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Therapeutic Effect of *Withania somnifera* (Ashwagandha) on Depression: A comprehensive review

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ABSTRACT: Ashwagandha (*Withania somnifera*), which is widely used in Ayurveda and other system of medicine, is best known for its ability to reduce depression and associated problems. Notably, important constituents of the body, such as enzymes, are intimately associated with the chemicals in plants; hence, supplementation is necessary to maintain overall health. This study collected reports of experimental studies primarily from various scientific sources like Scopus, Springer, PubMed, Google Scholar, etc. The findings of the review suggested that AS extract and its phytoconstituents significantly reduced depression and modulated oxidative stress and inflammation, which play a major role in neurological disorders, including depression. The growing research on ashwagandha emphasizes its potential as a useful natural depression remedy. However, further preclinical and clinical research is necessary to substantiate present observations to establish better methods for assessing the ashwagandha safety, effectiveness, bioavailability, purity, and precise mechanisms of action.

1. INTRODUCTION

For decades, since ancient times, scientists have been enthralled by plants, which have been utilised for their medicinal and tonic qualities. The oldest documented account of healing science can be found in the Vedas (Ž Šantić et al., 2017). In addition, the Ebers papyrus (16^{th} century B.C.) contains a detailed list of over 7000 herbal treatments and also mentions many medicinal plants. The Greco-Arabic system of medicine, often known as the Unani system, was founded by Middle Eastern civilization and is currently used throughout the Indian subcontinent. More than 80% of the drugs used in all of these systems come from plants (Pan et al., 2014). India is well-known for its traditional medical systems (IMS), such as Ayurveda, Siddha, and Unani, which utilize around 2000 species of medicinal plants and spices. Indian system of medicine is mentioned in the ancient Vedic scriptures about 2500 and 500 BC. The literal meaning of Ayurveda is "science of life," as the traditional IMS strongly emphasises understanding human health and disease (Ravishankar & Shukla, 2007).

Humans have used plants for years to treat numerous diseases (Ibrahim, Parveen, Zahiruddin, Gautam, et al., 2021) . As per WHO, most of the population uses herbal medicines to meet their psychological and physical health needs. Rural people heavily rely on traditional medicines because they cannot afford pharmaceutical industry products, even though they have a lack of healthcare facilities (S. Khan & Ibrahim, 2022; Sofowora et al., 2013). Traditional medicine is still used for primary health care in many developing countries' rural areas, and it has found a place in everyday life. These medications are safer and less expensive than synthetic or modern medications (Ahmad et al., 2019; Yuan et al., 2016). Rural residents may not be aware of the science underlying traditional medicines, but they know from personal experience that these therapies are a great way to maintain human health with natural ingredients (Ekor, 2014; Rahman et al., 2022). They are aware that certain medicinal herbs work best when ingested in therapeutic doses.

Plants are valuable medicinally because they contain certain chemicals that operate on the human body in a specific manner. They are naturally occurring, physiologically active chemical substances that provide humans with both macro- and micronutrients (Adusei et al., 2019). Plant-derived

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medicines are excellent antioxidants and scavenge free radicals, consuming them is linked to a decreased risk of developing a number of chronic diseases. Due to their intrinsic antioxidant properties, these may augment the body's requirements (Flora, 2009). Thousands of plants are utilised as medicine as well as nutraceuticals, and ashwagandha is one of them (Chandrasekara & Kumar, 2016).

Ashwagandha (*Withania somnifera*) Dunal (AS) is a Sanskrit name deriving from its utilization in the Indian traditional system of medicine (ISM). This species is one of the most reputed medical plants used throughout the world especially in the ISM to maintain humoral immunity of the body It can promote the healthiness of all the tissues and is classified as an adaptogen not only because of promotes homeostasis and also elicits complex responses as well (Murthy et al., 2012; Tamoli et al., 2022). According to cited research, AS has a crucial function in enhancing mood, memory, and focus in addition to building resistance to infections and ailments. In addition, it also improves the inflammation and oxidative stress in the biological system which will help to manage various diseases and disorders including depression (Speers et al., 2021).

Depression is a prevalent mental health condition that has detrimental effects on an individual's fitness. It has been found that many various forms of mental diseases share some molecular alterations and that the pathophysiology of depression is complex (M.A. Khan et al., 2021). The pathophysiology of depression has focused a lot of attention in recent decades on the disruption of monoamine transmission systems, including lower levels of dopamine, norepinephrine, and 5-hydroxytryptamine (Bondy, 2002) Due to a common mechanism among many treatments, the idea led to the discovery of numerous antidepressant medications, including herbal medicine, that precisely limits these neurotransmitters' reuptake in the brain in order to up-regulate them. Meanwhile, many plant-based medicines act as antidepressants by increasing serotonin receptor sensitivity or inhibiting monoamine oxidases (Liu et al., 2015).

Many diseases and disorders, including depression, are influenced by oxo-inflammatory conditions. Because of the role of inflammation in depression, researchers have been looking into the effects of peripheral inflammation on the brain (Miller & Raison, 2016). Tumour necrosis factor-alpha induces alterations in the blood-brain barrier (BBB) endothelial cells in vitro and in animal models, leading to increased permeability, larger extracellular gaps, and decreased expression of tight junction protein. These changes are remedied by anti-inflammatory medications (Rochfort et al., 2016). TNF-a and other proinflammatory cytokines have been found to be higher in depressed patients. Recently, there has been a focus on the role of the body's inflammatory response as one of the causes of depression or mood disorders (Miller et al., 2009). Furthermore, reactive oxygen species (ROS) play key roles in cellular signalling. Overproduction of ROS and the depletion of antioxidant defences trigger proinflammatory signalling, which damages essential macromolecules and induces cellular apoptosis. Proinflammatory mediators are produced as a result of cell necrosis, which happens when cells are unable to maintain redox homeostasis (Nita & Grzybowski, 2016). Moreover, the brain is more susceptible to oxidative stress (OS) due to its increased lipid content, increased oxygen demand, and weakened antioxidative defence. It is well-established that oxidative stress plays a significant role in the pathophysiology of major depression and is a primary cause of neurodegeneration. According to research, oxo-inflammatory signalling has become a significant factor in the pathophysiology of severe depression. One potential treatment approach for depression could utilize suitable phyototherapy like ashwagandha by modulating the aforementioned alterations (Bhatt et al., 2020; Miller & Raison, 2016).

2. METHODS

2.1. Literature search and study design

We evaluated the scientific literature using databases like Google Scholar, Web of Science and PubMed to conduct our literature search, taking into account all works published between November 2003 and October 2023. The following keywords were used: "Ashwagandha, "*Withania somnifera*", "herbal medicine," "brain-related disorders," "depression" "inflammation," "oxidative stress," and "plant". The study only uses publications from well-indexed journals (systematic, meta-analysis, research, and review articles) that are linked to brain-related diseases or disorders. The search results were filtered using the titles and abstracts of the reputed journal (S. Khan & Ibrahim, 2022). Furthermore, from many reports, relevant publications were considered and rigorously examined in order to advance the discussion on the experimental evaluation of ashwagandha in the management of brain-related disorders.

2.2. Inclusion criteria

This study included a review or research article with good repute in scientific journals about the prevalence of brain disorders, plants and their ingredients, molecular techniques for oxidative and inflammatory stress, and a thorough discussion of the study (Abdulazeez et al., 2021).

2.3. Exclusion criteria

Ethnopharmacological evidence does not include relevant field studies, study localities, ethical information, and data which is not fully accessible to prevent the misappropriation of comprehensives (Moher et al., 2010).

3. RESULTS

A total of 87 records were retrieved from various databases. Out of these only 42 records were examined for eligibility after duplicates were removed. Figure 1 also illustrates how the studies were chosen. Following screening, 18 preclinical and clinical studies that satisfied the inclusion requirements were chosen for the systematic review.

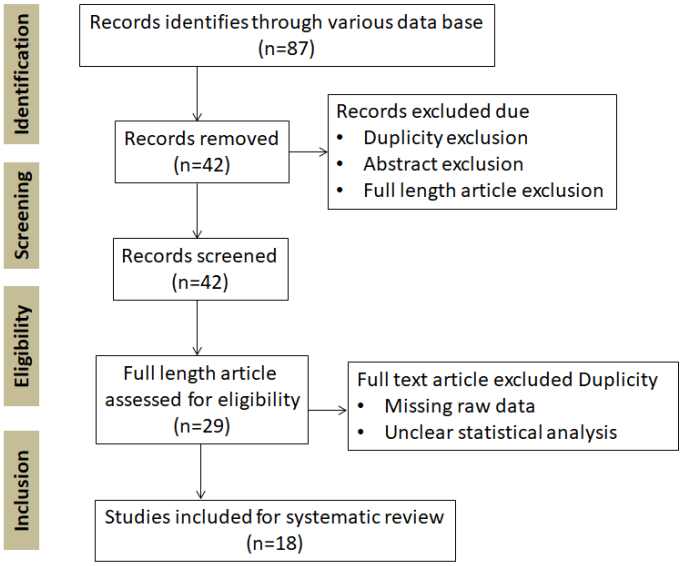

Figure 1. Flowchart illustrating a systematic review.

3.1. Rationale for the use of Ashwagandha

For centuries, ashwagandha has frequently been utilised as a most important herbal medicine in various traditional systems to improve numerous diseases and disorders including stress and depression (Ibrahim, Parveen, Zahiruddin, Parveen, et al., 2021). Depending on the complexity of the ailment, ashwagandha either alone or in combination with other remedies is typically advised to use. Ashwagandha had a number of phytoconstituents like withanolides, and other alkaloids that are pharmacologically and medicinally important in neurological disorders including stress and depression. TNF-α, IL-6, LPO, SOD, and GSH are examples of inflammatory makers and brain oxidative stressors that ashwagandha modulates (Mikulska et al., 2023). It also reduces apoptosis and modulates multiple inflammatory pathways. This suggests that ashwagandha in conjunction with essential components, may alter the pharmacological efficacy. In this work, we examine a subgroup of ashwagandha that is beneficial for depression, taking into account their features, functional traits, and phytochemical effects. These plants were chosen because it has a long record of being used in Indian medical practices for memory-related disorders, such as stress and depression; (a) phytochemicals from these plant sources have been identified for their potential in treating depression or stress; (b) these herbs' antidepressant and antistress properties have been determined; and (c) preclinical or clinical studies have been conducted to verify their reputation.

3.2. Antidepressant effect of Ashwagandha

Possibly the most well-known advantage of ashwagandha is its capacity to diminish stress. It belongs to the class of molecules known as adaptogens, which aid the body in adjusting to stress and depression. Additionally, it lessens the activity of the body's hypothalamic-pituitary-adrenal (HPA) axis, which controls your reaction to depression (Salve et al., 2019). A short study on the 58 participants found that those who consume ashwagandha extract (250 or 600 mg) for approx. 56 days experienced significantly less stress than those who took a placebo (Salve et al., 2019). When compared to the placebo group, those who took the ashwagandha supplements also experienced improvements in the quality of their sleep. According to another study on 60 participants, anxiety levels significantly decreased in those who took ashwagandha extract (240 mg) daily for 60 days than in those who got a placebo (Speers et al., 2021).

Ashwagandha can have effects that are similar to imipramine's in terms of its antidepressant qualities. Research might be in favour of the usage of ashwagandha root-derived medications as mood stabilisers and for the treatment of anxiety and depression. Ashwagandha root may also improve learning and memory (Bhat et al., 2022; Yeung et al., 2018). Among the plant's bioactive phytochemicals are withaniamides, withaferin A, withanolide A and D. They all significantly affect its pharmacological properties and actions. A conventional root extract of ashwagandha produced with water and ghee, as well as aqueous, methanolic, and hydroalcoholic extract, showed antidepressant efficacy (Saleem et al., 2020). Additionally, ashwagandha enhanced the effectiveness of popular antidepressants and enhanced the antidepressant effects of fluoxetine, a selective serotonin reuptake inhibitor, and imipramine, a tricyclic antidepressant, in mice and rat models of depression (Speers et al., 2021).

3.3. Role of Ashwagandha in oxidative stress

Previous studies reported that ashwagandha leaf extracts have anticancer effects on several human cancer cell types. It has been demonstrated that low dosages of hydroethanolic extracts cause differentiation, whereas high doses cause cancer cells to undergo apoptosis or growth arrest (Mikulska et al., 2023). As a result, they were offered as potential natural medications for differentiation-based therapy. Moderate amounts of withanone and aqueous extract have also been demonstrated to be protective against the excitotoxicity and memory impairment caused by glutamate and scopolamine, respectively. There hasn't been any information on comparative research on how alcohol and water extracts react to oxidative stress, a major contributor to neurodegenerative illnesses (Kumar et al., 2014). Both C6 (glioblastoma) and IMR32 (neuroblastoma) cells demonstrated protection against stress and maintained the differentiation state after being treated to oxidative stress and recovering in media supplemented with either ethanol or aqueous extract. Antioxidant effects of Ashwagandha's and its active phytoconstituents neuroprotection against stress in rats (Kaul et al., 2016; Sharma & Kaur, 2018). A study investigated the beneficial effect of Ashwagandha on recognised indicators of oxidative stress and DNA damage (H2AX) using cell-based assays. It is known that DNA double-strand breaks cause the phosphorylation of H2AX at Ser139 in mammalian cells. Using an anti-H2AX antibody for immunostaining, DNA damage foci in the nucleus can be quickly detected as being composed

of the phosphorylated version of H2AX (H2AX) and other DNA damage response proteins (ATM, ATR, CHK-1, and CHK-2). These tests showed that ashwagandha extracts reduced the formation of ROS and H2AX generated by H2O2 and glutamate, indicating that their anti-oxidative characteristics had a role in neuroprotection, at least in part (Shah et al., 2015). This study reported that the protective effects of the water and alcohol extracts were equal (Shah et al., 2015). They reported recovering differentiated glial and neuronal cells in media supplemented with extract or withanone reduced glutamate-induced oxidative stress and DNA damage. Shah et al reported that better recovery was seen when extract and withanone were combined. The ability of the cells to survive was improved, along with the maintenance or induction of differentiation, as well as a decrease in ROS accumulation and the creation of H2AX foci (a sign of a reaction to DNA damage). Reductions in GFAP (a marker of glial cell differentiation), NF-200 (an axonal marker), and MAP2 (a diagnostic of dendritic structure) indicate that either H_2O_2 or glutamate-induced oxidative stress affects the primary cytoskeletal elements (myelinated axons and microtubules), which are essential for differentiated neurons (Kataria et al., 2012; Rajasankar et al., 2009; Rajdev & Sharp, 2000). Furthermore, it has been observed that rats subjected to prolonged restraint stress experience changes in the expression and location of MAP2 in the cortex and hippocampus. It should be mentioned that in the current study, GFAP, NF-200, and MAP2 protein levels increased in cells treated with extract or withanone, indicating the preservation and protection of the functional states of both glial and neuronal cells (Kataria et al., 2012; Yan et al., 2010). These findings suggested that ashwagandha extracts and their constituent parts may have neuroprotective and neuro-differentiating properties, which are probably mediated via NF-200 and MAP2 signalling. Withanone was found to be less harmful to differentiated cells overall and to be more effective than withaferin A in all experiments (Kaul et al., 2016; Wang et al., 2021). It has been established that the alcoholic and water extracts of leaves contain different chemical components. The alcoholic extract contains withaferin A and withanone but not water; the latter was noted to include triethylene glycol. Because of the combined action of the active ingredients, which may exert their effects via several pathways, combination therapy is expected to provide improved protection. More investigation is necessary given the molecular characterization of these pathways (Shah et al., 2015). It's interesting to note that, in the absence of retinoic acid (RA), nuclear mortalin was shown to enhance the malignant properties of cancer cells by inactivating p53 and activating telomerase and hnRNP-K proteins. Mortalin was observed to translocate into the nucleus of neuroblastoma cells treated with retinoic acid, bind to retinoic acid receptors, and then increase their recruitment to the retinoic acid response element, where they were transcriptionally activated to produce genes involved in neuronal differentiation and reduce their proteasome-mediated degradation (Ryu et al., 2014; Shih et al., 2011). Mortalin was demonstrated to have a new role in actively promoting neuronal development by causing a significant drop in RA-triggered gene expression when it was knocked down (Grover et al., 2012). Ashwagandha extract or withanone administration was seen to generate nuclear enrichment of mortalin in IMR32 cells, which is similar to the impact of RA and suggests that these phytochemicals have the capacity to promote neuro-differentiation (Shah et al., 2015; Shih et al., 2011). Withanone and Ashwagandha leaf extracts are suggested as strong natural neurotherapeutic medicines based on these findings, which include (i) protection against oxidative stress, DNA damage, and glutamate excitotoxicity, and (ii) maintenance and activation of differentiation (Shah et al., 2015). To determine the signalling pathways and mechanisms involved in the therapeutic potential of each of these extracts and phytochemicals alone and in combination, more research is necessary.

3.4. Role of A shwagandha in inflammation

In preclinical research, ashwagandha water extract reduced lipopolysaccharide-induced neuroinflammation by inhibiting inflammatory cytokines such as TNF-α, IL-1, and IL-6 as well as the production of nitrooxidative stress enzymes (Mikulska et al., 2023). Previous observation pointed to the possible utility of Ashwagandha in reducing inflammation of the nervous system linked to numerous neurological illnesses. In another study, it was found that inhibition of inflammatory markers including cytokines (TNF-a and IL-6), NO, and ROS, this plant has been shown in preclinical trials to be able to control mitochondrial activity, regulate apoptosis, and lessen inflammation. Meanwhile, the inhibitory effect of Ashwagandha powder was shown in circumstances such as proteinuria and nephritis in a mouse model of lupus (Dar et al., 2015). Rats in the positive control group (control group) received phenylbutazone treatment. Along with a notable decrease in inflammation, changes in the amounts of a variety of serum proteins, including 2 glycoproteins, acute phase protein 1, and albumin, were seen. In an investigation using the HaCaT human keratinocyte cell line, it was found that a water extract of ashwagandha root inhibited the NF-kB and MAPK (mitogen-activated protein kinase) pathways by decreasing the expression of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12, and TNF-a and increasing the expression of anti-inflammatory cytokines such as (TGF)-β1 (Rasool & Varalakshmi, 2006; Sikandan et al., 2018). These findings suggest that Ashwagandha's anti-inflammatory properties may one day be applied to the prevention of skin irritation.

3.5. Clinical trials of Ashwagandha related to depression

The effects of ashwagandha extract on depression have been the subject of inconsistent clinical trial research; nonetheless, numerous clinical trials have been conducted to assess the herb's effectiveness in connection to human intake, and the results have been favourable.

Table 1
Use of Ashwagandha in herbal commercial formulations for brain- related disorders

Product	Ingredients	Used as/against	Manufacturer
Ashwagandha capsule	Ashwagandha	Adaptogenic, reduces stress and depression	Himalayan Organics
Ashwagandha gold plus	Ashwagandha root, Swarn bhasm, Black Musli root, Gokshura fruit	Improve strength, Energy, Immunity, Relive depression	Himalayan Organics
Ashvagandha Capsule	Ashvagandha	Improve stress	Himalaya Drug Company
Mentat Syrup	Brahmi, Madhukaparni, Ashwagandha	Enhancing memory and learning capacity	Himalaya Drug Company
Stress Relief Massage Oil	Ashwagandha, Indian Tinospora, Country Mallow, Indian Madder	Relief stress	Himalaya Drug Company
Manoll Nutra Syrup and capsule	Ashwagandha, Yastimadhu, Guduchi, Amalaki,	Relief of stress and improved immunity	Charak Pharma
Evanova Capsule	Soya, Ashwagandha, Brahmi, Jyotishmati, Arjuna	Insomnia	Charak Pharma
Sumenta Tablet	Ashwagandha, Brahmi, Jyotishmati, Tagar, Jatamansi	Protect neuron- damage	Charak Pharma
Cognium Tablet and syrup	Ashwagandha, Shankhapushpi, Arjun, Jyotishmati, Brahmi,	Cognitive functions	Charak Pharma
ZZOWIN Tablets	Ashwagandha, Tagar, Yashtimadhu, Jatamansi, Mandukparni, Pippali	Anxiety, relaxation, sleep deprivation	Charak Pharma
Ashwagandha Churna and Capsule	Ashwagandha	Relieve stress	Patanjali
Muniprajna Tablets	Brahmi, Shankhapushpi, Jyotishmati, Ashwagandha	Neuroprotection	Muniyal Ayurveda
Ashwagandha powder and Capsules	Ashwagandha	Anti-stress	Herbsforever
Ashwagandha Bala Shatavari Oil	Ashwagandha, Shatavari, Bala,	Nerve strengthening	Herbsforever
Shardardaghna	Jatamansi, Brahmi, Ashvagandha, Nagarmotha, Khurasni	Migraine	Dr. Vaidya's
Stresscom Capsule and Syrup	Ashwagandha powder	Reduce anxiety, depression and stress	Dabur
Dabur Shila-X Oil	Ashwagandha, Shuddha Shilajatu, Nutmeg oil, Amalaki, Bala, Clove Oil, Shatavari, Shveta Chandana, Jivanti, Yashtimadhu, Kumkuma, Kamala, Utpala, Sukshmaila	Strong nervous tissues	Dabur
Ashwagandharishta	Ashwagandha, Mushali, Manjishtha, Haritaki, Haldi	Depression, Anxiety and Stress	Dabur
Mood Elixir	Ashwagandha, Anantmool, Bramhi	Mood management	Cureveda
Stress Shield	Ashwagandha, Jatamansi, Brahmi	Anxiety and stress support	Cureveda
Trankula Capsules and Tonorex Syrup	Ashvagandha, Brahmi, Shankhapushpi	Hyper tension	Amar Healthcare
Ashwagandha Root Extract Capsule	Ashwagandha	Relief stress	Avestia Pharma

Continued on next page

Table 1 continued

Ashwagandha Capsule	Ashwagandha	Relief stress	Morpheme Remedies
	Ashwagandha, Jyotishmati, Brahmi, Jatamansi, Mandukparni, Shankpushpi, Yastimadhu, Vacha	Memory, focus and clarity	Morpheme Remedies
Stress Suppress Capsule	Ashwagandha, Brahmi, Jatamansi, Tagara	Stress management	Morpheme Remedies
	Brahmi, Ashwagandha, Vacha, Licorice, Indian Sandalwood, Shankhpushpi	Mental alertness	Morpheme Remedies
Withania somnifera Mother Tincture	Ashvagandha	Reduce depression	SBL
Ashwagandha Mother Tincture	Ashvagandha	Reduce stress	Dr. Reckeweg
Ashwagandha Mother Tincture	Ashvagandha	Reducing stress and strain	ADEL
Ashwagandha Capsules	Ashvagandha	Reducing stress,	Livestamin
Brento Forte Tablets	Bramhi, Shankhpushpi, Mandukparni, Ashwagandha, Jyotishmati	Ameliorate mental retardation, dementia	Zandu
Brento Tablets and Syrup	Shankhpushpi, Ashwagandha, Kath, Vacha, Yashtimadhu, Sarpagandha, Brahmi, Jatiphala, Chandroday	Ameliorate mental retardation, dementia. Reduce memory loss	Zandu
Alpitone syrup	Ashwagandha, Rasna, Shatavari, Bala, Gokshur, Draksha, Guduchi, Ginger, Chitrak	Reduced stress, anorexia, fatigue	Zandu
AyurSip Stress Control	Ashwagandha, Brahmi, Licorice, Vaca, Saunf, Amalaki, Jaiphal, Vidarikand, Mandukparni, Lavanga, Arjuna	Physical and mental stress	Zandu
Ashwagandhahills Capsule	Ashwagandha	Antistress and revitaliser	Herbal Hills
Anti-Stress Capsules	Ashwagandha, Brahmi, Gotu Kola, Piperine	Stress Relief	SUNOVA
Avalife Stress-Free	Ashwagandha, Bacopa, Holy basil	Stress Relief	Avalife
Ashwagandha Gold Capsules	Ashwagandha, Shilajit, Black musli, Gokshura, Kaunch beej	Enhance cognitive functions, relieve stress and anxiety	Kapiva
Ashwagandha Capsule	Ashwagandha	Reduce Depression and Anxiety	Riffway International
Ashwagandha Capsule	Ashwagandha	Relieves Stress And Anxiety	Sabates
Ashwagandha Capsule	Ashwagandha	Relieves stress, and anxiety and uplifts mood	AIIMIL pharmaceuticals

Intake of 1000 mg/day of ashwagandha extract for 12 weeks ameliorates symptoms of depression and anxiety associated with schizophrenia, according to a randomized, double-blind controlled research (Chandrasekhar et al., 2012). Oral intake of ashwagandha standardized extract on 66 patients for a period of 12 weeks improved anxiety and depression. Another study found that taking 300 mg twice a day of ashwagandha root extract for 60 days significantly decreased perceived scores of stress and depression, which dropped to 44% from 5.5% in the placebo group. Serum cortisol levels were similarly lower in the ashwagandha root extract group than in the placebo group (Kelgane et al., 2020; Speers et al., 2021).

3.6. Safety of Use

Ashwagandha has been used medicinally for a very long time, which is mainly proof of its efficacy and the body's high tolerance. In recent years, liver damage caused by ashwagandha has been experienced globally, hence, to dispel concerns regarding its use, a number of experts are currently collaborating. The pharmaceutical industry for herbal supplements is substantial and growing, both domestically and globally. It is therefore even more important to verify its safety (Langade et al., 2019).

The first evidence linking ashwagandha to liver damage was found in Japan in 2004. It concerned a 20-year-old male patient with congestive liver damage who recovered fully after quitting ashwagandha and taking ursodeoxycholic acid and phenobarbitone for two months to address his symptoms (Siddiqui et al., 2021). Björnsson et al. claim that ashwagandha caused liver damage in the five volunteers. These incidents demonstrate Ashwagandha's potential hepatotoxic consequences. Liver damage typically manifests as cholestatic jaundice and pruritus, although it is a self-limiting illness that resolves in one to five months with normal liver test findings (Björnsson et al., 2020). Furthermore, a 39-year-old lady in the UK was reported to have had nausea and jaundice after using an over-the-counter herbal medication that contained ashwagandha extract (Lubarska et al., 2023). Hepatotoxic consequences have only sometimes and erratically been documented (Bokan et al., 2023). On the other hand, no toxicity of ashwagandha was confirmed by an Indian investigation including eighty perfectly healthy participants. Each participant took 300 mg of ashwagandha root extract orally twice a day for eight weeks. To ascertain this, variables such as plasma haemoglobin, neutrophil and platelet counts, alkaline phosphatase, aspartate transaminase, alanine transaminase, and body weight were monitored. At the conclusion of the study, there was no discernible change in the values of the aforementioned indicators between the 40 participants in the extract-using group and the 40 participants in the placebo-taking group. Triiodothyronine, thyroxine, and TSH levels were measured in the blood to assess thyroid function; however, no appreciable changes in these hormone levels were observed (Langade et al., 2021; Verma et al., 2021).

A second study using a smaller sample size (18 volunteers) confirms the lack of significant effects on bilirubin, plasma protein levels, WBC percentage, RBC count, and ESR value. Conversely, blood urea nitrogen levels decreased and serum creatinine increased (Liang et al., 2017). The specialists of the study concluded that this event resulted from the concurrently documented increase in muscle mass. Over the course of ten days, participants ingested ashwagandha sluggard root aqueous extracts at increasing doses, beginning at the equivalent of 6 g and finishing at the equivalent of 10 g (Mikulska et al., 2023). Even though the plant has a lot going for it, pregnant or breastfeeding women shouldn't eat it. At this point, there is not enough information to say with certainty whether or not it is safe to use ashwagandha-containing products during such sensitive developmental periods. Some understanding of this aspect of safety can be gained from studies looking at how ashwagandha extract affects pregnant rats (Mikulska et al., 2023). The majority of emphasis was focused on the first five to nineteen days of pregnancy. Crucially, this is an exceptionally fragile period due to the fetus's accelerated organogenesis and histogenesis. The maximum dosage, administered orally, was 2000 mg/kg/day. The number of corpus luteum, body weight, or embryo implantation of the pregnant women did not alter as a result of the study, and there were no negative side effects (Mikulska et al., 2023).

4. CONCLUSIONS AND FUTURE PROSPECTIVE

Ashwagandha has been utilized for ages as a therapeutic regimen in brain-related disorders including depression, especially in Ayurvedic medicine for thousands of years. However, it is important to keep in mind that ashwagandha research is still in its early stages because of its safety and efficacy. The safety of ashwagandha must always be taken into account, especially when taking it in combination with other prescription drugs or dietary supplements. Consequently, further research on ashwagandha is needed to ascertain the possible advantages and disadvantages of utilizing ashwagandha as an antidepressant remedy, particularly in clinical research because we still struggle to comprehend the exact mechanisms underlying the potential medicinal effects.

CONFLICTS OF INTEREST

None.

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AUTHOR CONTRIBUTIONS

M.I; Design study, write and correct the paper. GP, BG-collected data, formatted manuscript. SK, MM, and NK; helped in preparing the manuscript and data collection.

REFERENCES

Abdulazeez, M.A., Muhammad, S.A., Saidu, Y., Sallau, A.B., Arzai, A.A., Tabari, M.A., Hafiz, A., Gwarzo, M.Y., Manosroi, J., Idi, A., Bashir, M., Pedro, S.L., 2021. A systematic review with meta-analysis on the antihypertensive efficacy of Nigerian medicinal plants. Journal of Ethnopharmacology. 279, 114342. https://doi.org/10.1016/j.jep.2021.114342

Adusei, S., Otchere, J.K., Oteng, P., Mensah, R.Q., Tei-Mensah, E., 2019. Phytochemical analysis, antioxidant and metal chelating capacity of *Tetrapleura tetraptera*. Heliyon. e02762. https://doi.org/10.1016/j.heliyon.2019.e02762

Ahmad, A., Ibrahim, M., Chester, K., Khan, W., Ahmad, S., Ansari, S., 2019. Antithrombocytopenic potential of bioactivity guided fractions of traditionally used *Psidium guajava* Linn. leaves in busulfan induced-thrombocytopenic rats. Pharmacognosy Magazine. 15, 440. https://doi.org/10.4103/pm.pm_608_18

Bhat, J.A., Akther, T., Najar, R.A., Rasool, F., Hamid, A., 2022. *Withania somnifera* (L.) Dunal (Ashwagandha); current understanding and future prospect as a potential drug candidate. Frontiers in Pharmacology. 13, 1029123. https://doi.org/10.3389/fphar.2022.1029123

Bhatt, S., Nagappa, A.N., Patil, C.R., 2020. Role of oxidative stress in depression. Drug Discovery Today. 25(7), 1270–1276. https://doi.org/10.1016/j.drudis.2020.05.001

Björnsson, H.K., Björnsson, E.S., Avula, B., Khan, I.A., Jonasson, J.G., Ghabril, M., Hayashi, P.H., Navarro, V., 2020. Ashwagandha-induced liver injury: A case series from Iceland and the US Drug-Induced Liver Injury Network. Liver International. 40(4), 825–829. https://doi.org/10.1111/liv.14393

Bokan, G., Glamočanin, T., Mavija, Z., Vidović, B., Stojanović, A., Björnsson, E.S., Vučić, V., 2023. Herb-Induced Liver Injury by Ayurvedic Ashwagandha as Assessed for Causality by the Updated RUCAM: An Emerging Cause. Pharmaceuticals. 16(8), 1129. https://doi.org/10.3390/ph16081129

Bondy, B., 2002. Pathophysiology of depression and mechanisms of treatment. Dialogues in Clinical Neuroscience. 4(1), 7–20. https://doi.org/10.31887/DCNS.2002.4.1/bbondy

Chandrasekara, A., Kumar, T., 2016. Roots and tuber crops as functional foods: A review on phytochemical constituents and their potential health benefits. International Journal of Food Science. 2016, 3631647. https://doi.org/10.1155/2016/3631647

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, 255–262. https://doi.org/10.4103/0253-7176.106022

Dar, N.J., Hamid, A., Ahmad, M., 2015. Pharmacologic overview of *Withania somnifera*, the Indian Ginseng. Cellular and Molecular Life Sciences, 4445–4460. https://doi.org/10.1007/s00018-015-2012-1

Ekor, M., 2014. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front. Neurol. 4, 177. https://doi.org/10.3389/fphar.2013.00177

Flora, S.J.S., 2009. Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. Oxidative Medicine and Cellular Longevity. 2, 873634. https://doi.org/10.4161/oxim.2.4.9112

Grover, A., Priyandoko, D., Gao, R., Shandilya, A., Widodo, N., Bisaria, V.S., Kaul, S.C., Wadhwa, R., Sundar, D., 2012. Withanone binds to mortalin and abrogates mortalin-p53 complex: Computational and experimental evidence. International Journal of Biochemistry & Cell Biology. 44, 496–504. https://doi.org/10.1016/j.biocel.2011.11.021

Ibrahim, M., Parveen, B., Zahiruddin, S., Gautam, G., Parveen, R., Ahmed, M., Arun, K., Sayeed, G., 2021. Analysis of polyphenols in *Aegle marmelos* leaf and ameliorative efficacy against diabetic mice through restoration of antioxidant and anti-inflammatory status. Journal of Food Biochemistry. 46(4), e13852. https://doi.org/10.1111/jfbc.13852

Ibrahim, M., Parveen, B., Zahiruddin, S., Parveen, R., Khan, M.A., Gupta, A., Ahmad, S., 2021. Uplc/ms based phytochemical screening and antidiabetic properties of *Picrorhiza kurroa* in mitigating glucose-induced metabolic dysregulation and oxidative stress. Farmacia. 69, 749–755.

Kataria, H., Wadhwa, R., Kaul, S.C., Kaur, G., 2012. Water extract from the leaves of *Withania somnifera* protect ra differentiated c6 and IMR-32 cells against glutamate-induced excitotoxicity. PLoS One. 7(5), e37080. https://doi.org/10.1371/journal.pone.0037080

Kaul, S.C., Ishida, Y., Tamura, K., Wada, T., Iitsuka, T., Garg, S., Kim, M., Gao, R., Nakai, S., Okamoto, Y., Terao, K., Wadhwa, R., 2016. Novel methods to generate active ingredients-enriched Ashwagandha leaves and extracts. PLoS One. 11(12), e0166945. https://doi.org/10.1371/journal.pone.0166945

Kelgane, S.B., Salve, J., Sampara, P., Debnath, K., 2020. Efficacy and Tolerability of Ashwagandha Root Extract in the Elderly for Improvement of General Well-being and Sleep: A Prospective, Randomized, Double-blind, Placebo-controlled Study. Cureus. 12(2), e7083. https://doi.org/10.7759/cureus.7083 https://doi.org/10.7759/cureus.7083

Khan, M.A., Srivastava, V., Kabir, M., Samal, M., Insaf, A., Ibrahim, M., Zahiruddin, S., Ahmad, S., 2021. Development of Synergy-Based Combination for Learning and Memory Using in vitro, in vivo and TLC-MS-Bioautographic Studies. Frontiers in Pharmacology. 12, 1–14. https://doi.org/10.3389/fphar.2021.678611

Khan, S., Ibrahim, M., 2022. A systematic review on hepatoprotective potential of grape and polyphenolic compounds : molecular mechanism and future prospective. Natural Resources for Human Health. 3(2), 196–213. https://doi.org/10.53365/nrfhh/156261

Kumar, P., Singh, R., Nazmi, A., Lakhanpal, D., Kataria, H., Kaur, G., 2014. Glioprotective effects of ashwagandha leaf extract against lead induced toxicity. BioMed Research International. 2014, 182029. https://doi.org/10.1155/2014/182029

Langade, D., Kanchi, S., Salve, J., Debnath, K., Ambegaokar, D., 2019. Efficacy and Safety of Ashwagandha (*Withania somnifera*) Root Extract in Insomnia and Anxiety: A Double-blind, Randomized, Placebo-controlled Study. Cureus. 11(9), e5797. https://doi.org/10.7759/cureus.5797 https://doi.org/10.7759/cureus.5797

Langade, D., Thakare, V., Kanchi, S., Kelgane, S., 2021. Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. Journal of Ethnopharmacology. 264, 113276. https://doi.org/10.1016/j.jep.2020.113276

Liang, H., Xin, M., Zhao, L., Wang, L., Sun, M., Wang, J., 2017. Serum creatinine level and ESR values associated to clinical pathology types and prognosis of patients with renal injury caused by ANCA-associated vasculitis. Experimental and Therapeutic Medicine. 14, 6059–6063. https://doi.org/10.3892/etm.2017.5306

Liu, L., Liu, C., Wang, Y., Wang, P., Li, Y., Li, B., 2015. Herbal Medicine for Anxiety, Depression and Insomnia. Current Neuropharmacology. 13, 481–493. https://doi.org/10.2174/1570159X13041508311227 34

Lubarska, M., Hałasiński, P., Hryhorowicz, S., Mahadea, D.S., Łykowska-Szuber, L., Eder, P., Dobrowolska, A., Krela-Kaźmierczak, I., 2023. Liver Dangers of Herbal Products: A Case Report of Ashwagandha-Induced Liver Injury. International Journal of Environmental Research and Public Health. 20(5), 3921. https://doi.org/10.3390/ijerph20053921

Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O.P., Paczkowska-Walendowska, M., Gościniak, A., Cielecka-Piontek, J., 2023. Ashwagandha (*Withania somnifera*)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics. 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057 https://doi.org/10.3390/pharmaceutics15041057

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Biological Psychiatry. 65(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: From evolutionary imperative to modern treatment target. Nature Reviews Immunology. 16, 22–34. https://doi.org/10.1038/nri.2015.5

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery. 8(5), 336–341. https://doi.org/10.1016/j.ijsu.2010.02.007

Murthy, M.R.V., Ranjekar, K., Ramassamy, P., Deshpande, C., M., 2012. Scientific Basis for the Use of Indian Ayurvedic Medicinal Plants in the Treatment of Neurodegenerative Disorders: 1. Ashwagandha. Central Nervous System Agents in Medicinal Chemistry. 10, 238–246. https://doi.org/10.2174/1871524911006030238

Nita, M., Grzybowski, A., 2016. The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults. Oxidative Medicine and Cellular Longevity. 2016, 3164734. https://doi.org/10.1155/2016/3164734

Pan, S.Y., Litscher, G., Gao, S.H., Zhou, S.F., Yu, Z.L., Chen, H.Q., Zhang, S.F., Tang, M.K., Sun, J.N., Ko, K.M., 2014. Historical perspective of traditional indigenous medical practices: The current renaissance and conservation of herbal resources. . Evidence-Based Complementary and Alternative Medicine. 2014, 525340. https://doi.org/10.1155/2014/525340

Rahman, A., Ibrahim, M., Siddiqui, J.I., Ansari, S.A., Ahmad, S., 2022. Metabolomic profiling and antidiabetic potential of *Rumex vesicarius* seed extract in high-fat diet and streptozotocin-induced diabeticrat. Brazilian Journal of Pharmaceutical Sciences. 58, e21032. https://doi.org/10.1590/s2175-97902022e21032

Rajasankar, S., Manivasagam, T., Surendran, S., 2009. Ashwagandha leaf extract: A potential agent in treating oxidative damage and physiological abnormalities seen in a mouse model of Parkinson's disease. Neuroscience Letters. 454, 11–15. https://doi.org/10.1016/j.neulet.2009.02.044

Rajdev, S., Sharp, F.R., 2000. Stress Proteins as Molecular Markers of Neurotoxicity. Toxicology Pathology. 28, 105–112. https://doi.org/10.1177/019262330002800113

Rasool, M., Varalakshmi, P., 2006. Immunomodulatory role of *Withania somnifera* root powder on experimental induced inflammation: An in vivo and in vitro study. Vascular Pharmacology. 44, 406–410. https://doi.org/10.1016/j.vph.2006.01.015

Ravishankar, B., Shukla, V.J., 2007. Indian systems of medicine: A brief profile. African Journal of Traditional, Complementary and Alternative Medicines. 4(3), 319–337. https://doi.org/10.4314/ajtcam.v4i3.31226

Rochfort, K.D., Collins, L.E., Mcloughlin, A., Cummins, P.M., 2016. Tumour necrosis factor-α-mediated disruption of cerebrovascular endothelial barrier integrity in vitro involves the production of proinflammatory interleukin-6. Journal of Neurochemistry. 136, 564–572. https://doi.org/10.1111/jnc.13408

Ryu, J., Kaul, Z., Yoon, A.R., Liu, Y., Yaguchi, T., Na, Y., Ahn, H.M., Gao, R., Choi, I.K., Yun, C.O., Kaul, S.C., Wadhwa, R., 2014. Identification and functional characterization of nuclear mortalin in human carcinogenesis. Journal of Biological Chemistry. 289, 24832–24844. https://doi.org/10.1074/jbc.M114.565929

Saleem, S., Muhammad, G., Hussain, M.A., Altaf, M., Bukhari, S.N.A., 2020. *ithania somnifera* L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iranian Journal of Basic Medical Sciences. 23(12), 1501–1526. https://doi.org/10.22038/ijbms.2020.44254.10378

Salve, J., Pate, S., Debnath, K., Langade, D., 2019. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. Cureus. https://doi.org/10.7759/cureus.6466 https://doi.org/10.7759/cureus.6466

Shah, N., Singh, R., Sarangi, U., Saxena, N., Chaudhary, A., Kaur, G., Kaul, S.C., Wadhwa, R., 2015. Combinations of Ashwagandha leaf extracts protect brain-derived cells against oxidative stress and induce differentiation. PLoS One. 10, e0120554. https://doi.org/10.1371/journal.pone.0120554

Sharma, A., Kaur, G., 2018. *Tinospora cordifolia* as a potential neuroregenerative candidate against glutamate induced excitotoxicity: An in vitro perspective. BMC Complementary Medicine and Therapies. 18, 268. https://doi.org/10.1186/s12906-018-2330-6

Shih, Y.Y., Lee, H., Nakagawara, A., Juan, H.F., Jeng, Y.M., Tsay, Y.G., Lin, D.T., Hsieh, F.J., Pan, C.Y., Hsu, W.M., Liao, Y.F., 2011. Nuclear GRP75 binds retinoic acid receptors to promote neuronal differentiation of neuroblastoma. PLoS One. 6(10), e26236. https://doi.org/10.1371/journal.pone.0026236

Siddiqui, S., Ahmed, N., Goswami, M., Chakrabarty, A., Chowdhury, G., 2021. DNA damage by Withanone as a potential cause of liver toxicity observed for herbal products of Withania somnifera (Ashwagandha). Current Research in Toxicology. 2, 72–81. https://doi.org/10.1016/j.crtox.2021.02.00

Sikandan, A., Shinomiya, T., Nagahara, Y., 2018. Ashwagandha root extract exerts anti-inflammatory effects in HaCaT cells by inhibiting the MAPK/NF-κB pathways and by regulating cytokines. International Journal of Molecular Medicine. 42, 425–434. https://doi.org/10.3892/ijmm.2018.3608

Sofowora, A., Ogunbodede, E., Onayade, A., 2013. The role and place of medicinal plants in the strategies for disease prevention. African Journal of Traditional, Complementary and Alternative Medicines. 10(5), 210–219. https://doi.org/10.4314/ajtcam.v10i5.2

Speers, A.B., Cabey, K.A., Soumyanath, A., Wright, K.M., 2021. Effects of *Withania somnifera* (Ashwagandha) on Stress and the Stress- Related Neuropsychiatric Disorders Anxiety, Depression, and Insomnia. Current Neuropharmacology. 19, 1468–1495. https://doi.org/10.2174/1570159X19666210712151556

Tamoli, S., Gokarn, V., Ibrahim, M., Ahmad, S., 2022. Comparative investigation of Ashwagandha FMB extract and standardized extract for their antioxidant, anti-inflammatory and immunomodulatory potential. Annals of Phytomedicine. 11(1), 405–412. http://dx.doi

.org/10.54085/ap.2022.11.1.46
Verma, N., Gupta, S.K., Tiwari, S., Mishra, A.K., 2021. Safety of Ashwagandha Root Extract: A Randomized, Placebo-Controlled, study in Healthy Volunteers. Complementary Therapies in Medicine. 57, 102642. https://doi.org/10.1016/j.ctim.2020.102642
Ž Šantić, Pravdić, N., Bevanda, M., Galić, K., 2017. The historical use of medicinal plants in traditional and scientific medicine. Psychiatria Danubina. 29, 787–792.
Wang, J., Zhang, H., Kaul, A., Li, K., Priyandoko, D., Kaul, S.C., Wadhwa, R., 2021. Effect of ashwagandha withanolides on muscle cell differentiation. Biomolecules. 11, 1454. https://doi.org/10.3390/biom11101454
Yan, J., Sun, X.B., Wang, H.Q., Zhao, H., Zhao, X.Y., Xu, Y.X., Guo, J.C., Zhu, C.Q., 2010. Chronic restraint stress alters the expression and distribution of phosphorylated tau and MAP2 in cortex and hippocampus of rat brain. Brain Research. 1347, 132–141. https://doi.org/10.1016/j.brainres.2010.05.074
Yeung, K.S., Hernandez, M., Mao, J.J., Haviland, I., Gubili, J., 2018. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. Phytotherapy Research. 32(5), 865–891. https://doi.org/10.1002/ptr.6033
Yuan, H., Ma, Q., Ye, L., Piao, G., 2016. The traditional medicine and modern medicine from natural products. Molecules. 21(5), 559. https://doi.org/10.3390/molecules21050559