Extended|Longevity

Unlimited Product Information Sheet

Unlimited™ contains **Phytotherapeutic** Extracts of ***Huperza serata, Rhodiola Rosea, Theobromine, Ginkgo Biloba, Bacopa Monnieri, Panax Ginseng, Hericium Erinaceus Lion's Mane Mushroom, Curcuma longa and Cinnamomum vera*.**

Unlimited is a phytotherapeutic formulation that aims to enhance cognitive function, similar to the fictional drug in "Limitless," can be approached by using a combination of various plant extracts known for their potential nootropic (cognitive enhancing) effects. It improves brain function. It helps memory by protecting nerve cells and has been used as a treatment for Alzheimer's disease and vascular dementia in Asia. Components reversibly inhibit AChE in vitro and in vivo to affect other neurotransmitter systems to improve memory, so has potential in treating AD symptoms.

1. ***Huperzia serrata*** - Extracted from the Chinese club moss Huperzia serrata, Huperzine A acts as an acetylcholinesterase inhibitor, which helps increase acetylcholine levels by preventing its breakdown in the brain.
2. ***Rhodiola Rosea*** - This herb is known for its ability to reduce fatigue and improve resilience to stress. It can also enhance cognitive function by improving the brain's resistance to physical and mental stress.
3. ***Theobromine*** - Derived from cocoa beans, theobromine is a mild stimulant that can improve mood and increase alertness. It has a similar but milder effect compared to caffeine.
4. ***Ginkgo Biloba*** - This plant extract is well-known for its ability to improve blood circulation and enhance cognitive function, particularly memory and focus. It is one of the most commonly used ingredients in cognitive supplements.
5. ***Bacopa Monnieri*** - Often used in traditional Ayurvedic medicine, Bacopa Monnieri can improve memory formation and speed of recall. It's known for its antioxidant properties and its ability to support brain health.
6. ***Panax Ginseng*** - Ginseng is reputed for its ability to improve mental clarity, energy, and endurance. It may also help improve the effectiveness of other cognitive enhancers in the mix.
7. ***Lion's Mane Mushroom*** - This mushroom is known for its potential neuroprotective benefits. It contains compounds that can stimulate the growth of brain cells and potentially improve cognitive function.
8. ***Curcuma longa*** (from Turmeric) - Curcumin has potent anti-inflammatory and antioxidant properties, which may help in maintaining cognitive function by protecting against oxidative stress and inflammation in the brain.
9. ***Cinnamomum verum***. Contains antioxidants, including polyphenols, phenolic acid and flavonoids.

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frontiers in Pharmacology

ORIGINAL RESEARCH
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Huperzia serrata Extract 'NSP01' With Neuroprotective Effects-Potential Synergies of Huperzine A and Polyphenols

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Huperzia serrata (Thunb.) Trevis is widely used in traditional asiatic medicine to treat many central disorders including, schizophrenia, cognitive dysfunction, and dementia. The major alkaloid, Huperzine A (HA), of *H. serrata* is a well-known competitive reversible inhibitor of acetylcholinesterase (AChE) with neuroprotective effects. Inspired by the tradition, we developed a green one-step method using microwave assisted extraction to generate an extract of *H. serrata*, called NSP01. This green extract conserves original neuropharmacological activity and chemical profile of traditional extract. The neuroprotective activity of NSP01 is based on a precise combination of three major constituents: HA and two phenolic acids, caffeic acid (CA) and ferulic acid (FA). We show that CA and FA potentiate HA-mediated neuroprotective activity. Importantly, the combination of HA with CA and FA does not potentiate the AChE inhibitory property of HA which is responsible for its adverse side effects. Collectively, these experimental findings demonstrated that NSP01, is a very promising plant extract for the prevention of Alzheimer's disease and memory deficits.

Keywords: huperzia serrata, neuroprotective activity, NSP01, huperzine A, caffeic acid, ferulic acid, synergistic combination, ERK pathway

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INTRODUCTION

Alzheimer's disease (AD) is the commonest cause of dementia in the world with huge implications for individuals and society. Although the etiology of AD remains uncertain, the chronic memory loss and cognitive decline are thought to be due, at least in part, to a progressive deposition of senile plaques and neurofibrillary tangles in cerebral cortex and basal forebrain (the amyloid and tangle cascade hypothesis) (Jan et al., 2010; Callizot et al., 2013). Other relevant factors, including cholinergic dysfunction, neuroinflammation, oxidative stress, mitochondria dysfunctions, disturbance of neuronal plasticity, age-related loss of sex hormones are important and contribute to the understanding of AD pathology (Richter et al., 2014; Heneka et al., 2015; Jang and Chung, 2016; Swerdlow, 2018).

Despite the growing population of patients affected of AD, only four drugs are currently approved to treat the cognitive symptoms of AD in European Union; these include three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and one *N*-methyl-D-aspartate (NMDA) receptor antagonist (Hyde et al., 2013; Tan, 2014). However, none of them profoundly affects the advancement of the disease.

nutrients

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Article

Theobromine Improves Working Memory by Activating the CaMKII/CREB/BDNF Pathway in Rats

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Abstract: Theobromine (TB) is a primary methylxanthine found in cacao beans. cAMP-response element-binding protein (CREB) is a transcription factor, which is involved in different brain processes that bring about cellular changes in response to discrete sets of instructions, including the induction of brain-derived neurotropic factor (BDNF). Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) has been strongly implicated in the memory formation of different species as a key regulator of gene expression. Here we investigated whether TB acts on the CaMKII/CREB/BDNF pathway in a way that might improve the cognitive and learning function in rats. Male Wistar rats (5 weeks old) were divided into two groups. For 73 days, the control rats (CN rats) were fed a normal diet, while the TB-fed rats (TB rats) received the same food, but with a 0.05% TB supplement. To assess the effects of TB on cognitive and learning ability in rats: The radial arm maze task, novel object recognition test, and Y-maze test were used. Then, the brain was removed and the medial prefrontal cortex (mPFC) was isolated for Western Blot, real-time PCR and enzyme-linked immunosorbent assay. Phosphorylated CaMKII (p-CaMKII), phosphorylated CREB (p-CREB), and BDNF level in the mPFC were measured. In all the behavior tests, working memory seemed to be improved by TB ingestion. In addition, p-CaMKII and p-CREB levels were significantly elevated in the mPFC of TB rats in comparison to those of CN rats. We also found that cortical BDNF protein and mRNA levels in TB rats were significantly greater than those in CN rats. These results suggest that orally supplemented TB upregulates the CaMKII/CREB/BDNF pathway in the mPFC, which may then improve working memory in rats.

Keywords: theobromine; cacao; working memory; behavior; CaMKII; CREB; BDNF

1. Introduction

Coffee, cocoa, and chocolate are among the most frequently consumed substances in the world [1]. Coffee has various beneficial effects on human health, as it appears to be cardio-protective,

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Article

Thebromine Targets Adenosine Receptors to Control Hippocampal Neuronal Function and Damage

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Abstract: Theobromine is a caffeine metabolite most abundant in dark chocolate, of which consumption is linked with a lower risk of cognitive decline. However, the mechanisms through which theobromine affects neuronal function remain ill-defined. Using electrophysiological recordings in mouse hippocampal synapses, we now characterized the impact of a realistic concentration of theobromine on synaptic transmission and plasticity. Theobromine (30 μM) facilitated synaptic transmission while decreasing the magnitude of long-term potentiation (LTP), with both effects being blunted by adenosine deaminase (2 U/mL). The pharmacological blockade of A_1R with DPCPX (100 nM) eliminated the theobromine-dependent facilitation of synaptic transmission, whereas the $A_{2A}R$ antagonist SCH58261 (50 nM), as well as the genetic deletion of $A_{2A}R$, abrogated the theobromine-induced impairment of LTP. Furthermore, theobromine prevented LTP deficits and neuronal loss, respectively, in mouse hippocampal slices and neuronal cultures exposed to $A\beta_{1–42}$ peptides, considered a culprit of Alzheimer's disease. Overall, these results indicate that theobromine affects information flow via the antagonism of adenosine receptors, normalizing synaptic plasticity and affording neuroprotection in dementia-related conditions in a manner similar to caffeine.

Keywords: theobromine; caffeine; adenosine receptors; synaptic transmission; synaptic plasticity; Alzheimer's disease

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1. Introduction

Caffeine is the most widely consumed psychoactive drug, enhancing well-being, alertness and attention [1]. Epidemiological studies have also shown that the regular consumption of a moderate amount of coffee (3–5 cups per day) increases memory consolidation [2,3] and decreases cognitive decline and, in particular, the risk of developing AD (e.g., [4–6]). Accordingly, animal studies indicate that caffeine triggers pro-cognitive adaptive changes in the brain [7] and attenuates memory deficits in the animal models of different brain disorders (reviewed in [8]), including AD (e.g., [9,10]). Caffeine modulates information flow in neuronal circuits, enhancing basal synaptic transmission through the antagonism of adenosine A_1 receptors (A_1R) [11,12] and dampens hippocampal long-term potentiation (LTP) [11,13], a form of synaptic plasticity considered the neurophysiological basis of memory [14], through the antagonism of adenosine A_{2A} receptors ($A_{2A}R$). The neuroprotective effect of caffeine in different animal models of neuropsychiatric disorders, including AD [9,10], has been linked to the ability of caffeine to normalize synaptic plasticity via $A_{2A}R$ (reviewed in [15]), since the overactivation of hippocampal $A_{2A}R$ is sufficient to trigger memory impairment [16–18] and is critically necessary for the emergence of synaptic and memory deficits in different animal models of early AD [19–22].

In a recent attempt to correlate the levels of caffeine with the currently established neurochemical markers of AD, we were surprised to conclude that it was the levels of theobromine rather than caffeine that correlated inversely with the altered cerebrospinal fluid levels of $A\beta_{1–42}$ and modified tau proteins [23]. This was particularly surprising, since

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Review

The Effectiveness of *Rhodiola rosea* L. Preparations in Alleviating Various Aspects of Life-Stress Symptoms and Stress-Induced Conditions—Encouraging Clinical Evidence

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Abstract: *Rhodiola rosea* L. has a long history of use in traditional medicine to stimulate the nervous system, treat stress-induced fatigue and depression, enhance physical performance and work productivity and treat gastrointestinal ailments and impotence. Apart from its well-established traditional use, a significant number of publications on the clinical efficacy of various *R. rosea* preparations can be found in the literature. The majority of these studies are related to the efficacy of *R. rosea* in terms of cognitive functions and mental performance, including various symptoms of life-stress, fatigue and burnout. The beneficial effects of this medicinal plant on enhancing physical performance have also been evaluated in professional athletes and non-trained individuals. Moreover, even though most evidence originates from pre-clinical trials, several clinical studies have additionally demonstrated the remediating effects of *R. rosea* on cardiovascular and reproductive health by addressing non-specific stress damage and reversing or healing the disrupted physiologies and disfunctions. Overall, in accordance with its aim, the results presented in this review provide an encouraging basis for the clinical efficacy of *R. rosea* preparations in managing various aspects of stress-induced conditions.

Keywords: *Rhodiola rosea*; roseroot; golden root; medicinal plants; phytotherapy; clinical studies; adaptogen; stress protection

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1. Introduction

Rhodiola rosea L. (syn. *Sedum rhodiola* DC.; *Sedum roseum* (L.) Scop), also known as "roseroot", "golden root" or "arctic root", belongs to the plant family Crassulaceae. The yellow-flowered herbaceous perennial naturally grows at high altitudes in dry sandy soil, on sea cliffs and in the crevices of mountain rocks of the Arctic regions of Europe and Asia (mainly Siberia), as well as the eastern coastal regions of North America [1]. *R. rosea* L. has appeared as a valuable medicinal plant in the traditional and popular medicine of a number of European and Asian countries, including Sweden, Norway, France, Germany and Iceland, as well as Russia and China. Traditionally, *R. rosea* has been used for centuries to increase physical endurance, work productivity, longevity, resistance to high-altitude sickness, to treat fatigue, depression, anemia, impotence, for gastrointestinal ailments, infections and nervous system disorders [2–5].

The long, well-established traditional medicinal use of *R. rosea* has stimulated extensive modern scientific research leading to the identification of *R. rosea* as an "adaptogen", a substance that nonspecifically increases the resistance of an organism, does not disturb normal biological parameters and has a normalizing influence on physiology [6,7]. The term adaptogen dates to 1947 and has been credited to the Russian scientist Nikolai Lazarev, who defined it as an agent that allows for an organism to counteract adverse physical, chemical, or biological stressors by generating non-specific resistance [6]. To successfully combat stress and stressful situations, adaptation is required. Adaptation might be best thought of as an organism's ability to resist a stressor by responding with either decreased or no characteristic perturbations in homeostasis. Plant adaptogens have the capacity to

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SYSTEMATIC REVIEW
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Preclinical Evidence and Possible Mechanisms of *Rhodiola rosea L.* and Its Components for Ischemic Stroke: A Systematic Review and Meta-Analysis

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Background: *Rhodiola rosea L.* has long been used as traditional medicines in Europe and Asia to treat a variety of common conditions and diseases including Alzheimer's disease, cardiovascular disease, cognitive dysfunctions, cancer, and stroke. Previous studies reported that *Rhodiola rosea L.* and its components (RRC) improve ischemia stroke in animal models. Here, we conducted a systematic review and meta-analysis for preclinical studies to evaluate the effects of RRC and the probable neuroprotective mechanisms in ischemic stroke.

Methods: Studies of RRC on ischemic stroke animal models were searched in seven databases from inception to Oct 2021. The primary measured outcomes included the neural functional deficit score (NFS), infarct volume (IV), brain water content, cell viability, apoptotic cells, terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick end labeling (TUNEL)-positive cells, B-cell lymphoma-2 (Bcl-2) level and tumor necrosis factor-α (TNF-α) level. The secondary outcome measures were possible mechanisms of RRC for ischemic stroke. All the data were analyzed via RevMan version 5.3.

Results: 15 studies involving 345 animals were identified. Methodological quality for each included studies was accessed according to the CAMARADES 10-item checklist. The quality score of studies range from 1 to 7, and the median was 5.53. Pooled preclinical data showed that compared with the controls, RRC could improve NFS (Zea Longa ($p < 0.01$), modified neurological severity score (mNSS) ($p < 0.01$), rotarod tests ($p < 0.01$), IV ($p < 0.01$), as well as brain edema ($p < 0.01$). It also can increase cell viability ($p < 0.01$), Bcl-2 level ($p < 0.01$) and reduce TNF-α level ($p < 0.01$), TUNEL-positive cells ($p < 0.01$), apoptotic cells ($p < 0.01$).

Conclusion: The findings suggested that RRC can improve ischemia stroke. The possible mechanisms of RRC are largely through antioxidant, anti-apoptosis activities, anti-inflammatory, repressing lipid peroxidation, antigliosis, and alleviating the pathological blood brain barrier damage.

Keywords: Rhodiola rosea L, traditional medicine, ischemia stroke, possible mechanisms, preclinical evidence

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More than just caffeine: psychopharmacology of methylxanthine interactions with plant-derived phytochemicals

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ABSTRACT

In general, preparations of coffee, teas, and cocoa containing high levels of polyphenols, L-theanine and other bioactive compounds selectively enhance mood and cognition effects of caffeine. This review summarizes the bioactive components of commonly consumed natural caffeine sources (e.g. guayusa, mate and camellia teas, coffee and cocoa) and analyzes the psychopharmacology of constituent phytochemicals: methylxanthines, polyphenols, and L-theanine. Acute and chronic synergistic effects of these compounds on mood and cognition are compared and discussed. Specific sets of constituent compounds such as polyphenols, theobromine and L-theanine appear to enhance mood and cognition effects of caffeine and alleviate negative psychophysiological effects of caffeine. However, more research is needed to identify optimal combinations and ratios of caffeine and phytochemicals for enhancement of cognitive performance.

1. Introduction

Methylxanthines (MX) have evolved in many different botanical species because of their pesticidal properties, being toxic for insects and many other potentially harmful pathogens. Humans, however, discovered that consuming MX has diverse health benefits. Today, the main source of caffeine is from brewed coffee, followed by tea, colas and, increasingly, 'energy' drinks. (Table 1).

Given its widespread consumption, the chronic effects of caffeine have been studied extensively in the past decades. Interestingly, although some reports caution against excessive caffeine consumption, research on moderate caffeine use predominantly reports health-promoting effects of caffeine use and a correlation of reduced mortality (Heck and De Mejia, 2007). For instance, there is a clear association of chronic health benefits from moderate coffee consumption, such as a lower incidence of type-2-diabetes and Parkinson's disease (see umbrella review by Grosso et al. (2017)). A review by Panza et al. (2015) found that there was a lower risk of cognitive decline in subjects with higher tea intake. However, well-designed interventional placebo-controlled studies are still missing.

Adverse effects have been attributed to typical levels of caffeine consumption, such as increased nervousness, anxiety, tachycardia and an increase in blood pressure. Yet there is increasing evidence that other constituent compounds in caffeine-containing drinks, for example polyphenols, may antagonize some of the negative effects of caffeine. In fact, recent studies have found that compounds commonly consumed along with caffeine in tea, coffee or cocoa may have synergistic effects with caffeine, or are protective against caffeine's acute and chronic side-effects. The aim of this review is to describe key research on natural sources of caffeine and theobromine, comparing and contrasting psychopharmacological activities of commonly consumed MX-containing plants. Given that there is little evidence that plant-derived theophylline has cognitive effects, we have focused on caffeine and theobromine. Furthermore, by summarizing research on interactions of other constituent compounds found in MX species (e.g. flavanols, L-theanine, chlorogenic acids) we highlight gaps in current understanding and future research directions in terms of acute and chronic effects of MX interactions.

We chose the form of a narrative review in order to capture all the relevant research. To outline the most relevant bioactive phytochemicals in terms of their neurocognitive effects, this paper reviewed the main sources of MX. Those species that were associated with a high use within specific populations as a food or beverage and had sufficient levels of either caffeine or theobromine (per 100 g) to exert an effect on cognition were included in this review. Secondly, the most relevant bioactive compounds were then reviewed based on their putative acute

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