.

CONCLUSION:

This pilot study indicates that Relora may offer some relief for premenopausal women experiencing mild transitory anxiety. There were no safety concerns or significant adverse events observed in this study.

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Psychopharmacology (Berl). 2001 Jan 1;153(2):219-24.

Anxiolytic properties of botanical extracts in the chick social separation-stress procedure.

Sufka KJ, Roach JT, Chambliss WG Jr, Broom SL, Feltenstein MW, Wyandt CM, Zeng L.

Abstract

RATIONALE:

The recent growth in sales of natural products labeled as dietary supplements in the United States has renewed scientific interest in the study of the therapeutic effects of multi-component botanical products.

OBJECTIVES:

This study sought to determine whether botanical extracts derived from the Rutaceae family, Acori graminei, the Magnoliaceae family, Alchemilla vulgaris and Primula veris, which had previously been identified in bioassays as having potential anxiolytic activity, were active in the chick social separation-stress procedure.

METHODS:

Eight-day-old chicks received IP injections of test articles 30 min before being tested in the presence of two social companions or in isolation for a 3-min observation period. Dependent measures were: a) latency to adopt a ventral recumbent posture to index sedation, b) number of vocalizations to index separation-distress and c) a composite pain score (comprised of footlift frequency and footlift duration in response to 50 microl of 0.10% formalin injected into the plantar surface of the foot) to index stress-induced analgesia.

RESULTS:

Proprietal extracts NPS00033 from the Rutaceae plant family and NPS00039 (Relora) from the Magnoliaceae plant family screened positive in this chick model without causing sedation.

CONCLUSIONS:

These results suggest that botanical extracts Relora and NPS00033 may be useful in modulating anxiety states.

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