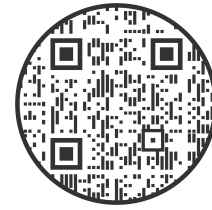




Intelligent Remedies, Inc.

www.intelligentremedies.com



BRAINfactor™

Product Information



BRAINfactor™ is a phytotherapeutic formulation combining extracts of *Coffea arabica* fruit, *Petroselinum crispum*, *Camellia sinensis*, *Curcuma longa*, and *Cinnamomum verum*, produced using advanced laboratory extraction apparatus and proprietary production protocols employing both hydrophilic and hydrophobic extraction methods. This formulation brings together a synergistic blend of historically valued botanicals, each selected for its documented role in traditional herbal practice supporting cognitive vitality, mental clarity, and overall well-being.

Coffea arabica (Coffee Fruit) Cultivated across tropical regions worldwide and prized in traditional practice for its energizing and restorative properties, the fruit of the coffee plant has a long history of use in wellness traditions across Africa, the Middle East, and the Americas. BRAINfactor™ sources its coffee fruit from Kona, Hawai'i, where volcanic soil, tropical rainfall, and elevation create exceptional growing conditions for *Coffea arabica*. Researchers have investigated constituents found in the coffee fruit — including chlorogenic acid, quinic acid, and ferulic acid — for their interactions with oxidative stress pathways and neurotrophic signaling processes, and

botanical literature has explored how these polyphenolic compounds may influence cellular mechanisms related to cognitive and metabolic function.

Petroselinum crispum (Parsley) Cultivated across Mediterranean and European herbal traditions for centuries, parsley has been historically valued as both a culinary and botanical herb, traditionally prepared to support vitality and digestive ease. Researchers have investigated apigenin and related flavonoid constituents found in *Petroselinum crispum* for their interactions with cellular energy metabolism pathways, and botanical literature has explored how these compounds may influence intracellular signaling processes related to neuronal and metabolic function.

Camellia sinensis (Green Tea) Steeped in the herbal traditions of East Asia for thousands of years, green tea has been historically prepared as a restorative botanical tonic to support mental clarity and overall vitality. Researchers have investigated EGCG and related catechin constituents found in *Camellia sinensis* for their interactions with oxidative stress and neurotrophic signaling pathways, and botanical literature has explored how these polyphenolic compounds may influence cellular processes related to cognitive and immune function.

Curcuma longa (Turmeric) Cultivated across South and Southeast Asia for thousands of years, turmeric has been a fixture in Ayurvedic and Traditional Chinese herbal practice, historically prepared as a warming botanical to support digestive comfort and overall vitality. Researchers have investigated curcuminoid constituents found in *Curcuma longa* for their interactions with oxidative stress and inflammatory signaling pathways, and botanical literature has explored how these compounds may influence processes related to cellular resilience and cognitive function.

Cinnamomum verum (Ceylon Cinnamon) Prized across South Asian and Middle Eastern herbal traditions for thousands of years, Ceylon cinnamon has been historically prepared as a warming botanical tonic. Researchers have investigated polyphenol and phenolic acid constituents found in *Cinnamomum verum* for their interactions with oxidative stress and metabolic cellular pathways.

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.

Coffee Fruit and Quinic Acid Derivatives as Modulators of Brain Functions: Biological Actions, Molecular Mechanisms and Their Effects

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Accumulating evidence suggests that diet and lifestyle can play an important role in delaying the onset or halting the progression of age-related health disorders and to improve cognitive function. In particular, polyphenols have been reported to exert their neuro-protective actions through the potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuro-inflammation, and the potential to promote memory, learning, and cognitive function. Despite significant advances in our understanding of the biology of polyphenols, they are still mistakenly regarded as simply acting as antioxidants. Recent evidence suggests that their beneficial effects involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling and neurohormetic effects leading to the expression of genes that encode antioxidant enzymes, phase-2 enzymes, neuro-trophic factors, and cytoprotective proteins.[1]

Coffee fruit (*Coffea Arabica*) and its polyphenol constituents, when extracted from coffee fruit harvested in the Kona, Hawaii region's coffee plantations, is known to contain 29% Quinic acid by volume of extract. This is a significant discovery in the dietary use of coffee fruit derived supplements and beverages. Quinic Acid and its esters and related compounds, namely Caffeic Acid, Ferrulic acid, and Chologenic acid have demonstrated polyphenolic properties consistent with decreases in oxidative/inflammatory stress signaling, increases in protective signaling and neurohormetic effects leading to the expression of genes that encode antioxidant enzymes, phase-2 enzymes, neurotrophic factors, and cytoprotective proteins.

1. Introduction

It has been postulated that the behavioral and neuronal declines associated with age-related neurodegenerative disorders are triggered by multifactorial events including neuroinflammation, glutamatergic excitotoxicity, increases in iron, and/or depletion of endogenous antioxidants [2-4]. Therefore, it becomes imperative to develop health strategies that exert neuro-protective actions in order to prevent or even reverse age-related health disorders. One possibility is the use of nutritional substances such as polyphenols. While historical research focused on their antioxidant properties [18], recent data supports the view that polyphenols, and their *in vivo* metabolites, do not act as conventional hydrogen-donating antioxidants but may exert modulatory actions in cells through actions at protein kinase and lipid kinase signalling pathways [19] and may even involve hormetic



effects to protect neurons against the oxidative and inflammatory stressors. Neuroprotective mechanisms, through the ability of polyphenols to interact with neuronal signaling pathways, mediate endogenous cellular defense systems.

1.1 Polyphenols and Aging

Polyphenols, occurring in fruit and vegetables, wine tea, extra virgin olive oil, chocolate, and other cocoa products, have been demonstrated to exert beneficial effects in a large array of disease states, including cancer, cardiovascular disease, and neurodegenerative disorders. Many of the biological effects of polyphenols have been attributed to their antioxidant properties, either through their reducing capacities per se or through their possible influences on intracellular redox status. As such, polyphenols

Research Article

BDNF Protein and BDNF mRNA Expression of the Medial Prefrontal Cortex, Amygdala, and Hippocampus during Situational Reminder in the PTSD Animal Model

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Whether BDNF protein and BDNF mRNA expression of the medial prefrontal cortex (mPFC; cingulate cortex area 1 (Cg1), prelimbic cortex (PrL), and infralimbic cortex (IL)), amygdala, and hippocampus (CA1, CA2, CA3, and dentate gyrus (DG)) was involved in fear of posttraumatic stress disorder (PTSD) during the situational reminder of traumatic memory remains uncertain. Footshock rats experienced an inescapable footshock (3 mA, 10 s), and later we have measured fear behavior for 2 min in the footshock environment on the situational reminder phase. In the final retrieval of situational reminder, BDNF protein and mRNA levels were measured. The results showed that higher BDNF expression occurred in the Cg1, PrL, and amygdala. Lower BDNF expression occurred in the IL, CA1, CA2, CA3, and DG. BDNF mRNA levels were higher in the mPFC and amygdala but lower in the hippocampus. The neural connection analysis showed that BDNF protein and BDNF mRNA exhibited weak connections among the mPFC, amygdala, and hippocampus during situational reminders. The present data did not support the previous viewpoint in neuroimaging research that the mPFC and hippocampus revealed hypoactivity and the amygdala exhibited hyperactivity for PTSD symptoms. These findings should be discussed with the previous evidence and provide clinical implications for PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a severe and chronic mental illness. PTSD symptoms can be caused by severe traumatic events, including illness (e.g., cancer [1, 2]), situations of conflict (e.g., war [3]), and natural disasters (e.g., earthquakes [4]). According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), PTSD has numerous critical symptoms [5]. For example, patients may persistently suppress stimuli associated with the traumatic stimulus and

induce emotional numbing [6] by reexposing the environmental stimulus (i.e., the conditioned stimulus (CS)) associated with previous traumatic events (i.e., the unconditioned stimulus (US)) [7]. Patients with PTSD often experience persistent traumatic events as well as feelings of fear, helplessness, and horror [8, 9]. In the animal model of PTSD, growing studies employed the procedure of the situational reminder to imitate PTSD patients who continuously experience traumatic events [10–14]. Therefore, the present study used the procedure of situational reminder to test fear for PTSD symptoms.

Flavonoid Apigenin Is an Inhibitor of the NAD⁺ase CD38

Implications for Cellular NAD⁺ Metabolism, Protein Acetylation, and Treatment of Metabolic Syndrome

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Metabolic syndrome is a growing health problem worldwide. It is therefore imperative to develop new strategies to treat this pathology. In the past years, the manipulation of NAD⁺ metabolism has emerged as a plausible strategy to ameliorate metabolic syndrome. In particular, an increase in cellular NAD⁺ levels has beneficial effects, likely because of the activation of sirtuins. Previously, we reported that CD38 is the primary NAD⁺ase in mammals. Moreover, CD38 knockout mice have higher NAD⁺ levels and are protected against obesity and metabolic syndrome. Here, we show that CD38 regulates global protein acetylation through changes in NAD⁺ levels and sirtuin activity. In addition, we characterize two CD38 inhibitors: quercetin and apigenin. We show that pharmacological inhibition of CD38 results in higher intracellular NAD⁺ levels and that treatment of cell cultures with apigenin decreases global acetylation as well as the acetylation of p53 and RelA-p65. Finally, apigenin administration to obese mice increases NAD⁺ levels, decreases global protein acetylation, and improves several aspects of glucose and lipid homeostasis. Our results show that CD38 is a novel pharmacological target to treat metabolic diseases via NAD⁺-dependent pathways. *Diabetes* 62:1084–1093, 2013

Obesity is a disease that has reached epidemic proportions in developed and developing countries (1–3). In the U.S., >60% of the population is overweight (1,3,4). Obesity is a feature of metabolic syndrome, which includes glucose intolerance, insulin resistance, dyslipidemia, and hypertension. These pathologies are well-documented risk factors for cardiovascular disease, type 2 diabetes, and stroke (4). It is therefore imperative to envision new strategies to treat metabolic syndrome and obesity.

Recently, the role of NAD⁺ as a signaling molecule in metabolism has become a focus of intense research. It was shown that an increase in intracellular NAD⁺ levels in tissues protects against obesity (5,6), metabolic syndrome, and type 2 diabetes (5–7). Our group was the first to demonstrate that an increase in NAD⁺ levels protects against high-fat diet-induced obesity, liver steatosis, and metabolic

syndrome (5). This concept was later expanded by others using different approaches, including inhibition of poly-ADP-ribose polymerase (PARP)1 (6) and stimulation of NAD⁺ synthesis (7).

The ability of NAD⁺ to affect metabolic diseases seems to be mediated by sirtuins (8). This family of seven NAD⁺-dependent protein deacetylases, particularly SIRT1, SIRT3, and SIRT6, has gained significant attention as candidates to treat metabolic syndrome and obesity (9). Sirtuins use and degrade NAD⁺ as part of their enzymatic reaction (8), which makes NAD⁺ a limiting factor for sirtuin activity (9). In particular, silent mating information regulation 2 homolog 1 (SIRT1) has been shown to deacetylate several proteins, including p53 (10), RelA/p65 (11), PGC1- α (12), and histones (13), among others. In addition, increased expression of SIRT1 (14), increased SIRT1 activity (15), and pharmacological activation of SIRT1 (16) protect mice against liver steatosis and other features of metabolic syndrome when mice are fed a high-fat diet. Given the beneficial consequences of increased SIRT1 activity, great efforts are being directed toward the development of pharmacological interventions aimed at activating SIRT1.

We previously reported that the protein CD38 is the primary NAD⁺ase in mammalian tissues (17). In fact, tissues of mice that lack CD38 contain higher NAD⁺ levels (17,18) and increased SIRT1 activity compared with wild-type mice (5,17). CD38 knockout mice are resistant to high-fat diet-induced obesity and other aspects of metabolic disease, including liver steatosis and glucose intolerance, by a mechanism that is SIRT1 dependent (5). These multiple lines of evidence suggest that pharmacological CD38 inhibition would lead to SIRT1 activation through an increase in NAD⁺ levels, resulting in beneficial effects on metabolic syndrome.

Recently, it was shown that in vitro, CD38 is inhibited by flavonoids, including quercetin (19). Flavonoids are naturally occurring compounds present in a variety of plants and fruits (20). Among them, quercetin [2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one] and apigenin [5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] have been shown to have beneficial effects against cancer (21–24). In fact, apigenin and quercetin ameliorate atherosclerosis (25) and reduce inflammation (26–28). However, the mechanisms of action of flavonoids remain largely unknown. We hypothesized that the effect of some flavonoids in vivo may occur through inhibition of CD38 and an increase in NAD⁺ levels in tissues, which lead to protection against metabolic syndrome.

Here, we show that CD38 expression and activity regulate cellular NAD⁺ levels and global acetylation of proteins, including SIRT1 substrates. We confirmed that quercetin is a CD38 inhibitor in vitro and in cells. Importantly, we

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