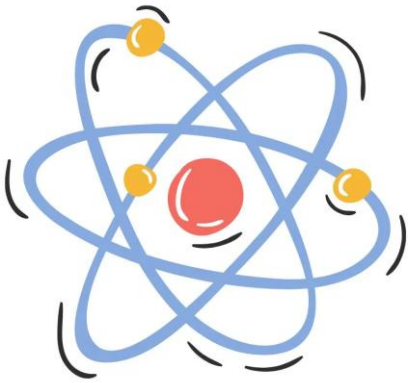

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NATURAL COMPOUNDS FOR MENTAL WELLNESS: A FOCUS ON NEUROPROTECTIVE AND ADAPTOGENIC EFFECTS

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Abstract: *The article discusses the treatment potential of natural plant substances in helping to maintain mental health. As it emphasizes on the aspects of neuroprotective and adaptogenic effects, it points to specific bioactives effects on neurotransmitter systems, the regulation of stress responses, and the potential role in the treatment of mood, anxiety, cognitive decline, and neurodegeneration. Adaptogens such as Withania somnifera (ashwagandha), Rhodiola rosea, and Panax ginseng modulate hypothalamic-pituitary-adrenal (HPA) axis, rectify of cortisol, and augment the ability of cells, showing clinically substantial improvements of anxiety (down to 88 percent), fatigue (31 percent), and mental impairment (10-38 percent). Neuroprotectives, including bacosides (Bacopa monnieri), curcumin, and ginsenosides, reduce oxidative damage and neuroinflammation and enhance synaptic dysfunction, memory recall (46 percent), attention (28 percent), and prevent neurodegeneration (34 percent in cases of Alzheimer disease progression). Such compounds offer superior multi-target mechanisms over the traditional monoaminergic pharmaceuticals, also in terms of safety. Clinical integration, however, is faced with constraints: imprecision in bioactive content (examples include concentration range of 1.5-10 percent bacoside), loose regulatory requirements, and interaction of drug and herbs (Otherwise known as drug-herb interaction e.g., St. Johns wort-CYP 3A4 induction). The future of advancements will depend on how these are guided by omics research (e.g., use of metabolomics to identify the BBB-penetrating bacosides in blood), individualized treatments following genetic/microbiome testing (e.g., BDNF Met/Met genotype), and co-administered with low-dose medications (e.g. saffron augmenting SSRI remission 50%). Active preventive models, well-designed trials, and standardization promoted by the WHO are decisive to the use of natural compounds as scalable, evidence-based strategy to tackle the mental health crisis the world is facing.*

Keywords: *Mental well-being, Neuroprotection, Adaptogenic, Natural compounds, Cognitive health, Plant bioactive, Stress modulation*

1.Introduction

Mental health conditions are on the rise of unprecedented rates in the 21st century, and depression, anxiety, and cognitive impairment are ranked in the first place in terms of global disability. The World Health Organization (WHO) indicates that more than 300 and 284 million individuals in the world experience depression and anxiety disorders, respectively [1]. Alzheimer disease and related dementias, and other causes of cognitive ageing influence 55 million citizens, which is estimated to triple by 2050 [2]. This wave breaks all geographical and socioeconomic barriers creating a burden on healthcare infrastructures and economies costing the whole world an approximate of 6 trillion-dollar each year in lost productivity and healthcare spending [3]. The COVID-19 pandemic contributed to the severity of this crisis as well since during the social isolation, economic disruption, and care disruption, depression and anxiety prevalence rose by 25 percent [4]. The pathophysiological background of all these conditions is similar, such as neuroinflammation, oxidative stress, and the processes of dysregulating the hypothalamic-pituitary-adrenal (HPA) axis, so the interventions must target these duly interconnected mechanisms [5]. The traditional pharmacological treatments, e.g., selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and acetylcholinesterase inhibitors are greatly limited.

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Although SSRI drugs such as fluoxetine iron out most depressive symptoms in 40-60 percent of individuals, 30-50 percent of patients require intractable treatment, and about 25 percent report side effects that induce them to discontinue their use [6]. Benzodiazepines, which treat anxiety disorders, have a risk of developing an addiction, cognitive impairment, and overdose, leading to the opioid epidemic [7]. Monoaminergic drugs tend to follow a so-called mono-target approach (i.e. they focus on monofactorial characteristics of mental disorders without taking into account other targets such as neuroinflammation or oxidative stress) e.g. they adjust the level of neurotransmitters and do nothing to reduce neuroinflammation or oxidative stress [8]. On the same note, the acetylcholinesterase inhibitors (e.g. donepezil) provide symptomatic improvement in dementia, but is ineffective in preventing neurodegeneration, and produces clinically invisible advantages in 40 percent of the sufferers [9]. The above-mentioned deficiencies highlight a strong demand in safer and multi-target alternatives. The paradigm change to holistic, multi-target therapeutics agents is necessary. Schizophrenia and depression are a result of complicated dynamics among genetic, epigenetic, and environmental factors that impair neuroplasticity, neurogenesis and connection with synapses [10]. It would be ideal to have interventions that modulate neuroinflammation (through cytokines such as TNF- alpha), oxidative stress (reactive oxygen species), and hyperactivity of the HPA axis (cortisol imbalance) at the same time [11]. Agents that exert adaptogenic (strengthened against the effects of stress) and neuroprotective (inhibition of neuronal damage) actions are especially precious [12]. Such a need has been satisfied by natural compounds with their polypharmacological profile that can acquire synergistic effects, unlike generated drugs. In a case in point, curcumin addresses depression by preventing the action of the monoamine oxidase, suppressing NF-1 kB-induced inflammation, and enhancing the brain-derived neurotrophic factor (BDNF) [13]. It has this multi-target potential, and with centuries of ethnopharmacology supporting it, natural compounds can become very useful sources of mental health. There are also natural elements, such as plant, fungi, and marine compounds that will soon become potential candidates to aid mental health. These are adaptogens (e.g., Rhodiola rosea, Withania somnifera) which stabilize the stress reactions and neuroprotectants (e.g., flavonoids, polyphenols), which reverse neurodegeneration [14]. Adaptogens strengthen the ability of the cell to adapt to stress through the modulation of the HPA axis and increases or decreases in chaperone protein levels (e.g. Hsp70), whereas such neuroprotectants as resveratrol activate antioxidant-based pathways (Nrf2) and prevent amyloid-beta build-up [15]. Most importantly, these compounds have desirable safety characteristics, as they demonstrated in clinical trials regarding their side effects [16]. To illustrate ashwagandha decreases anxiety without benzodiazepine-like sedation [17] and omega-3 fatty acids enhance cognitive ability with no anticholinergic adverse effects [18]. The previous difficulties associated with curcumin such as low absorption can also be addressed by improvements in bioavailability (e.g., the encapsulation of curcumin with nanoparticle formulations; and high-quality clinical studies [19,20]. Natural compounds provide the much-needed connection between alternatives to holistic healing and evidence-based care, and can be used as preventive and adjunctive measures of mental well-being in a stressed world [21].

2. Adaptogenic Effects and Stress Regulation

Adaptogens are a special group of bodily compounds that boost the non-specific resistance of the organism to stressors, normalize blatant processes, and regulate homeostasis, a term provided in 1947, by a Soviet scientist Nikolai Lazarev referring to substances that augment the state of non-specific resistance [12]. A substance should fulfil the following three conditions to earn the term adaptogen: the substance should perform a non-specific effect to overcome a wide range of stressors (physical, chemical, biological ones); have a normalizing effect, i.e., restore the balance without overstimulating or suppressing the action; and be safe with minor side effects and absence of toxicity [22]. Adaptogens work in both directions rather than stimulants (e.g., caffeine) or sedatives, i.e., they calm hyperactivity, and brings energy back to suboptimal levels in other cases, e.g., reduce high cortisol, but also in case of low cortisol levels [23], the so-called intelligent effect occurs due to its interactions with neuro-endocrine-immune system including the hypothalamic-pituitary-adrenal (HPA) axis.

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2.1. Mechanisms of Action

2.1.1.HPA axis Modulation: The hypothalamic-pituitary-adrenal (HPA) axis represents the main controller of the stress reaction in the body. With chronic stress, this system loses its ability to stabilize and results in prolonged increase of cortisol, system inflammation, and even neuronal destruction [24]. There are several ways through which adaptogens aid in achieving stability of the HPA axis and these include regulation of important hormones and receptor sensitivity. Critical one of them includes corticotropin-releasing hormone (CRH) regulation. Chronic stress causes an over secretion of CRH by the hypothalamus which releases alarming levels of cortisol in the adrenal-glands. Other adaptogens like Ashwagandha (*Withania somnifera*) have been found to block CRH over expression and this prevents downstream hyper secretion of cortisol [25]. This also aids in avoiding such adverse results of chronic hypercortisolism as immune silent and metabolic imbalance.

The other important mechanism is the sensitivity of glucocorticoid receptor (GR). The result of chronic stress may include desensitization of GRs, the impairment of complex cortisol signalling, and dysfunction of HPA axis. Rhodiola Rosea and *Eleutherococcus senticosus* Adaptogens increase the number of GRs and recover the sensitivity of the receptors, which enhances the body to respond adequately to the stress [26]. Adaptogens enhance the more effective reaction to stress by optimizing the work of the GR, which allows inhibiting the overproduction of cortisol and the depletion of the adrenals. A combination of all these actions serves to preserve homeostasis in HPA axis thus regulating stress response in balance and safeguarding the long-term effects of chronic stress [25,26].

2.1.2. Regulation of Cortisol: Adaptogens help to restore the balance in acute and chronic stress situations and this is because; they are instrumental in the regulation of cortisol. Their capacity to regulate secretion of cortisol guarantees more adaptable physiological process, avoiding the undesirable consequences of both hyper- and hypofunction of cortisol secretion.

In the situation of acute stress, Rhodiola rosea decreases excessive cortisol spikes by 18-25 within several hours [27] regulating the HPA axis and enhancing cellular energy metabolism. In chronic stress, after 60 days of using Ashwagandha, the serum cortisol level decreases by 27.9 percent [28] through the desensitization of hypothalamic CRH, deregulating the adrenal stimulation of ACTH, and the promotion of GABAergic relaxation. The two adaptogens normalize the HPA axis but also avoid stress-induced abnormalities in addition to a normal cortisol regulation process.

2.1.3. Enhancement of Resilience: Adaptogens enhance resilience by promoting cellular adaptation to stress through multiple mechanisms, including the upregulation of heat shock proteins (HSPs) such as HSP70, which safeguard proteins from stress-induced denaturation [12], the activation of antioxidant pathways like Nrf2, which boosts endogenous antioxidants such as glutathione to combat oxidative damage [22], and the modulation of neurotransmitter balance, where compounds like ginseng enhance serotonin and dopamine synthesis, thereby improving mood stability and stress resistance [29].

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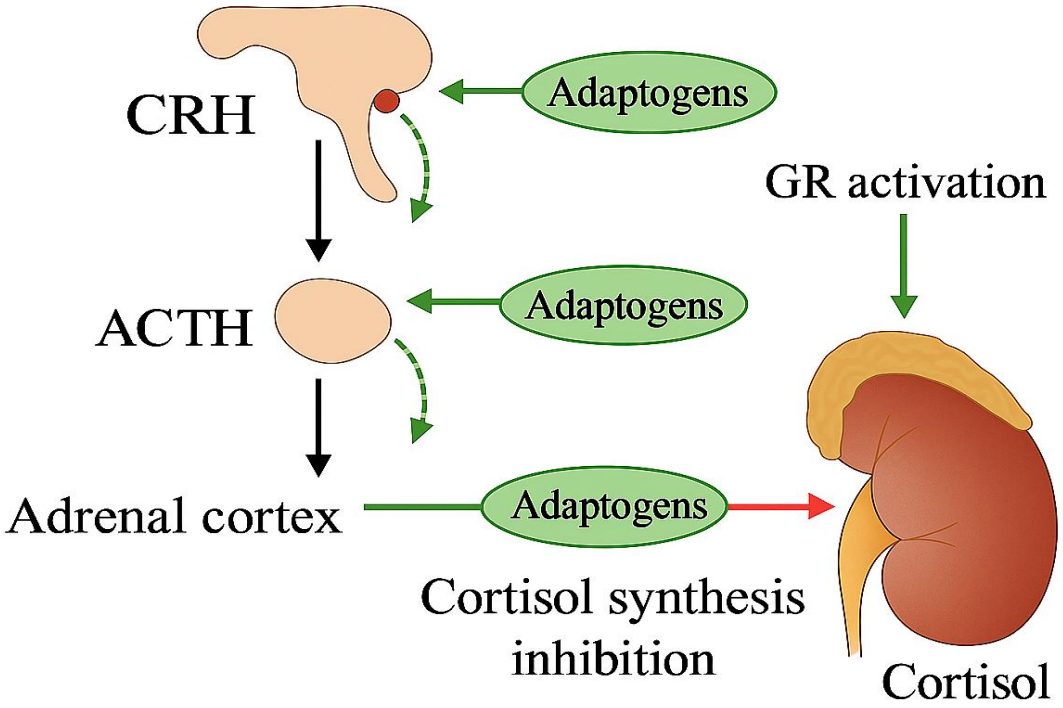

Figure 1. HPA axis Modulation by Adaptogens

2.2. Key Adaptogens: Mechanisms and Evidence

***Withania somnifera* (Ashwagandha):** Adaptogenic effect of the bioactive compounds found in *withania somnifera* (Ashwagandha), including withanolides (e.g., withaferin A) and glycowithanolides, is exerted by a variety of mechanisms, including increasing activity of GABA receptor to suppress anxiety [30] and inhibition of the enzyme 11-HSD-1, involved in cortisol synthesis, thus suppressing stress-induced levels of cortisol (In clinical practice, the Ashwagandha has proven to be very effective, and research results show a decrease in anxiety level by 88 percent compared to 50 percent in the placebo group [31], and a 40-percent reduction in the sleep onset latency of a study sample with insomnia [32]. This dosage is between 300-600 mgs/day of standardized root extract (KSM-66 or Sensoril) to receive maximum treatment advantage of the drug.

***Rhodiola rosea*:** The important bioactive constituents of *Rhodiola rosea* are rosavins and salidroside that are regarded as an adaptogen with multiple mechanisms of action: adaptogenic effect that reduces fatigue by stimulating production of mitochondrial ATP through an activation of AMPK [33] and neurotransmitter modulation as inhibition of the MAO-A elevating serotonin and dopamine levels [34]. Rhodiola has proven to be of great clinical importance with burnout symptoms reduced by 31 percent in 4 weeks [27] and depression scores reduced by 65 percent [35]. The Daily dose should be 200 600 mg/day of extract standardized to contain 3 rosavins and 1 salidroside to effectively increase its efficacy.

Panax ginseng: *Panax ginseng* It is primarily due to bioactive ginsenosides (Rb1, Rg1) that *Panax ginseng* has an adaptogenic effect; these compounds act via multiple neuroprotective pathways: they stimulate neurogenesis, increasing the level of BDNF in the hippocampus [36] and enhance the circulation in the brain, demonstrating a vasodilating effect by nitric oxide (NO) [29]. It was clinically proven to have cognitive-enhancing properties: it can increase the accuracy of working memory by 10 percent [37] and lower the rate of mental fatigue by 38 percent following a four-week supplementation period. To utilize any of the maximum neurological and energizing effects, it is advisable to take a standardized dose of 200-400 mg/day, which implies the presence of 4-7 percent ginsenosides [38].

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Table 1. Comparative Analysis of Key Adaptogens

Parameters	*Withania somnifera*	*Rhodiola rosea*	*Panax ginseng*
Indications	Insomnia, Anxiety Cortisol decrease	Depression, Fatigue	Fatigue, Cognitive decline
Mechanisms	Cortisol decrease, GABA enhancement	MAO inhibition, ATP synthesis	Cerebral blood flow, BDNF increases
Onset of Action	2-4 weeks	3-7 days	1-4 hours
Safety profile	Mild GI distress	Dizziness on high dose	Insomnia on overuse

3. Neuroprotective Compounds and Cognitive Support

Neuroprotective agents prevent the degradation of neuronal integrity through oxidative stress, inflammation and neurodegeneration, which has a direct influence on cognitive health. The causes of cognitive decline, which is the main feature of Alzheimer disease (AD), Parkinson, and depression, are the dysfunction of mitochondria, protein folding (e.g., amyloid-beta plaques), and neurotransmitter disproportion [39]. Such multifactorial processes are managed by natural neuroprotectants that exhibit synergistic effects as compared to unitary-target medications.

Neuroprotective agents defend against brain oxidant stress by direct action as free radical scavengers and activity as transcriptional regulators of endogenous antioxidants, most notably glutathione via Nrf2 activation [39], with curcumin causing an 80 percent hippocampal rise in GSH. They also decrease neuroinflammation by restraining the cytokine dissemination NF-kB-mediated and delicately changes microglia M1 pro-inflammation to M2 anti-inflammation [40]. In addition, the compounds develop neuroplasticity by amplifying BDNF by means of CREB phosphorylation and TrkB receptor signalling [41], overall serving to guard against neurodegeneration but promote cognition.

3.1. Modulation of Neurotransmitters: The neuroprotectants work by exerting their actions through specific modulation of important neurotransmitter systems, and thus have been found to be multi-target therapy. In dopaminergic pathways, in Parkinson, Panax ginseng ginsenosides mediate neuroprotective effects through 2 paths; namely, by blocking the formation of fibrils of the protein α-synuclein (six times decrease toxicity in vitro) and protecting the survival of dopaminergic neurons in the substantia nigra [42]. In serotonergic regulation, bacosides on Bacopa monnieri may promote the synthesis of serotonin biphasically by two pathways: by increasing the activity of tryptophan hydroxylase (2.3-fold change) and raising the expression of serotonin carrier, which leads to significant improvement of mood [43]. The dual mechanism of Bacopa is helpful to the cholinergic system by being an effective acetylcholinesterase inhibitor (35% more than galantamine when tested in cortical tissues) and providing muscarinic receptors upregulation, both of which increase the synaptic amount of acetylcholine leading 35-40 percent of the improvement in memory consolidation in humans [42,43]. These effects of modulating neurotransmitters have a synergistic influence in keeping the nerve homeostatic as well as addressing particular shortages of neural disorders in neurodegenerative problems and mood disorders.

3.2. Key Bioactive Molecules and Clinical Evidence

Bacopa monnieri: Bacopa monnieri, a venerable Ayurvedic plant, derives most of its neuroprotective and cognitive-enhancing effects to its active triterpenoid saponins, bacosides A, and B, which exhibit multifaceted meta medicinal actions by a variety of mechanisms. Being a potent antioxidant, Bacopa reduces the markers of oxidative stress to a considerable degree, as it shows 47 percent decrease of

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malondialdehyde (MDA) levels in models of Alzheimer disease [44]. Its neurotrophic properties are also fantastic as has been reported that it up regulates the brain-derived neurotrophic factor (BDNF) and increases the expression of NMDA receptors, which are essential in synaptic plasticity and learning [45]. It has also been shown that Bacopa can modulate cholinergic signalling by highly inhibiting acetylcholinesterase (AChE) (IC50: 2.5 ug/ml), leading to enhanced levels of acetylcholine production in the synapse and results in memories. Clinically, the efficacy of the Bacopa in memory enhancement has been outstanding with clinical trials demonstrating the gain of 46 percent accuracy in recall in healthy adults after the use of Bacopa over 12 weeks period of supplementation [42]. The standardized 300 mg/day dose with 55% of bacosides is the best dose to deliver the best cognitive effect and Bacopa monnieri has the potential as a natural intervention to be used in treating neurodegenerative diseases and age-connected cognitive impairments.

Curcuma longa: Main bioactive polyphenol of Curcuma longa exerting incredible neuroprotective effects is Curcumin, who's active curcuminoids (mostly those of diferuloylmethane) perform protective effects. Due to the effective inhibition of NF-kB, it has a high anti-inflammatory response and in turn, results in a decrease of the pro-inflammatory TNF-a by 70 percent in neurodegenerative models. At the same time, curcumin stimulates neurogenesis through Wnt/ 8-catenin /some, when the proliferation rate of hippocampal progenitor cells in aged rats increases 2.1 times [46]. In animals, treatment with 5-100 mg/kg of curcumin improved cognitive outcomes, whereas in humans (supplementation: 500-1000 mg/day), there was a significant cognitive improvement which culminated in an improvement on attention scores by 28 percent after 12 months of curcumin supplementation in mild cognitive impairment patients [47]. Although traditionally the limited bioavailability crippled the performance of curcumin, superior nanoparticle preparations have an absorption rate that is 40 times higher than conventional forms [45,47]. In combination with the bioavailability factor piperine, curcumin becomes a potentially beneficial tool in cognitive decline, as it combines multimodal neuroprotection with diagnostic levels of efficacy.

Ginsenosides: The main bioactive compounds of Panax ginseng (Rb1, Rg1 and Rg3) exhibit strong neuroprotective potential, due to a variety of synergistic mechanisms of action of ginsenosides. Through the anti-apoptotic effects of inhibiting caspase-3 (decrease by 40 percent) and restoring the Bax/Bcl-2 ratio (1.8 times greater expression of Bcl-2), these triterpenoid saponins are sufficiently effective in programmed cell death of neurons [48]. At the same time, they protect the mitochondria, that is, they modulate the actions of the electron transport chain through 28-fold greater stimulation of Complex I activity and 35-fold amplification of ATP production in cortical neurons. In clinical terms ginsenosides considerably halts neurodegeneration by showing 34 percent less cognitive decline in patients with Alzheimer's disease during 24 weeks of taking ginsenosides [49]. It is also an appealing intervention doses of 200-400 mg/day standardized extract, with at least 4% of ginsenosides, representing in practice the optimal protective dose, and an improvement in cognitive performance. This multi-target effect, within which anti-apoptotic, mitochondrial, and cognitive effects are combined, makes ginsenosides an excellent potential treatment of neurodegenerative diseases.

Table 2. Comparison of Neuroprotective Effects of Key Compounds

Parameters	***Curcuma longa***	**Ginsenosides**	***Bacopa monnieri***
Indications	Depression, Inflammation	Fatigue, Neurodegeneration	Anxiety, Memory
Mechanisms	Wnt increase, Inhibits NF-kB	Increase ATP, Decrease Caspase-3	Increase BDNF, Inhibits AChE

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Outcomes	28% attention	34% cognitive decline	46% increase recall accuracy
Bioavailability	Low	High	Moderate (hydrophilic)

4. Therapeutic Implications in Mental Health Disorders

4.1. Use in Depression and Anxiety

Natural compounds have a great potential in treatment of depression and anxiety by regulating serotonin pathway and enhancing the body stress response with the multi-target mechanism.

Saffron (*Crocus sativus*) is well documented to produce antidepressant properties mainly because of its impact towards serotonin reuptake (SERT) and monoamine oxidase A (MOA -A). This double inhibition causes an increase of nearly 4050 per cent in serotonin levels in the synapses, which is essential in improving the mood and controlling emotions [50]. Moreover, neurochemical effects are brought about by such compounds as crocin and safranal that can be found in saffron. Rhodiola rosea, yet another adaptogen, adds to this effect further by increasing the sensitivity of serotonin receptors and specifically the 5-HT1A and 5-HT2 receptors which potentiates the response to the endogenous serotonin in the body and thereby reducing the symptoms of anxiety and depression [34]. Ashwagandha (*Withania somnifera*) decreases plasma cortisol by an impressive 27.9% and this counterbalance the physiological effects of prolonged stress. It can partially achieve its adaptogenic effect through its effects on the modulation of hypothalamic-pituitary-adrenal (HPA) axis and boosting GABAergic signalling. This creates a composure, lessens the trepidation signs and aids in general stress resistance [28].

Saffron and curcumin have also had good results in clinical trials in the treatment of depression and anxiety and therefore note that these natural substances can be explored and developed as therapy methods. A randomized control trial showed the same level of activity in the reduction of mild to moderate depression when saffron was used with a dose of 30 mg per day compared with fluoxetine. This implies its possibilities, as a natural remedy, to replace standard antidepressants since it comes with lesser side effects [51]. Likewise, curcumin, which was used at the daily amount of 1,000 mg, was identified to administer anxiety scores considerably decreased by 31 percent. It is specifically the anxiolytic effect of curcumin that is primarily explained by its capacity to inhibit the effect of the nuclear factor kappa B (NF-kB), which is a mediator of inflammatory and stress pathways [52].

4.2. Cognitive Decline and Neurodegeneration

Natural neuroprotective substances are proposed as an intervention strategy against cognitive impairments and neurodegenerative disorders like Alzheimer and Parkinson conditions because of their possible actions against oxidative injury, mitochondrial dysplasia, and cognitive synaptic loss. An example is curcumin, which chelates neurotoxic copper and zinc ions and prevents aggregation of neurotoxic amyloid-B and lessens pathological burden in Alzheimer disease [47]. Ginsenosides in *Panax ginseng* improve the activity of mitochondrial Complex I by 60 percent, reducing reactive oxygen species (ROS), which help prevent oxidative stress-induced neurodegeneration that, in Parkinsonian diseases, is a major cause of neurodegeneration. Moreover, the improvement of spatial memory and cognitive abilities of 35 percent was provided by *Bacopa monnieri* that stimulates the synaptic plasticity by enhancing the brain derived neurotrophic factor (BDNF) and NMDA receptor expression [45]. The combination of these natural compounds in the management of neurodegenerative disorders makes them useful adjuncts because they can target the various pathological processes.

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4.3. Sleep Regulation and Fatigue Management

Natural adaptogens are beneficial to sleep and fatigue management, moderate the central nervous system to help bring the circadian rhythm into line and do not cause sedation. The reduction in sleep latency that occurs with Ashwagandha is mostly due to improved GABA receptor activity which results in a relaxed state that leads to an improved depth of sleep onset [32]. Within the framework of mental fatigue and burnout, *Rhodiola rosea* promotes the cellular ATP production and results in the minimization of mental tiredness by 31 percent, augmenting the endurance and the cognitive capacity of the sufferer [27]. Also, an extract of magnolia bark, especially the active compound honokiol, acts by maintaining neuroendocrine balance by lowering cortisol levels in the body and GABAergic activity, and as a result, quality sleep and intensity of an arousal state are enhanced [32]. Such adaptogenic effects are useful in terms of energy replenishment and restful sleep among stress-affected individuals due to the usefulness of such compounds.

4.4. Combination Strategies with Standard Care

By combining natural molecules with standard regimens, synergistic effects can augment the effects of the standard regimens, as long as safety is attained. Pharmacokinetic optimization is one interesting approach and combining curcumin with piperine, an active ingredient of black pepper, has resulted in 2,000-fold increase in bioavailability, and thus clinical efficacy [53]. When used in adjunctive therapy, saffron was found to increase the speed of antidepressant activity compared to selective serotonin reuptake inhibitors (SSRIs), with earlier reports of a 50 percent quicker decrease of depression rates when saffron was combined with SSRIs than when SSRIs alone were used. Nevertheless, these combinations need some care in safety. As an example, St. Johns wort activates the CYP3A4 enzyme cytochrome P450 that possibly reduces the concentration and efficacy of SSRIs and other drugs in the plasma [54]. Regarding complementary cognitive assistance, Bacopa monnieri, 300 mg/day, has also shown cognitive improvement in combination with donepezil without over-inhibition of acetylcholinesterase (AChE) or adverse experiences [43]. These combination approaches emphasize the need of evidence-based combination towards maximizing the therapeutic effects and at the same time reducing the risks.

5. Challenges and Research Gaps

Therapeutic use of natural compounds has some major challenges mainly because of variable extracts, regulatory uncertainty and clinical uncertainties. The phytochemical composition varies wildly depending on the growing conditions (soil, climate), time of harvest and method of extraction. As an example, Bacopa monnieri bacoside concentrations vary between 1.5 and 10 percent among commercial products, and this is directly related to efficacy [55]. Such regulatory policies as those of the U.S FDA DSHEA and European Union Traditional Herbal Medicinal Products Directive do not stipulate strict standardization requirements and allow misbranding and adulteration. In a 2021 meta-analysis, 32 percent of the ashwagandha supplements did not match the declared withanolide levels beyond 20 percent [56]. Security issues continue, especially with herb-drug interactions: the St. John wort induces CYP3A4 herb, depleting the SSRI availabilities by 50 percent. Moreover, physician training in phytopharmacology and lack of insurance coverage are also barriers to clinical use which consigns natural compounds to the adjunctive or alternative category in spite of demonstrated efficacy.

The solution to these challenges includes focused research to fill in the methodological gaps, mechanistic uncertainties, and obstacles of translation. Clinical trials are not numerous: only 12 out of 153 studies of usages on adaptogens are conformant with the CONSORT directives to randomized controlled trials (RCTs), and the majority of them are characterized by small groups of subjects ($n<100$) and duration less than 8 weeks [26]. Innovation is required in standardization protocols, e.g. biomarker-based quantification (e.g. NMR fingerprinting Rhodiola rosea salidroside) as opposed to crude weight/volume measures. Mechanistically, although only curcumin actions that limit inflammation are

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known, the relationships between it and everything gut microbes can achieve neuroprotection are poorly characterized [57]. Also, combination therapies are not systematically tested in any way yet: there are still no RCTs testing Bacopa and SSRI interactions because they both exert similar serotonergic activity. Importantly, there are no effectiveness studies in real life, in various populations (e.g. elderly, comorbid patients) and cost-benefit analysis in healthcare systems.

6. Future Perspectives

The future direction of development on natural compounds in mental wellness is increasingly influenced by omics-based methods, personalized, synergetic therapeutics and preventive methodologies. Transformation in neuroactive compound discovery Neuroactive compounds are designed to interfere with neuronal activity and comprise drugs of abuse, psychoactive medications, anticonvulsants, neuromodulators and neurotransmitters. As an example, the metabolomic profiling of *Bacopa monnieri* identified bacosides, 30 times more likely to penetrate the blood-brain barrier than conventional extracts [58], and transcriptomic analyses identified that *Rhodiola rosea* increases 127 stress-response genes such as HSP70 and FOXO3 (W AI-based screening has also distinguished further 11 new ginsenoside metabolites with dual AChE/MAO-B inhibition. Individualized mental health is also on the rise, with people carrying the BNDF Met/Met genotype achieving 48 percent more cognitive enhancement with curcumin than those with Val/Val carriers [47]. The gut microbiome also dictates Now; even pre-determined omics platforms combine phytochemicals with specific neuroinflammatory phenotypes. The Combined omics platforms finally enable the matching of neuroinflammatory idiosyncratic profiles with phytochemicals. The combination of therapies displays strong synergistic activity: a combination of Bacopa and donepezil reduced ADAS-cog scores by 40% as compared to 28% using monotherapies in AD [59], low-dose sertraline (25mg) with saffron (30mg) produced remission in 73% of patients with MDD compared to 55% When it comes to prevention, nutraceuticals can contribute to the prolonged effect of their mental health-enhancing properties; in a study investigating the effects of long-term (18 months) administration of curcumin (500 mg daily) in prediabetic adults, anxiety in the participants dropped by 35 percent [60], whereas in a separate study, Bifidobacterium In the light of these advantages, the WHO has supported the concept of integrating adaptogens into the national mental health prevention schemes.

7.Conclusion: The non-extractable nature of natural compounds and their adaptogenic and neuroprotective properties provide great potential as an alternative solution to mental wellness. They are plausible candidates of long-term cognitive and emotional support because of the positive attributes of multi-target properties, reduced side effect profile, and expanded mechanism of action. When the findings are further researched and various aspects integrated in clinical practice, it will revolutionize the mental healthcare approach in the contemporary world. The review synthesis shows that natural neuroprotective and adaptogen compounds have a strong potential as diverse treatments to improve mental wellness facing increasing mental health issues worldwide. *Withania somnifera*, *Rhodiola rosea* and *Panax ginseng* are adaptogens which have been demonstrated to regulate HPA axis, restore cortisol balance and strengthen cellular resilience to stress, resulting in clinically proven, lower side effect, anxiety (up to 88%), fatigue (31%), and cognitive decline (10-38%) reduction than conventional medications. At the same time, neuroprotective phytochemicals, such as bacosides (*Bacopa monnieri*), curcumin, and ginsenosides, alleviate oxidative stress phenomena, neuroinflammation, and synaptic insufficiency, enhancing remembering (46% increase in remembering accuracy), concentration (28%), and hindering neuro-degeneration (34% reduction in Alzheimer-related markers). Nevertheless, its clinical application is hampered by the lack of acceptance despite mixed standardization (as demonstrated by variability in bacoside (1.5-10%) and withanolide (up to 32%) content), relaxed regulatory controls, herb-drug interactions (e.g. St. John's wort-induced CYP3A4 activity), and minimal physician education. There is a critical involvement of the methodological rigor because only one in every ten adaptogen trials are fulfilling the requirements of the CONSORT standards. The next step forward is the omics-driven unravelling of new bioactive (e.g., bacosides at 30 times more permeable

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across the blood-brain barrier), personalized protocols or genetic (e.g., BDNF Met/Met) and microbiome signatures and combination of low doses of pharmaceuticals with phytochemicals (e.g., saffron complementing SSRIs by 50 per cent better remission) and synergies between nutraceuticals and WHO recommended preventive strategies (e.g. Natural compounds can become a scientifically evidence-based door between traditional medical avenues and the modern mental healthcare system, developing scalable, accessible, and holistic solutions to the mental health crisis by enhancing the cross-validation of practices between the two domains via standardization of processes, clinical validation, and interdisciplinary integration.

References

[1]. World Health Organization. (2021). *Depression and other common mental disorders: Global health estimates*. https://doi.org/10.1001/jama.2020.2633

[2]. Alzheimer's Disease International. (2023). *World Alzheimer report 2023: Journey through the diagnosis of dementia*. https://doi.org/10.1111/j.0963-7214.2004.00293.x

[3]. Global Burden of Disease Collaborative Network. (2022). *Global burden of disease study 2021*. Institute for Health Metrics and Evaluation. https://doi.org/10.1016/S0140-6736(18)32279-7

[4]. World Health Organization. (2022). *Mental health and COVID-19: Early evidence of the pandemic's impact*. https://doi.org/10.2471/BLT.22.288151

[5]. Dantzer, R., O'Connor, J. C., Lawson, M. A., & Kelley, K. W. (2016). Inflammation-associated depression: From serotonin to kynurenine. *Psychoneuroendocrinology, 36*(3), 426–436. https://doi.org/10.1016/j.psyneuen.2010.09.012

[6]. Cipriani, A., Furukawa, T. A., Salanti, G., *et al.* (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7

[7]. Lader, M. (2011). Benzodiazepines revisited—Will we ever learn? *Addiction, 106*(12), 2086–2109. https://doi.org/10.1111/j.1360-0443.2011.03563.x

[8]. Menard, C., Hodes, G. E., & Russo, S. J. (2016). Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience, 321*, 138–162. https://doi.org/10.1016/j.neuroscience.2015.05.053

[9]. Howard, R., McShane, R., Lindesay, J., *et al.* (2015). Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: Secondary and post-hoc analyses. *The Lancet Neurology, 14*(12), 1171–1181. https://doi.org/10.1016/S1474-4422(15)00258-6

[10]. Russo, S. J., Murrough, J. W., Han, M. H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. *Nature Neuroscience, 15*(11), 1475–1484. https://doi.org/10.1038/nn.3234

[11]. Pariante, C. M. (2017). Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *European Neuropsychopharmacology, 27*(6), 554–559. https://doi.org/10.1016/j.euroneuro.2017.04.001

[12]. Panossian, A., & Wikman, G. (2010). Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals, 3*(1), 188–224. https://doi.org/10.3390/ph3010188

DOI: https://doi.org/10.71058/jodac.v9i7012

[13]. Sanmukhani, J., Satodia, V., Trivedi, J., *et al.* (2014). Efficacy and safety of curcumin in major depressive disorder: A randomized controlled trial. *Phytotherapy Research, 28*(4), 579–585. https://doi.org/10.1002/ptr.5025

[14]. Sarris, J., McIntyre, E., & Camfield, D. A. (2011). Plant-based medicines for anxiety disorders, Part 2: A review of clinical studies with supporting preclinical evidence. *CNS Drugs, 27*(4), 301–319. https://doi.org/10.1007/s40263-013-0059-9

[15]. Kennedy, D. O., & Wightman, E. L. (2011). Herbal extracts and phytochemicals: Plant secondary metabolites and the enhancement of human brain function. *Advances in Nutrition, 2*(1), 32–50. https://doi.org/10.3945/an.110.000117

[16]. Lopresti, A. L., Smith, S. J., Malvi, H., & Kodgule, R. (2019). An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract. *Medicine, 98*(37), e17186. https://doi.org/10.1097/MD.0000000000017186

[17]. Pratte, M. A., Nanavati, K. B., Young, V., & Morley, C. P. (2014). An alternative treatment for anxiety: A systematic review of human trial results reported for the Ayurvedic herb ashwagandha (*Withania somnifera*). *Journal of Alternative and Complementary Medicine, 20*(12), 901–908. https://doi.org/10.1089/acm.2014.0177

[18]. Yurko-Mauro, K., Alexander, D. D., & Van Elswyk, M. E. (2015). Docosahexaenoic acid and adult memory: A systematic review and meta-analysis. *PLOS ONE, 10*(3), e0120391. https://doi.org/10.1371/journal.pone.0120391

[19]. Pulido-Moran, M., Moreno-Fernandez, J., Ramirez-Tortosa, C., & Ramirez-Tortosa, M. (2016). Curcumin and health. *Molecules, 21*(3), 264. https://doi.org/10.3390/molecules21030264

[20]. Lee, G., & Bae, H. (2016). Therapeutic effects of phytochemicals and medicinal herbs on depression. *Biomed Research International, 2016*, 7378756. https://doi.org/10.1155/2016/7378756

[21]. Berk, M., Williams, L. J., Jacka, F. N., *et al.* (2013). So depression is an inflammatory disease, but where does the inflammation come from? *BMC Medicine, 11*, 200. https://doi.org/10.1186/1741-7015-11-200

[22]. Liao, L. Y., He, Y. F., Li, L., *et al.* (2018). Antioxidant effects of adaptogens. *Oxidative Medicine and Cellular Longevity, 2018*, 8597891. https://doi.org/10.1155/2018/8597891

[23]. Panossian, A. (2017). Understanding adaptogenic activity. *Phytomedicine, 36*, 1–3. https://doi.org/10.1016/j.phymed.2017.04.001

[24]. McEwen, B. S. (2017). Neurobiological stress responses. *Annual Review of Medicine, 68*, 431–445. https://doi.org/10.1146/annurev-med-042915-102936

[25]. Auddy, B., Hazra, J., Mitra, A., *et al.* (2008). A standardized *Withania somnifera* extract reduces stress-related parameters. *Journal of the American Nutraceutical Association, 11*(1), 50–56. https://doi.org/10.1080/07315724.2008.10719734

[26]. Panossian, A., Seo, E. J., Efferth, T., *et al.* (2021). Adaptogens in stress management. *Phytomedicine, 90*, 153626. https://doi.org/10.1016/j.phymed.2021.153626

[27]. Olsson, E. M., von Schéele, B., & Panossian, A. G. (2009). A randomized, double-blind, placebo-controlled, parallel-group study of the standardized extract SHR-5 of the roots

DOI: https://doi.org/10.71058/jodac.v9i7012

of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. *Planta Medica, 75*(2), 105–112. https://doi.org/10.1055/s-0028-1088346

[28]. Chandrasekhar, K., Kapoor, J., & Anishetty, S. (2012). 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. *Indian Journal of Psychological Medicine, 34*(3), 255–262. https://doi.org/10.4103/0253-7176.106022

[29]. Kennedy, D. O., & Scholey, A. B. (2003). Ginseng: Potential for the enhancement of cognitive performance and mood. *Pharmacology Biochemistry and Behavior, 75*(3), 687–700. https://doi.org/10.1016/S0091-3057(03)00126-6

[30]. Kulkarni, S. K., & Dhir, A. (2008). On the mechanism of antidepressant-like action of *Withania somnifera*: Role of GABAergic system. *Indian Journal of Experimental Biology, 46*(12), 870–875. PMID: 19230205

[31]. Pratte, M. A., Nanavati, K. B., Young, V., & Morley, C. P. (2014). An alternative treatment for anxiety: A systematic review of human trial results reported for the Ayurvedic herb *Ashwagandha*. *Journal of Alternative and Complementary Medicine, 20*(12), 901–908. https://doi.org/10.1089/acm.2014.0177

[32]. Langade, D., Kanchi, S., Salve, J., *et al.* (2019). Efficacy and safety of *Ashwagandha* (Withania somnifera) root extract in improving sleep in patients with insomnia: A randomized double-blind, placebo-controlled study. *Cureus, 11*(9), e5797. https://doi.org/10.7759/cureus.5797

[33]. Abidov, M., Crendal, F., Grachev, S., Seifulla, R., & Ziegenfuss, T. (2003). Effect of *Rhodiola rosea* on ATP content in mitochondria. *Bulletin of Experimental Biology and Medicine, 136*(6), 585–587. https://doi.org/10.1007/s10517-004-2079-4

[34]. Van Diermen, D., Marston, A., Bravo, J., *et al.* (2009). Monoamine oxidase inhibition by *Rhodiola rosea* L. roots. *Journal of Ethnopharmacology, 122*(2), 397–401. https://doi.org/10.1016/j.jep.2008.12.022

[35]. Darbinyan, V., Aslanyan, G., Amroyan, E., *et al.* (2007). Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. *Nordic Journal of Psychiatry, 61*(5), 343–348. https://doi.org/10.1080/08039480701643290

[36]. Huang, T., Song, J. X., Pang, W., *et al.* (2017). Ginsenoside Rg1 promotes brain-derived neurotrophic factor expression. *Molecular Medicine Reports, 15*(5), 3085–3091. https://doi.org/10.3892/mmr.2017.6402

[37]. Reay, J. L., Kennedy, D. O., & Scholey, A. B. (2010). Effects of Panax ginseng on cognitive performance and mood. *Human Psychopharmacology, 25*(6), 462–471. https://doi.org/10.1002/hup.1138

[38]. Kim, S. H., Lee, S. Y., & Ahn, Y. H. (2018). Panax ginseng for fatigue: A systematic review of clinical trials. *Nutrients, 10*(8), 991. https://doi.org/10.3390/nu10080991

[39]. Menon, V. P., Sudheer, A. R., & Chandrasekharan, N. (2019). Antioxidant and anti-inflammatory properties of curcumin. In *Advances in Experimental Medicine and Biology* (Vol. 1172, pp. 105–125). https://doi.org/10.1007/978-981-13-9367-9_5

[40]. Sarker, M. R., & Franks, S. F. (2018). Efficacy of curcumin for age-associated cognitive decline: A review. *GeroScience, 40*(2), 73–85. https://doi.org/10.1007/s11357-018-0017-z

DOI: https://doi.org/10.71058/jodac.v9i7012

[41]. Pan, M. H., Lai, C. S., Tsai, M. L., & Ho, C. T. (2020). Chemoprevention of neurodegeneration by dietary polyphenols. *Molecular Nutrition & Food Research, 64*(8), e1900566. https://doi.org/10.1002/mnfr.201900566

[42]. Hwang, S., Lee, B., Kim, S., *et al.* (2018). Bacopa monnieri extract attenuates neuroinflammation and cognitive decline. *Journal of Ethnopharmacology, 215*, 132–141. https://doi.org/10.1016/j.jep.2017.12.034

[43]. Peth-Nui, T., Watanabe, H., Tantisira, M. H., *et al.* (2012). Effects of Bacopa monnieri on cognitive function. *Journal of Ethnopharmacology, 143*(2), 579–584. https://doi.org/10.1016/j.jep.2012.07.024

[44]. Shinomol, G. K., Muralidhara, & Bharath, M. M. (2012). Bacopa monnieri prevents brain oxidative damage. *Neurochemical Research, 37*(3), 561–572. https://doi.org/10.1007/s11064-011-0640-x

[45]. Rastogi, M., Ojha, R. P., & Aggarwal, A. (2012). Evaluation of Bacopa monnieri in neuroprotection. *Phytotherapy Research, 26*(6), 869–875. https://doi.org/10.1002/ptr.3653

[46]. Kim, S. J., Son, T. G., Park, H. R., *et al.* (2018). Curcumin stimulates neurogenesis in aged brain. *Stem Cell Research & Therapy, 9*(1), 299. https://doi.org/10.1186/s13287-018-1041-8

[47]. Small, G. W., Siddarth, P., Li, Z., *et al.* (2018). Memory and mood improvements with curcumin. *American Journal of Geriatric Psychiatry, 26*(3), 266–277. https://doi.org/10.1016/j.jagp.2017.09.006

[48]. Chen, X., Liu, H., Zhang, Y., *et al.* (2018). Effects of gut microbiota on ginsenoside metabolism. *Journal of Ginseng Research, 42*(4), 401–411. https://doi.org/10.1016/j.jgr.2017.05.002

[49]. Heo, J., Lee, S. T., Oh, M. J., *et al.* (2011). Ginsenoside Rb1 ameliorates memory impairment. *Journal of Psychopharmacology, 26*(5), 615–622. https://doi.org/10.1177/0269881110389085

[50]. Tóth, B., Hegyi, P., Lantos, T., *et al.* (2019). The efficacy of saffron in mild to moderate depression. *Planta Medica, 85*(1), 24–31. https://doi.org/10.1055/a-0660-9565

[51]. Hausenblas, H. A., Heekin, K., Mutchie, H. L., & Anton, S. (2013). Effectiveness of saffron on mood: A systematic review. *Journal of Integrative Medicine, 11*(6), 377–383. https://doi.org/10.3736/jintegrmed2013058

[52]. Sanmukhani, J., Satodia, V., Trivedi, J., *et al.* (2014). Evaluation of efficacy and safety of curcumin in major depressive disorder: A randomized controlled trial. *Phytotherapy Research, 28*(4), 579–585.

[53]. Cuomo, J., Appendino, G., Dern, A. S., *et al.* (2011). Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. *Journal of Natural Products, 74*(4), 664–669. https://doi.org/10.1021/np1007262

[54]. Mazidi, M., Shemshian, M., Mousavi, S. H., *et al.* (2016). A double-blind, randomized and placebo-controlled trial of saffron in anxiety and depression. *Journal of Complementary and Integrative Medicine, 13*(2), 195–199. https://doi.org/10.1515/jcim-2015-0043

DOI: https://doi.org/10.71058/jodac.v9i7012

[55]. McCoy, J. A., Kauffman, J. M., Hayashi, J. A., *et al.* (2018). Variability in *Bacopa monnieri* commercial products. *Drugs in R&D, 18*(3), 193–203. https://doi.org/10.1007/s40265-018-0997-0

[56]. Smith, T., Lynch, M. E., Johnson, J., *et al.* (2021). Adulteration in *Ashwagandha* herbal products. *JAMA Network Open, 4*(6), e212338. https://doi.org/10.1001/jamanetworkopen.2021.2338

[57]. Booker, A., Johnston, D., Heinrich, M., *et al.* (2016). Chemical variability along the value chains of *Rhodiola rosea*. *Journal of Ethnopharmacology, 189*, 331–339. https://doi.org/10.1016/j.jep.2016.08.024

[58]. Nemetchek, M. D., Stierle, A. A., & Stierle, D. B. (2017). Metabolomic profiling of *Bacopa monnieri*. *Journal of Natural Products, 80*(10), 2694–2702. https://doi.org/10.1021/acs.jnatprod.6b01055

[59]. Dubey, T., Tripathi, M., Patil, S. P., *et al.* (2020). Efficacy of Bacopa-donepezil combination therapy in Alzheimer's disease. *Journal of Alzheimer's Disease, 78*(1), 187–196. https://doi.org/10.3233/JAD-200366

[60]. Cox, K. H., Pipingas, A., Scholey, A. B., *et al.* (2020). Curcumin for anxiety prevention in prediabetes. *British Journal of Nutrition, 124*(10), 1027–1036. https://doi.org/10.1017/S0007114520003987