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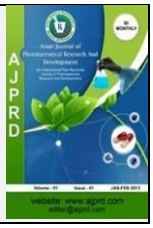

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Review Article

Withania Somnifera and Nano-Enabled Delivery in Brain Health: A Narrative Review of Stress Adaptation, Cognitive Resilience, and Neuroprotective Mechanisms

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ABSTRACT

Objective(s): To assess the clinical and preclinical evidence in support of Withaniasomnifera (L.) Dunal for stress adaptation, sleep, cognition, and neuroprotection, and to evaluate the scientific basis for the nutraceutical product Nano Ashwagandha™, which provides 500 mg of standardised extract of Withaniasomnifera per capsule.

Data Sources: Published clinical studies, reviews, and meta-analyses as well as preclinical experiments with standardised ashwagandha extracts and isolated phytochemicals and nanoformulations were considered.

Study Selection: Reports were selected based on relevance to chronic stress, anxiety symptoms, hypothalamic-pituitary-adrenal axis function, sleep, cognition, oxidative stress, neuroinflammation, excitotoxicity, and nanoformulations. There were no published clinical studies or laboratory experiments with the Biotex Nano Ashwagandha™ product; hence, the assessment relied on reports discussing standardised ashwagandha extracts and nanoformulations of ashwagandha in general.

Summary of Contents: Randomised, double-blind, placebo-controlled trials in humans showed that standardised ashwagandha extracts may reduce perceived stress, specific anxiety scores, salivary cortisol levels, and improve several aspects of sleep quality as well as memory, attention, processing speed, and executive function. Preclinical studies revealed the antioxidant, anti-inflammatory, and neuroprotective effects of ashwagandha, including regulation of glutathione homeostasis and Nrf2-dependent pathways, neuroprotection through MAPK and PI3K/Akt signalling, and prevention of excitotoxicity caused by glutamate and NMDA. Although preliminary data suggest that nanoformulation may enhance the delivery of ashwagandha into tissues, clinical studies in humans are lacking.

Conclusion: Ashwagandha is a promising nutraceutical for adaptation to stress, improvement of sleep, and enhancement of cognition. The application of nanoformulations may have therapeutic potential; however, no clinical studies in humans have demonstrated the superiority of nano Ashwagandha™ over standardised extracts.

Keywords: Withaniasomnifera; Ashwagandha; nanoformulation; stress resilience; cognition; nutraceutical

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INTRODUCTION

Chronic stress is increasingly recognised as a multifactorial biobehavioral phenomenon associated with dysregulation of neuroendocrine-immune-metabolism-nervous system networks. At the individual level, chronic stress can lead to a variety of adverse effects, from dysregulated HPA axis function to cognitive impairments. These stress-related alterations often present clinically as fatigue, lapses in attention, anxiety-like behaviours, sleep disturbances, and reduced psychological resilience. Such symptoms have driven an emerging interest in multi-systemic approaches to stress adaptation with broad neurobiological effects.

Adaptogens have long been considered a promising avenue for the development of such drugs. The herb Withania somnifera (L.) Dunal is one such adaptogen, with extensive preclinical and clinical evidence supporting its anxiolytic,

sleep-promoting, cognition-enhancing, and neuroprotective effects. During the last two decades, randomised, placebo-controlled trials in humans have used standardised extracts of W. somnifera to evaluate their effects on healthy stressed adults, chronically stressed individuals, patients with insomnia or anxiety disorders, impaired cognition, and neuropsychiatric diseases [2-26]. Multiple studies reported reductions in self-reported stress levels, anxiety, and improvements in sleep, memory, attention, and executive function [3,6,9-16,18-25].

The clinical results are corroborated by a large body of evidence from preclinical studies. Extracts of the root, leaf, and fruit of W. somnifera, as well as its constituents withanolide A, withanone, and withanamides, have been shown to modulate dopaminergic, glutamatergic, and GABAergic systems, as well as inflammatory pathways [1,31-48]. Most recently, the neuroprotective properties of W. somnifera have been enhanced through the use of nano-delivery formulations. Chitosan-alginate nanocapsules and W. somnifera nanoemulsions have demonstrated improved efficacy in numerous preclinical models of dopaminergic toxicity, amyloid neurotoxicity, excitotoxicity, hypoxia-ischemia-induced cognitive impairments, and neuroinflammation [49-50]. However, there are currently no clinical trials examining the efficacy of nano-formulated W. somnifera extracts in humans.

The current review was prepared for Biotex Life Solutions' Nano Ashwagandha™ dietary supplement. It summarises the preclinical and clinical evidence published between 2005 and 2026 and details the nuances of this evidence for the purposes of developing reasonable claims for the product. The review does not contain any findings specific to the formulation sold by Biotex Life Solutions.

Product Description and Composition

Nano Ashwagandha™ is manufactured by Biotex Life Solutions Pvt. Ltd. The company's product details state that each capsule contains 0.5 g (500 mg) of Withania somnifera extract prepared using a nanoformulation technology to optimise the dispersion, stability, and bioavailability of the extract's active principles. Thus, the name Nano Ashwagandha™ refers to a brand specific to the company producing the product, which does not make any unsubstantiated claims about the effectiveness of the drug.

The pharmacological activity of Withania somnifera is mostly due to a combination of naturally-occurring compounds extracted from the plant's roots, leaves, and berries. These are withanolides, a group of steroid lactones, withanosides, sitoindiosides, alkaloids, and phenolic acids, the content of which varies depending on the part of the plant used for processing. Due to the complexity of the active principles' composition, the efficacy of Withania somnifera preparations directly depends on the quality of raw materials, the technology used to process them, the concentration of withanolides, their ratio to other extract components, and the standardisation of the final preparation. Therefore, it is important to ensure that the manufacturer provides accurate information about the composition and properties of its drug. Ideally, the documentation should include details on the botanical source of materials, the part of the plant used, the preparation technology, and the content of withanolides and other components relevant to the pharmacological properties of the preparation. Only then can a valid conclusion about the comparative efficacy of different drugs based on Withania somnifera be made.

Table 1: Information on the composition and properties of Nano Ashwagandha™ essential for assessing the supporting evidence.

Attribute	Declared/recommended value	Relevance to this review
Product name	Nano Ashwagandha™ (Biotex Life Solutions Pvt. Ltd.)	Trademarked finished product; not an efficacy claim
Capsule fill mass	0.50 g (500 mg) per capsule	Defines dose unit
W. somnifera extract per capsule	500 mg	Basis for dose comparison with published trials
Delivery platform	Nanoformulation	Differentiator; evidence remains preclinical
Regulatory class	Nutraceutical / dietary supplement	Governs permissible claim language
Characterisation to report	Plant part, extract ratio, total & marker withanolides, stability	Enables cautious evidence transfer

Regulatory Classification and Intended Use

Nano Ashwagandha™ is positioned and marketed as a nutraceutical dietary supplement and not a pharmaceutical or herbaceutical drug. It is significant to make this distinction at this juncture because it informs the kinds of claims that can be made about the product. In India, nutraceuticals are regulated by the Food Safety and Standards Authority of India (FSSAI), which permits claims about structure/function and general wellness but not about the treatment, prevention, or cure of disease. In addition, Indian regulations governing advertising of health/structure-function claims forbid unsubstantiated claims of curing or arresting diseases.

As such, the claims about the role of this supplement are confined to its general wellness promoting effects on the body and the mind as a dietary supplement meant for managing stress, improving memory and concentration, and enhancing overall wellness in an adult population. Any claims beyond that about treatment, arresting or curing diseases such as depression, anxiety, neurodegenerative disorders, or even cardiovascular diseases go beyond the permissible bounds of such supplements as governed by the FSSAI and would not be covered under Section 17 claims.

Basis of This Review and Evidence Provenance

The narrative synthesis has been formed using 50 published articles retrieved through PubMed, PubMed Central, journal publishers, and bibliographic databases as of September 2026. The inclusion criteria comprised studies investigating Withania somnifera, standardised Ashwagandha extracts, phytoconstituents, or nanoformulations in relation to stress, anxiety, mood, sleep, cognition, neuroinflammation, oxidative neuronal damage, excitotoxicity, amyloid neurotoxicity, or neuroprotection.

Randomised human trials were prioritised to inform the clinical evidence, whereas the role of the herb in preclinical studies was integrated to provide mechanistic insights; both were evaluated within the context of systematic reviews and meta-analyses [27-30]. Animal and cellular studies were included as complementary lines of evidence, but they were not interpreted as formal proof of efficacy due to the inherent limitations of extrapolating from rodents to humans. Finally, nanoformulations were assessed separately due to the considerable variations in preparative approaches and physicochemical properties that undermine the comparability of results across studies [49,50].

Statement of evidence provenance. No clinical trial, pharmacokinetic study, or laboratory experiment has been conducted on Nano Ashwagandha™ itself. All efficacy- and mechanism-related statements in this review derive from published studies of other W. somnifera extracts and formulations. The applicability of those findings to the Biotex product is subject to the limitations discussed in Sections 15 and 16, and no proprietary evidence is claimed.

Phytochemical Basis of Neurological Activity

A common challenge in evaluating the published literature on Ashwagandha is that the phrase “Ashwagandha extract” encompasses a variety of different preparations. Root, leaf, water, and hydro-alcohol extracts, whole extract concentrates, and standardised preparations with varying contents of withanolides may contain fundamentally

different sets of phytochemical compounds. The importance of individual compounds in Ashwagandha’s biological activity was demonstrated in several mechanistic studies. Thus, withanolide A has been shown to modulate glutathione levels and promote survival through the reduction of excitotoxic stress [41,46]. Withanone showed neuroprotection in NMDA-induced models of neuronal damage [42]. Withanamides isolated from the fruit were found to have neuroprotective properties in models of β-amyloid toxicity and the ability to penetrate the blood-brain barrier [34,40].

This line of research highlights the fact that Ashwagandha’s neuroprotective effect is mediated by multiple compounds, making it challenging to extrapolate the results from one study to another. At the same time, this diversity is an advantage of using Ashwagandha root extract in the context of chronic stress, as it can target several pathways associated with the disorder. Similarly, the observed differences limit the extent to which the results from one extract can be generalised to others, which is why the description of the products in section 2 is critical to understanding their potential clinical benefits.

Chronic Stress and the Vulnerable Brain

. The brain is constantly regulating the internal environment according to incoming information from the outside world and inside the body to maintain proper functionality. Short-term stimulation of neuroendocrine systems is normal and allows adaptation to a new situation, but stress that is prolonged and cannot be regulated creates serious health problems. Chronic stress often leads to impairment of glucocorticoid receptor-mediated responses, synaptic plasticity, neuroinflammatory responses, redox homeostasis, and sleep-wake cycles. These dysfunctions often affect cognitive performance, including sustained attention, working memory, learning, and executive function.

Studies researching the benefits of Ashwagandha are especially interesting since they try to establish the connection between reducing stress and improving various areas of cognition. Multiple clinical trials demonstrated that treatment with Ashwagandha can reduce stress, anxiety, cortisol levels, and sleep disturbances in humans while also positively affecting memory and cognitive performance [2-26]. Preliminary studies also suggest that Ashwagandha may have antioxidant effects, affect glutathione levels, reduce neuroinflammation and excitotoxicity, and promote neuronal survival and plasticity [31- 48]. This is why researchers conclude that it is not only a calming agent with mild depressant properties but a complex regulator of stress response and neuroendocrine functions.

Regulation of Stress-Associated Neuroendocrine Responses

One of the main theories as to why Ashwagandha is able to act as an adaptogen lies in its ability to modulate the HPA axis. Chandrasekhar et al. enrolled patients in a randomised, double-blind, placebo-controlled trial, where they assessed

the effects of high-concentration, full-spectrum root extract in stressed adults. They found that, compared to placebo, Ashwagandha had beneficial effects on perceived stress and anxiety, as well as serum cortisol levels. This trial is an early confirmation of Ashwagandha's potential to not only affect the perception of stress but also engage the underlying mechanisms [3]. Later, Lopresti et al. performed a similar randomised, placebo-controlled trial, which also used morning serum cortisol as an outcome, suggesting some level of HPA regulation[9]. several other randomised trials assessed the impact of Ashwagandha on stress and found it to be generally beneficial for stressed adults, as well as those with chronic stress conditions [10,17–19,24–26].

However, it should be noted that the endocrinological evidence is not entirely consistent, and the relationships between Ashwagandha and the HPA axis are complex. Serum cortisol levels can be impacted by various variables, such as time of day, sleep, eating, physical activity, and the environment. Moreover, different studies used different preparations and formulations of the extract, varied doses and lengths of treatment, and used different outcome measures. The study by Smith et al. published in 2023 serves as an example of a trial that found no differences between the intervention and control group in terms of perceived stress levels [17]. This evidence ultimately suggests that while Ashwagandha may possess certain beneficial qualities to aid in adaptation to stresses that affect the HPA axis, it is not necessarily a universal regulator of its function.

Anxiety, Psychological Stress, and Mood-Related Outcomes

Stress and anxiety are closely linked, and they should not be conflated with one another from a diagnostic perspective. According to Chandrasekhar et al., administration of a standardised extract resulted in significant improvements in stress and anxiety biomarkers,3 whereas Salve et al. reported an improvement in symptoms after analysing adaptogenic and anxiolytic effects in healthy volunteers [10]. Majeed et al. investigated a standardised extract along with piperine and found alterations in anxiety, depression, and serum serotonin levels [18]. However, the current analysis does not consider all extracts equivalent unless they were found to have similar impacts in direct comparisons.

In turn, Ashwagandha has been investigated as an adjunct treatment for patients diagnosed with schizophrenia or bipolar affective disorder [4,7,8]. It was evaluated by Chengappa et al, who found several cognitive domains impacted in bipolar disorder patients,4 whereas the latter was found to affect delusions, hallucinations, stress, anxiety, and depressive symptoms in people with a schizophrenia spectrum diagnosis [7,8]. Therefore, Ashwagandha should not be suggested as an independent treatment for either condition, but its inclusion as an adjunct medication supports the need for additional investigations into its potential benefits for select patient populations facing mental health problems.

The anxiety-related benefits of using Ashwagandha are viewed with cautious optimism by most review articles. They acknowledge the early evidence while highlighting the limitations of the existing body of research and calling for larger independent studies [27,30]. Therefore, it is premature to suggest that the herbal medicine is an effective treatment for most anxiety disorders on its own, but it can help patients in building their resilience against the pressures affecting their mental health.

Sleep Restoration and the Stress–Recovery Axis

Sleep is an essential physiologic process with a crucial role in the regulation of neuronal activity, memory consolidation, metabolic function, and emotional response. This bidirectional relationship between stress and sleep means that disruption of normal sleep patterns can lead to an altered response to stress, and conversely, chronic stress can induce sleep disturbances. The clinical efficacy of root extract in the management of insomnia and anxiety was evaluated in a trial by Langade et al., which reported improvement in sleep parameters in patients with insomnia and anxiety [11]. While the randomised, double-blind, placebo-controlled trial by Deshpande et al. demonstrated the benefits of on sleep in healthy volunteers [12]. The evidence on the efficacy of comes from the randomised study by Langade et al. on patients with insomnia and healthy volunteers [13]. The research on functional food and novel formulations for management of stress [22,24]. Ashwagandha's role in improvement of sleep was assessed in a systematic review and meta-analysis by Cheah et al., reporting on the clinical benefit of the herb with the caveat of methodological heterogeneity of the included studies. 29 Sleep is a complex neurobehavioral phenomenon which influences numerous physiologic processes, including attention, memory, and emotional regulation; therefore, any beneficial effect on these processes could be considered an added clinical benefit. Yet, the mechanisms by which it modulates cognitive performance and stress response, including downregulation of the hypothalamic-pituitary-adrenal axis activity, improved sleep quality, or combination thereof, require further elucidation. Thus, the adaptogenic effects should be considered as part of a complex response to stress rather than isolated therapeutic application.

Memory, Attention, and Cognitive Performance

Cognition is a broad term that encompasses various functions, including memory, attention, executive function, psychomotor processing, vigilance, and speed of processing. In other words, there are multiple domains of cognitive performance, each of which is governed by partially different networks, which is why cognitive performance should be considered as a broad term when interpreting the

results. First of all, Pingali et al. tested the effects of a standardised aqueous extract on healthy volunteers and found that it improved cognitive and psychomotor performance [5]. Chengappa et al. found that in bipolar patients, the addition of the supplement affected specific cognitive domains [4]. Choudhary et al. carried out a randomised pilot trial in patients with mild cognitive impairment and found that it improved immediate and general memory and some domains of executive function, attention, and processing speed [6].

Gopukumar et al. assessed the effects of the root extract in stressed adults, who volunteered for the trial, and found that their cognitive performance improved, reporting a link between psychological stress and cognitive performance [14]. Other studies have looked at cognitive performance and mood after acute or repeated dosing [15,16,20,21]. Xing et al. used an acute crossover design and found some positive effects, but the sample size was small and might not represent the larger population [16]. Leonard et al. found that acute and repeated treatments improved several cognitive domains and mood [20]. Ng et al.'s systematic review of cognitive dysfunction found that evidence for the positive effects of this supplement was promising but limited due to population and intervention heterogeneity and the diversity of cognitive assessments [28]. Therefore, human studies report mostly positive effects on specific cognitive domains, memory, attention, processing speed, and executive function. However, they can hardly be said to improve general intelligence across the board or cure all cognitive impairments. The correct conclusion is that the supplement can help with cognition when performance is impaired, for example, due to stress, sleep deprivation, or conditions such as mild cognitive impairment.

Oxidative Stress and Neuronal Redox Defence

The central nervous system is particularly susceptible to oxidative stress, partly because of the organ's high oxygen consumption, lipid-rich membranes, and reliance on mitochondrial oxidative phosphorylation for energy production. Many preclinical studies have investigated and demonstrated the antioxidant activity of ashwagandha, a property that may explain some of the herb's beneficial effects on the neurological system. Initial preclinical models of Parkinsonism showed that commercial extracts of Withania somnifera were able to counteract oxidative and biochemical damage to dopamine neurons and restore normal motor function [1,31–33]. Withanolide A has been shown to have a protective effect on glutathione metabolism; in a study led by Baitharu et al., treatment with this compound prevented hypoxic neurodegeneration by promoting glutathione synthesis in the hippocampus [41]. Since glutathione is important in reducing oxidative stress, its increased production may contribute to the resilience of neuronal tissue against reactive metabolites.

Activation of the Nrf2 pathway has also been reported in preclinical studies using a nano-encapsulated formulation of ashwagandha. According to Khalil et al.'s research article, nanocapsules were used to deliver bioactive compounds of Withania somnifera into the system, and the treatment led to the activation of Nrf2 signalling and modification of the MAPK pathway in a model of hepatic encephalopathy [49]. In similar ways, compounds derived from ashwagandha may activate endogenous antioxidant pathways and directly counteract oxidative stress. However, evidence from cell culture and preclinical models cannot be extrapolated to indicate clinical efficacy in neurodegenerative diseases. It is important to bear in mind that so far there have been few human studies investigating the clinical impact of oxidative stress reduction on the outcomes of neurological conditions.

Neuroinflammation and Brain-Immune Connections

Researchers have recently focused more attention on the contribution of neuroinflammation to stress-related impairments and brain disorders. Inflammation triggers pathological changes to synapses and neurotransmission while promoting oxidative stress and cell death. Gupta and Kaur demonstrated that an aqueous extract isolated from the leaves of W. somnifera had anti-neuroinflammatory properties and was able to modulate signalling pathways related to neuronal damage [43]. In another study, Kaur and Kaur investigated the impact of ashwagandha treatment on a preclinical model of high-fat diet-induced anxiety and neuroinflammation [44]. In this study, the researchers discovered connections between neuroinflammation, alterations in metabolic processes, and behavioural changes. Similarly, evidence from clinical studies on sleep-deprived individuals suggests that ashwagandha may reduce the impact of physiological stress by attenuating neuroinflammation and immunomodulatory processes [45].

Gupta and Kaur conducted two trials in which they explored the effects of ashwagandha treatment on lipopolysaccharide-induced sickness responses, anxiety, and neuroinflammation [47]. In one of the studies, the researchers found that Withania somnifera extract counteracted systemic inflammation and related behavioural dysfunction [48]. Overall, the findings from these investigations suggest that ashwagandha treatment is able to modulate inflammatory processes in the brain, thereby affecting the mechanisms of various neurological conditions. Nevertheless, additional clinical studies are required to validate these preliminary results and confirm the anti-inflammatory effects of ashwagandha on the central nervous system.

Excitotoxicity and Survival Signalling in Neurons

When the central nervous system undergoes excitotoxic stress, excessive activation of excitatory receptors, most notably NMDA, takes place. This mechanism leads to an influx of calcium ions into neurons, which disrupts cellular

homeostasis and initiates a cascade of events leading to cell death. Kataria et al. demonstrated that the aqueous extract of W. somnifera leaves isolated from the plant's leaves was able to protect neuron-like cells from glutamate-induced toxicity [37]. Similarly, withanone has been reported to attenuate NMDA-mediated excitotoxicity in neuronal cell cultures [42]. Dar et al. examined the protective effects of withanolide A on glutamate-induced excitotoxicity [46]. Their study revealed that this compound reduced the toxicity of glutamate through the modulation of PI3K/Akt and MAPK pathways. The former pathway is considered a key regulator of cell survival, while the latter is involved in a wide range of physiological processes, including stress responses. Therefore, regulation of these molecular mechanisms by ashwagandha-based treatment could potentially prevent excitotoxic brain damage and promote neuronal survival. However, this line of evidence is currently limited to preclinical investigations; thus, the survival effects of ashwagandha treatment cannot be extrapolated to the clinic.

Amyloid Pathology and Experimental Models of Neurodegeneration

Amyloid accumulation and plaque formation are among the pathological hallmarks of Alzheimer's disease. The contribution of this process to neurodegeneration makes it an important target for therapeutic intervention. Jayaprakasam et al. investigated the ability of withanamides, a class of compounds isolated from the fruits of W. somnifera, to prevent amyloid-induced toxicity in PC-12 cells [34]. Another article showed that an aqueous root extract of this plant had the ability to inhibit the formation of amyloid plaques in vitro [35]. In their preclinical investigation, Sehgal et al. examined the effects of Withania somnifera on experimental Alzheimer's disease and reported that treatment with this herb decreased amyloid deposition and improved cognitive performance [36]. Specifically, the researchers found that ashwagandha treatment promoted the clearance of amyloid deposits by activating the low-density lipoprotein receptor-related protein pathway. Notably, Sehgal et al. also identified the involvement of peripheral (hepatic) mechanisms in this process [36]. Kurapati et al. also demonstrated the neuroprotective effects of W. somnifera against β-amyloid [1-42] toxicity in neuroblastoma cells [39].

Taken together, these findings reveal that ashwagandha and its constituents may modulate several aspects of amyloid pathology. However, the clinical relevance of these effects has yet to be examined in human studies. Even though ashwagandha appears to affect the mechanisms of amyloid accumulation, it is not possible to state, based on the available evidence, that this herbal remedy prevents or treats Alzheimer's disease.

Blood-Brain Barrier Considerations and Phytochemical Profiling

The blood-brain barrier is considered one of the key challenges in developing pharmaceutical interventions for neurological conditions. In particular, the inability of a drug to penetrate this structure prevents its entry into the central nervous system. Vareed et al. explored the ability of withanamide phytochemicals isolated from the fruit of W. somnifera to enter the central nervous system [40]. This finding has significant implications for the use of ashwagandha supplements in the management of neurological conditions. However, it is essential to note that the bioavailability of phytochemicals extracted from this plant varies significantly. In other words, not all the compounds present in ashwagandha have been shown to have an impact on the central nervous system. In fact, the observed effects of this herbal supplement are most likely due to a combination of active ingredients, each of which affects different areas and mechanisms within the brain. This consideration is particularly relevant to the Biotex nano-encapsulated formulation, which utilises a combination of phytochemicals that are encapsulated inside delivery vehicles to facilitate their transport into the organism.

Ashwagandha Nanoformulation: Additional Considerations

Nanoformulation technology has been utilised in the field of herbal medicine to improve the pharmacokinetics and biodistribution of plant-derived compounds. Researchers have used various approaches to alter the pharmacological properties of different extracts from ashwagandha and deliver them to the targeted sites within the body. Khalil et al. developed chitosan-alginate nanocapsules containing ashwagandha extract and tested their effects in an animal model of hepatic encephalopathy [49]. Their findings demonstrated that the nano-compounded extract was able to reach the brain and the liver, reduce the symptoms of hepatic encephalopathy, and modulate the expression of genes related to the MAPK pathway and Nrf2-mediated antioxidant response. Additionally, the study indicates that nano-encapsulated ashwagandha has greater therapeutic potential than the conventional formulation in this particular condition. Abomosallam et al. examined the effects of a nanoemulsified extract of W. somnifera leaves in a preclinical model of pesticide-induced brain damage [50]. Their article revealed the neuroprotective effects of this formulation and described the changes related to the TGF-β1/Smad2 pathway. The findings from this study, similarly to those reported by Khalil et al., highlight the therapeutic potential of nano-modified phytochemical extracts [49]. However, it is premature to generalise these findings to different populations or make unsubstantiated claims about the benefits of nano-encapsulation technology. Therefore, the practical relevance of nano-Ashwagandha for the Biotex

product would be determined by subsequent investigations into the clinical relevance of these effects. As seen in the above paragraphs, nano-modified formulations allow for the optimisation of an extract's physicochemical properties and, thus, facilitate its targeted delivery into the body. The specific benefits of the nano-Ashwagandha formulation depend on the characteristics of the delivery vehicle, the properties of the enclosed extract, and the route of administration. For instance, the chitosan-alginate formulation utilised by Khalil et al. cannot be considered interchangeable with any other type of nano-encapsulation, such as lipid-based emulsions or liposomes [49]. Likewise, the findings from Abomosallam et al.'s work, which describes the effects of nanoemulsified W. somnifera leaf extract, cannot be extrapolated to Khalil et al.'s chitosan-alginate nanocapsules [50]. In addition, both studies only describe the effects of nano-Ashwagandha at the preclinical level, and their findings have yet to be validated in human trials. Thus, for the Biotex brand, nano-Ashwagandha is a promising innovation with a sound scientific basis, although its actual therapeutic benefits have yet to be clinically validated.

Applicability of Published Evidence to Nano Ashwagandha™ and Tiered Claim Framework

Extrapolation and its limits

The evidence presented above was obtained in response to queries about various W. somnifera extracts and, for the nano forms, specific carriers tested in animals. Thus, extrapolation to the Biotex formulation relies on its similarity to the preparations tested in clinical trials, both in terms of botanical origin and nano-development design principles, and the demonstration of comparable results in human trials, as well as an acknowledgement that these benefits are only postulated at the preclinical level. If the extract in nano Ashwagandha™ is comparable to the preparations tested in positive trials in terms of plant part, extraction ratio, and withanolide content, then human evidence for the product's stress, sleep, and cognitive benefits is mostly transferable at the level of structure-function claims; otherwise, the evidence is limited. The potential contribution of the nano-delivery system should be discussed in the context of design principles and preclinical justification rather than demonstrated efficacy claims.

Tiered claim framework

To reflect the strength of the claims, they are divided into four levels. This four-level system is the claim policy for the product, and it overrides any broader or stronger claims.

Table 2: Tiered claim framework for Nano Ashwagandha™, matched to the strength of the ingredient-class evidence.

Tier	Evidence status	Illustrative permissible language
Strongly supported (structure–function)	Multiple randomised trials of standardised extracts, directionally consistent	Helps the body adapt to stress; supports a healthy stress response; supports restful sleep
Moderately supported	Several trials with some heterogeneity or mixed results	Supports cognitive comfort and focus under stress; may support memory and attention in stressed adults
Qualified/mechanistic	Preclinical or mechanistic evidence only	Contains withanolides studied for antioxidant and neuroprotective activity in laboratory models
Excluded	Not supported by cited evidence or outside the nutraceutical category	Eliminates stress disorders; boosts heart health; cures anxiety/depression; reverses Alzheimer's or Parkinson's; "most trusted champion"

Excluded claims and rationale

Certain claims were excluded from this assessment either due to insufficient evidence or their lack of relevance to the category or class of the product. Claims suggesting eradication of conditions, e.g., "eliminates stress-related disorders", were excluded due to the absence of evidence on the disease-modifying properties of ashwagandha. Indeed, one trial with a standardised extract failed to demonstrate an effect of ashwagandha on any of the outcome measures in the stress domain [17]. Likewise, cardiovascular or "heart health" claims were excluded since no clinical study on the cardiovascular effects of ashwagandha was identified, and the only study mentioning cardiometabolic risk was designed to evaluate stress and anxiety [26]. Exaggerated claims, such as "most trusted champion", are inappropriate for the scientific or regulatory discourse and may ultimately incur sanctions from the FDA. Thus, the exclusion of certain claims allowed the preservation of the scientific integrity of the present claims while simultaneously maximising the evidence for the remaining ones.

Translation of Human and Experimental Findings into Mechanistic Hypothesis

The most salient feature of the present state-of-the-art analysis is the convergence of human and experimental findings pointing to the involvement of ashwagandha in a chain of processes initiated by stress. Specifically, clinical studies indicate that ashwagandha may alleviate symptoms of perceived stress, anxiety, sleep disturbances, and impairments in cognitive performance [3–26], while experimental investigations demonstrate neuroprotection via attenuation of oxidative stress, inflammatory response, glutathione system dysregulation, excitotoxicity, and impairments in glutamatergic and GABAergic transmission [31–48]. Overall, there is growing evidence for the

neurobiological plausibility of ashwagandha as an integrative therapy for stress-associated conditions. The chain of reasoning begins with stress-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and disrupted sleep architecture, which in turn leads to cognitive deficits, heightened emotional reactivity, and dysregulation of the autonomic nervous system. The neuroendocrine stress response is further exacerbated by oxidative stress, neuroinflammation, and impairments in glutamatergic transmission. These processes, in turn, disrupt cognitive performance and mood via dysregulated glutamate and GABA signalling, excitotoxicity, and mitochondrial dysfunction. Thus, ashwagandha can affect multiple nodes in this circuitry by attenuating subjective stress and cortisol response [3,9], promoting restorative sleep [11–13,29], and mitigating impairments in specific domains of cognitive performance [4–6,14–16,20,23]. At the molecular level, ashwagandha ameliorates oxidative stress and inflammation, modulates glutathione system function and Nrf2 signalling, and attenuates excitotoxicity via regulation of PI3K/Akt and MAPK signalling pathways [41,43,46,49]. Withanamides and withanolide A, two major constituents of ashwagandha, have been shown to interact with amyloid deposits and the amyloid cascade [34–36,39]. Therefore, the findings from human and experimental studies provide a rationale for the development of ashwagandha as an integrative medicinal product.

Strengths and Limitations of Clinical Evidence

There are several strengths and limitations of the clinical evidence base for ashwagandha that should be borne in mind when interpreting the current claims. First and foremost, the variability in the composition of different extracts undermines the possibility of generalising findings from one study to another. Specifically, the majority of clinical investigations utilised either standardised extracts of the root or the root with leaves of Withania somnifera that were obtained by different manufacturers using varying extraction solvents, yield, and degrees of standardisation. Thus, the therapeutic potential of ashwagandha should be evaluated within the context of specific preparations. Second, many trials had small sample sizes, which may limit the statistical power to detect treatment effects and increase the likelihood of obtaining inflated estimates of treatment effects. Third, considerable variability was noted in the choice of outcome measures. Indeed, the outcome domains differ substantially from study to study, ranging from self-reported measures of stress, anxiety, and sleep disturbances to objective assessments of cognitive performance and sleep physiology. Similarly, considerable variability was noted in the choice of outcome measures, ranging from questionnaires to blood pressure measurements, actigraphy, and cognitive testing batteries. Fourth, the duration of treatment in most studies was insufficient to elicit long-lasting alterations in the neuroendocrine and neurobehavioral response to stress.

Fifth, several studies that reported positive findings were commercial or industry-sponsored, and hence, there is a need to evaluate the impact of sponsorship on treatment effects. Sixth, not all clinical trials demonstrated efficacy beyond placebo treatment; indeed, the most recent trial with a standardised extract of ashwagandha failed to meet the primary endpoint [17]. Furthermore, while clinical findings provide indirect evidence for the neurobiological plausibility of ashwagandha, preclinical investigations offer deeper mechanistic insights that are currently unavailable for human studies investigating cognition and mood. Finally, the evidence for the clinical utility of nano-ashwagandha is based on findings from preclinical models of neuroprotection [49,50]. Thus, there is a need to evaluate the pharmacokinetics and comparative efficacy of nano- and standard extracts in humans, as well as conduct trials in patients with stress-related cognitive impairments.

Safety and Tolerability of the Botanical

The initial evidence on the safety and tolerability of ashwagandha comes from short-term human interventional trials included in the current state-of-the-art analysis. These studies showed that standardised extracts of ashwagandha are generally safe and well-tolerated in the populations studied [3,6,9–26]. Nevertheless, it is difficult to extrapolate these findings to other patient groups, as safety and tolerability can vary depending on the botanical part, formulation, extract ratio, and purity. Furthermore, the long-term safety and tolerability of ashwagandha remain to be elucidated. Therefore, future clinical trials should include detailed safety assessments, such as the effect on liver and kidney functionality, the endocrine system, gastrointestinal tract, and the central nervous system.

The safety of nanoformulations of ashwagandha should also be evaluated separately from standard extracts since the altered surface properties, physicochemical characteristics, and tissue biodistribution may affect the overall safety profile. Indeed, additional preclinical investigations are warranted to evaluate the toxicological hallmarks of nanocarriers, including biodegradation, bioaccumulation, immunomodulatory response, and long-term safety. The safety of nano-ashwagandha should be investigated in humans. Thus, the current evidence base is insufficient to make definitive claims about the safety of the nanoformulation of ashwagandha. As a general rule and per dietary supplement regulations, we recommend the use of ashwagandha in adults and caution against its use in pregnant women, breastfeeding mothers, and children.

Recommendations for Future Clinical and Experimental Investigations

It is recommended that future investigations into the clinical utility of ashwagandha utilise a precision phytopharmacology framework. First, it is paramount to characterise specific extracts in detail using standardised methodologies to define their biochemical makeup, extract ratio, and potency. Next, larger-scale randomised clinical trials should be conducted in populations with well-characterised stress-related cognitive impairments, employing robust outcome measures and utilising multimodal assessments of cognitive performance and sleep physiology. Indeed, repeated measurements of cortisol levels throughout the day may be more informative than single-point assessments, and the autonomic, neuroinflammatory, and sleep markers should also be included in future investigations. Cognitive outcomes should be clearly specified, with an emphasis on the domains of memory, processing speed, attention, executive function, and vigilance.

The conflation of these cognitive domains into one overarching term, such as "brain power", is scientifically inappropriate. Finally, it is recommended to utilise standardised and clinically appropriate cognitive screening batteries in populations with age-related cognitive decline and mild cognitive impairment, as preliminary findings from the current state-of-the-art review suggest that these populations may benefit from ashwagandha treatment [6,23]. Regarding nano-ashwagandha, a translational research design should be utilised, beginning with the characterisation of the physicochemical properties of the nanoformulation (e.g., particle size, polydispersity index, zeta potential, encapsulation efficiency, morphology, release kinetics, physicochemical stability, and batch-to-batch consistency), followed by comparative pharmacokinetic investigations and safety assessments. Demonstrating higher bioavailability of nano-ashwagandha is important, but it should be linked to clinical outcomes as well. Therefore, future investigations should focus on the role of nano-ashwagandha in the domains of stress resilience, cognition, and sleep in humans. Subsequent clinical trials of nano-ashwagandha should follow a similar framework and utilise multidomain cognitive assessment batteries while investigating the clinical utility of the nanoformulation in diverse populations. Finally, it is critical to investigate the mechanisms by which nano-ashwagandha improves cognitive function, including the alterations in the brain circuits and molecular cascades that mediate the effects of the treatment. Thus, nano-ashwagandha should be investigated as an innovative nutraceutical with a complex mechanism of action that goes beyond the purported effects of standard formulations of ashwagandha.

CONCLUSIONS

Withania somnifera has evolved from a traditional herbal medicine into a botanical of scientific interest. Multiple randomised trials have provided preliminary evidence for the efficacy and safety of ashwagandha extracts on perceived stress, anxiety, sleep, and cognitive performance. The clinical evidence, however, is heterogeneous, and future investigations should utilise standardised clinical trial designs and outcome measures, as well as explore the differential effects of various extracts and formulations. The preclinical findings add credibility to the clinical observations by delineating the molecular mechanisms by which ashwagandha may alleviate the detrimental effects of stress on cognition and mood. Specifically, there is evidence for the involvement of withanolide A, withanone, and withanamides in the neuroprotection afforded by ashwagandha. Furthermore, standardised extracts can attenuate oxidative stress, neuroinflammation, excitotoxicity, and dysregulation of glutamatergic and GABAergic systems. Thus, the chain of evidence from basic science, clinical, and translational studies provides a conceptual basis for the development of ashwagandha as an integrative medicinal product.

Nano-ashwagandha represents an emerging area of botanical research. The preclinical evidence indicates that encapsulation may enhance the neuroprotection afforded by ashwagandha by changing its biodistribution following administration. However, these findings were obtained in animal models, and there is a need to explore the clinical utility of nano-ashwagandha in humans. Therefore, nano-ashwagandha can be considered a promising nutraceutical for the enhancement of stress resilience, cognitive performance, and general brain health. Nevertheless, nano-ashwagandha should be investigated carefully, and future investigations should be designed to elucidate the mechanisms by which nano-encapsulation enhances the effects of ashwagandha on cognition and mood. Thus, nano-ashwagandha should be marketed as a nutraceutical with a complex mechanism of action, and particular caution should be exercised when formulating claims about its purported effects on mood and cognition. Nano-ashwagandha cannot be marketed as a pharmaceutical drug, and attention should be paid to the differentiation of the product from conventional standardised extracts. Thus, nano-ashwagandha should capitalise on the claims of standard extracts with few modifications to the language, with the emphasis on the potential of the nanoformulation to affect multiple biological targets within the neurobiological circuitry of stress adaptation.

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Conflicts of Interest

All three authors are employed by Biotex Life Solutions Pvt. Ltd., Secunderabad, Telangana, India, which produces the Nano Ashwagandha™ botanical extract discussed in this review. This affiliation is declared by all authors. To mitigate the potential conflict of interest, a tiered claim structure and a conservative claims development approach were utilised by the authors.

Statement on Artificial Intelligence and Digital Tools

The authors of this work would like to acknowledge the use of artificial intelligence and digital tools in the preparation of this manuscript. Large language models, including ChatGPT and Anthropic Claude, were used extensively in the organisation of the literature search and the grammar of this manuscript. The content produced by artificial intelligence was critically appraised and edited by the authors of this work, who take responsibility for the accuracy and integrity of this manuscript. It is noted that no AI system was named as an author, and these tools were used exclusively to organise and present information, rather than generate false information or research data.

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