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Antidepressant Potential Of Argyreia Nervosa Seeds: A Preclinical Review In Male Swiss Albino Mice

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Abstract: Depression is a prevalent and debilitating mental health disorder affecting over 300 million people worldwide. Current pharmacological treatments, including selective serotonin reuptake inhibitors and tricyclic antidepressants, are limited by delayed onset of therapeutic action, incomplete efficacy, and adverse side effects. This has stimulated growing interest in exploring natural products as alternative or complementary antidepressant agents. Argyreia nervosa, a climbing plant native to the Indian subcontinent and traditionally used in Ayurvedic medicine, has demonstrated promising neuropharmacological properties. The seeds of Argyreia nervosa are rich in bioactive compounds such as ergoline alkaloids, flavonoids, and polyphenols, which are implicated in modulating central nervous system functions.

This review critically examines preclinical evidence assessing the antidepressant potential of Argyreia nervosa seed extracts in male Swiss albino mice. Behavioral models widely used to evaluate depressive-like symptoms, including the Forced Swim Test and Tail Suspension Test, consistently show significant reductions in immobility time following administration of the extracts, indicating antidepressant-like effects comparable to standard drugs. Mechanistic studies highlight multiple pathways by which Argyreia nervosa exerts its effects, including enhancement of monoaminergic neurotransmission, inhibition of monoamine oxidase enzymes, antioxidant and neuroprotective activity, upregulation of brain-derived neurotrophic factor (BDNF), and normalization of the hypothalamic-pituitary-adrenal (HPA) axis.

Safety assessments indicate a favorable toxicity profile for Argyreia nervosa seed extracts at therapeutic doses. Taken together, these findings support the therapeutic potential of Argyreia nervosa seeds as a natural antidepressant and warrant further investigation, including clinical trials, to validate efficacy and safety in humans.

Keywords **-** Argyreia nervosa seeds, antidepressant potential, preclinical study, male Swiss albino mice, behavioral tests, Forced Swim Test, Tail Suspension Test, neurotransmitter modulation, monoamine oxidase inhibition, antioxidant activity, brain-derived neurotrophic factor, HPA axis regulation, phytochemicals, natural herbal antidepressants.

I. INTRODUCTION

Depression is a pervasive and debilitating psychiatric disorder characterized by persistent low mood, anhedonia, cognitive disturbances, and impaired social and occupational functioning.[1] It is estimated that more than 300 million people globally suffer from depression, making it a leading cause of disability worldwide.[2] The disorder is often chronic and recurrent, contributing substantially to morbidity, mortality, and socioeconomic burden.[3] Despite advances in pharmacotherapy, many patients experience incomplete remission, delayed therapeutic effects, and treatment resistance, underscoring the need for novel and safer antidepressant agents.[4]

Currently available antidepressants primarily target monoaminergic neurotransmission by modulating the levels of serotonin, norepinephrine, and dopamine in the brain. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) constitute the main classes of these drugs.[5] However, limitations such as side effects including sexual dysfunction, weight gain, sedation, and withdrawal symptoms, as well as the lag time for clinical efficacy, often result in poor patient compliance.[6] Moreover, these medications do not address the multifactorial pathophysiology of depression, which includes neuroinflammation, oxidative stress, impaired neuroplasticity, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.[7] These complexities highlight the importance of exploring alternative therapeutic approaches, particularly those derived from natural sources with multitarget mechanisms and favorable safety profiles.

Medicinal plants have historically played a crucial role in the management of mental health disorders. The use of botanicals in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, and Unani has provided valuable leads for modern drug discovery.[8] Plant-based compounds often exhibit a broad spectrum of biological activities including antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating effects, which may confer therapeutic advantages in complex disorders like depression.[9,10] The renewed interest in phytotherapy is supported by preclinical and clinical evidence validating the efficacy of various herbal extracts and isolated phytochemicals in mood disorders.[11]

Argyreia nervosa (Burm.f.) Bojer, commonly known as Hawaiian Baby Woodrose, is a perennial climbing plant native to the Indian subcontinent and belongs to the Convolvulaceae family.[12] Traditionally, its seeds have been used in Ayurveda and folk medicine for their sedative, anxiolytic, and neuroprotective properties.[13,14] The plant is also known for its psychoactive ergoline alkaloids, which are chemically related to compounds like lysergic acid diethylamide (LSD) but exhibit distinct pharmacological profiles.[15] These alkaloids, along with flavonoids, polyphenols, and other bioactive constituents, contribute to the therapeutic potential of *Argyreia nervosa* seeds.[16]

Phytochemical investigations have confirmed that *Argyreia nervosa* seeds contain several ergoline derivatives including ergine, isoergine, and lysergol, as well as flavonoids such as quercetin and kaempferol, and various phenolic compounds.[17] These molecules are known to modulate central nervous system function by interacting with serotonergic, dopaminergic, and adrenergic receptors, thereby influencing mood and behavior.[18] Experimental studies have demonstrated that seed extracts of *Argyreia nervosa* exhibit antidepressant-like activity in animal models through multiple mechanisms including monoamine neurotransmitter modulation, inhibition of monoamine oxidase enzymes, antioxidant effects, and neurotrophic factor upregulation.[19,20]

Male Swiss albino mice are commonly employed in preclinical behavioral paradigms to study depression and screen potential antidepressants due to their well-characterized genetic background and reproducible responses.[21] Standardized tests such as the Forced Swim Test (FST) and Tail Suspension Test (TST) assess behavioral despair and are predictive of antidepressant efficacy.[22] Studies involving *Argyreia nervosa* seed extracts have reported significant reductions in immobility time in these tests, indicative of antidepressant-like effects comparable to those produced by reference drugs like fluoxetine and imipramine.[23] Additionally, these extracts have been shown to normalize elevated corticosterone levels, suggesting regulatory effects on the HPA axis, which is frequently dysregulated in depression.[24]

Oxidative stress and neuroinflammation play pivotal roles in the pathogenesis of depression by impairing neuronal function and plasticity.[25] The antioxidant capacity of *Argyreia nervosa* seed extracts, attributed to its flavonoid and polyphenol content, may counteract these pathological processes and support neuronal survival.[26] Furthermore, the upregulation of brain-derived neurotrophic factor (BDNF), a critical mediator of neuroplasticity, has been observed following treatment with the seed extracts, providing a molecular basis for their antidepressant effects.[27]

Safety and toxicity are important considerations for any therapeutic candidate. Preclinical toxicity studies of *Argyreia nervosa* seed extracts have demonstrated a wide safety margin, with no significant adverse effects observed at doses effective for antidepressant activity.[28] This favorable safety profile, combined with the multifaceted mechanisms of action, makes *Argyreia nervosa* a promising candidate for further development as a natural antidepressant.

In summary, *Argyreia nervosa* seeds exhibit significant antidepressant potential through diverse pharmacological actions, including modulation of monoaminergic neurotransmission, antioxidant activity, neurotrophic factor enhancement, and HPA axis regulation. Preclinical evidence in male Swiss albino mice provides a strong foundation for future clinical evaluation. This review aims to synthesize existing knowledge on the antidepressant effects of *Argyreia nervosa* seeds, elucidate underlying mechanisms, and highlight directions for further research.

II. BOTANICAL AND ETHNOPHARMACOLOGICAL PROFILE

Argyreia nervosa (Burm.f.) Bojer, commonly known as Hawaiian Baby Woodrose or Elephant Creeper, is a perennial climbing vine belonging to the family Convolvulaceae. It is native to the Indian subcontinent but is now widely distributed across tropical and subtropical regions worldwide.[27] The genus *Argyreia* comprises around 100 species, but *A. nervosa* is one of the most extensively studied due to its ethnomedicinal significance and psychoactive properties.[28] The species is characterized by large, heart-shaped leaves with a velvety texture, and trumpet-shaped flowers ranging in color from pale pink to purple.[29] The plant produces distinctive seeds that are smooth, hard, and brownish, often used for traditional medicinal purposes.[30]

(a) (b)

Figure: Agyreia nervosa (a) flower, (b) seeds

The botanical classification of *Argyreia nervosa* is as follows:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Solanales
- Family: Convolvulaceae
- Genus: *Argyreia*
- Species: *A. nervosa* (Burm.f.) Bojer[31]

Morphologically, *Argyreia nervosa* grows as a vigorous climber, reaching lengths of up to 10 meters. Its woody stems are twining and flexible, enabling it to ascend trees and other supports in its natural habitat.[32] The seeds, the most pharmacologically relevant part, are oval and glossy, measuring approximately 1 cm in diameter.[33] These seeds contain bioactive compounds such as ergoline alkaloids, flavonoids, and polyphenols, which are responsible for the plant's wide range of pharmacological activities.[34]

From an ethnopharmacological perspective, *Argyreia nervosa* holds a significant place in traditional Ayurvedic medicine as well as in tribal and folk medicinal practices across India and other regions. In Ayurveda, the seeds are used for their reputed aphrodisiac, sedative, nervine tonic, and anti-inflammatory properties.[35] They are often employed to treat conditions like anxiety, insomnia, epilepsy, inflammation, and sexual dysfunction.[36] Additionally, the seeds have been used as a traditional remedy for nervous disorders, including depression and stress-related ailments, highlighting their neuropsychotropic potential.[37]

The psychoactive properties of *Argyreia nervosa* seeds are largely attributed to the presence of ergoline alkaloids such as lysergic acid amides (ergine), isoergine, and other related compounds. These alkaloids share structural similarity with lysergic acid diethylamide (LSD) but exhibit a milder psychoactive effect.[38] Due to these properties, the seeds have been used in various cultural and ritualistic contexts, particularly in some tribal communities where they serve as a natural hallucinogen or entheogen to induce altered states of consciousness.[39] However, traditional use emphasizes careful and controlled application due to potential toxicity at higher doses.[40]

Phytochemical investigations have revealed that besides ergoline alkaloids, *Argyreia nervosa* seeds are rich in flavonoids like quercetin and kaempferol, polyphenolic compounds, triterpenoids, and essential fatty acids.[41] These constituents confer a variety of pharmacological effects, including antioxidant, anti-inflammatory, and neuroprotective activities, making the seeds a multifaceted medicinal agent.[42] For example, flavonoids are well known for their ability to scavenge free radicals and reduce oxidative stress, which is implicated in the pathogenesis of depression and other neurodegenerative disorders.[43]

Ethnobotanical surveys in regions such as Maharashtra, Kerala, and West Bengal report the use of *Argyreia nervosa* seeds as a folk remedy for mental health disorders, reinforcing its role in traditional healing systems.[44] In some Ayurvedic formulations, the seeds are combined with other herbs to enhance cognitive function,

alleviate mental fatigue, and promote restful sleep.[45] Contemporary research has begun to validate many of these traditional claims through experimental models, supporting the integration of *Argyreia nervosa* into modern phytotherapeutics for neuropsychiatric conditions.[46]

The seeds also possess adaptogenic properties, which help the body resist stressors and maintain homeostasis. This adaptogenic action is crucial in managing depression, which is often precipitated or exacerbated by chronic stress.[47] Moreover, studies indicate that *Argyreia nervosa* extracts can modulate key neurotransmitter systems, including serotonergic, dopaminergic, and adrenergic pathways, which are central to mood regulation.[48,] This aligns well with the ethnomedical use of the seeds for calming the mind and enhancing emotional well-being.

Despite its widespread traditional use, it is important to note that *Argyreia nervosa* seeds contain compounds that may exhibit toxicity if misused. Cases of poisoning have been reported when seeds were ingested inappropriately or in excessive quantities.[49] Therefore, proper dosage, extraction methods, and preparation forms are essential to maximize therapeutic benefits while minimizing risks.[50] This emphasizes the need for standardization and thorough pharmacological evaluation of seed extracts to ensure safety and efficacy in clinical applications.

In summary, *Argyreia nervosa* is a botanically distinct plant with a rich ethnopharmacological heritage. Its seeds contain a complex mixture of bioactive compounds with diverse neuropharmacological effects. Traditional medicinal systems have long valued these seeds for their mental health benefits, particularly as a natural antidepressant and nervine tonic. Modern scientific investigations continue to uncover the mechanisms underlying these effects, paving the way for their potential use as safe and effective herbal therapeutics in neuropsychiatry.

III. PHYTOCHEMISTRY OF ARGYREIA NERVOSA

Argyreia nervosa, a member of the Convolvulaceae family, is rich in diverse phytochemical constituents that contribute to its wide range of pharmacological activities. The plant's seeds, leaves, and roots have been the focus of numerous phytochemical investigations, revealing a complex profile of bioactive compounds such as ergoline alkaloids, flavonoids, phenolic compounds, triterpenoids, and essential fatty acids. These chemical constituents are primarily responsible for the plant's therapeutic effects, especially its neuropharmacological properties.

The most distinctive and pharmacologically significant class of compounds isolated from *Argyreia nervosa* seeds are the **ergoline alkaloids**. Ergoline alkaloids belong to a group of indole alkaloids derived biosynthetically from the amino acid tryptophan. They include compounds structurally related to lysergic acid and its derivatives, which are known for their psychoactive properties.[51] Major ergoline alkaloids identified in *A. nervosa* include **ergine (lysergic acid amide, LSA)**, **isoergine**, **lysergol**, **ergometrine**, and other lysergic acid derivatives.[52] Ergine, in particular, has been the subject of extensive study due to its mild hallucinogenic effects and potential therapeutic applications in neuropsychiatric disorders.[53]

The concentration of these ergoline alkaloids in the seeds varies depending on the geographical location, extraction method, and plant maturity.[54] These alkaloids interact primarily with serotonergic receptors in the central nervous system, particularly 5-HT2A and 5-HT1A receptors, modulating neurotransmission and contributing to the plant's antidepressant, anxiolytic, and sedative effects.[55] Notably, unlike the potent synthetic analog LSD, ergine produces milder psychoactive effects with a lower risk of toxicity, which aligns with its traditional use in controlled therapeutic and ritual contexts.[56]

In addition to ergoline alkaloids, *Argyreia nervosa* seeds are rich in **flavonoids**—a class of polyphenolic compounds well-known for their antioxidant, anti-inflammatory, and neuroprotective properties.[57] Flavonoids such as **quercetin**, **kaempferol**, and their glycosides have been isolated from the seeds and leaves of the plant.[58] These compounds exert significant free radical scavenging activity, which is important in counteracting oxidative stress implicated in depression and other neurodegenerative diseases.[59] Flavonoids also influence intracellular signaling pathways and neurotrophic factors like brain-derived neurotrophic factor (BDNF), promoting neuronal survival and synaptic plasticity.[60]

Phenolic compounds and **polyphenols** are another prominent group of secondary metabolites found in *Argyreia nervosa*. These compounds are recognized for their broad spectrum of biological activities, including antimicrobial, anti-inflammatory, and antioxidant effects.[61] Total phenolic content in the seed extracts correlates with their antioxidant capacity, providing neuroprotection against oxidative damage caused by reactive oxygen species (ROS).[62] Polyphenols such as chlorogenic acid and caffeic acid derivatives have also been detected in the seeds and contribute to their therapeutic effects.[63]

Moreover, **triterpenoids** and **steroids** have been reported in the phytochemical profile of *Argyreia nervosa*. Triterpenoids like β-amyrin and ursolic acid are known for their anti-inflammatory and cytoprotective effects.[64] Steroidal compounds isolated from the seeds enhance the plant's adaptogenic and

immunomodulatory properties, which may be beneficial in managing stress-related disorders including depression.65

Essential fatty acids, including linoleic acid, oleic acid, and palmitic acid, have been identified in the seed oil of *Argyreia nervosa*. These fatty acids play an important role in maintaining neuronal membrane integrity and fluidity, thereby supporting optimal neurotransmission and brain function.[66] The presence of these lipids also contributes to the anti-inflammatory effects of the seed extract.[67]

The extraction methods used significantly influence the yield and profile of phytochemicals isolated from *Argyreia nervosa*. Solvent extraction using methanol, ethanol, or aqueous mixtures is commonly employed to maximize the recovery of both polar and non-polar compounds.[68] Advanced techniques such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy have been utilized to characterize the complex chemical profile of *A. nervosa* extracts with high precision.[69]

Recent phytochemical studies have also revealed the presence of minor compounds such as amino acids, sugars, and other water-soluble constituents that may contribute synergistically to the overall pharmacological profile of the plant.[70] The synergism between different classes of compounds—alkaloids, flavonoids, phenolics, and fatty acids—likely underpins the multifaceted neuropharmacological effects of *Argyreia nervosa* seeds, which include modulation of neurotransmitter systems, neuroprotection, and stress resistance.[71]

In summary, the phytochemistry of *Argyreia nervosa* seeds is marked by a rich and diverse array of bioactive compounds. Ergoline alkaloids, particularly ergine, serve as key psychoactive constituents, while flavonoids and phenolic compounds provide antioxidant and neuroprotective benefits. The presence of triterpenoids, steroids, and essential fatty acids further enhances the therapeutic potential of the seeds. These phytochemicals act through multiple mechanisms to exert antidepressant, anxiolytic, and adaptogenic effects, supporting the traditional medicinal uses of the plant and highlighting its promise for modern neuropsychiatric applications.

IV. Pharmacological Basis of *Argyreia nervosa*

Argyreia nervosa has garnered significant pharmacological interest due to its wide spectrum of bioactivities, primarily attributed to its diverse phytochemical profile. The therapeutic effects of *A. nervosa* seeds and extracts have been studied extensively, especially focusing on their neuropharmacological, anti-inflammatory, antioxidant, and adaptogenic properties. These pharmacological actions collectively underpin the traditional use of the plant in managing neurological and psychological disorders such as depression, anxiety, and cognitive impairment.

a) Neuropharmacological Effects

The neuropharmacological potential of *Argyreia nervosa* is among the most extensively investigated areas due to the presence of ergoline alkaloids, flavonoids, and phenolic compounds. Ergoline alkaloids like ergine act primarily on the central nervous system (CNS) by modulating serotonergic receptors (5-HT receptors), dopaminergic pathways, and adrenergic systems.[72] This receptor interaction influences mood, cognition, and emotional regulation, explaining the plant's traditional use as a nervine tonic and natural antidepressant.

Preclinical studies using rodent models have demonstrated significant **antidepressant-like effects** of *A. nervosa* seed extracts. In forced swim and tail suspension tests, which are standard behavioral paradigms for evaluating antidepressant activity, administration of seed extracts resulted in decreased immobility time, indicating enhanced mood and reduced depressive-like behavior.[73] These effects are believed to be mediated by increased serotonin and dopamine levels in brain regions critical for mood regulation, such as the hippocampus and prefrontal cortex.[74]

Moreover, *Argyreia nervosa* exhibits **anxiolytic activity**, likely due to the modulation of GABAergic and serotonergic neurotransmission.[75] Studies indicate that flavonoids within the seeds potentiate $GABA_A$ receptor function, which is associated with anxiolysis and sedation without the adverse effects seen in synthetic anxiolytics.[76] This property makes *A. nervosa* a potential natural alternative for anxiety management.

Neuroprotective effects have also been reported. The antioxidant constituents, particularly flavonoids and polyphenols, scavenge reactive oxygen species (ROS) and reduce oxidative stress in neuronal cells.[77] Oxidative stress is implicated in the pathophysiology of depression, neurodegeneration, and cognitive decline, making the antioxidative action of *Argyreia nervosa* therapeutically relevant[78] In vitro and in vivo studies demonstrate that *A. nervosa* seed extract protects against neuronal damage induced by oxidative insults, thereby preserving cognitive function and memory.[79]

b) Anti-inflammatory Activity

Chronic inflammation is closely linked to depression and neurodegenerative diseases. *Argyreia nervosa* exhibits potent **anti-inflammatory effects** by inhibiting pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[80] Triterpenoids and steroids isolated from the seeds have been shown to downregulate nuclear factor-kappa B (NF-κB) signaling, a key pathway in inflammation.[81] This anti-inflammatory action contributes not only to the plant's traditional use in treating inflammatory disorders but also to its neuroprotective and antidepressant effects, given the role of neuroinflammation in mood disorders.[82]

c) Antioxidant Properties

The rich content of flavonoids and phenolic compounds underlies the **antioxidant capacity** of *Argyreia nervosa*. Antioxidant activity has been confirmed through various in vitro assays, including DPPH radical scavenging, ferric reducing antioxidant power (FRAP), and lipid peroxidation inhibition tests.[83] These antioxidants mitigate cellular damage caused by free radicals, which are implicated in aging and numerous diseases, including depression and neurodegenerative conditions.[84]

Studies report that the antioxidant effect of *A. nervosa* not only protects neuronal cells but also improves mitochondrial function and energy metabolism in the brain, thus enhancing overall brain health.[85] This antioxidative mechanism synergizes with its anti-inflammatory properties to provide a multifaceted defense against neuropsychiatric disorders.

d) Adaptogenic and Immunomodulatory Effects

Argyreia nervosa is recognized as an **adaptogen**, meaning it helps the body resist physical, chemical, and biological stressors, thereby restoring homeostasis.[86] Adaptogenic activity is linked to the plant's ability to modulate the hypothalamic-pituitary-adrenal (HPA) axis, which governs the stress response. Experimental models have demonstrated that seed extracts reduce elevated corticosterone levels caused by chronic stress, attenuating behavioral and physiological stress responses.[87]

Furthermore, the immunomodulatory effects of *A. nervosa* contribute to its adaptogenic properties. Seed extracts stimulate immune cell proliferation and enhance macrophage activity, promoting a balanced immune response.[88] This is particularly important because chronic stress and depression are often associated with immune dysregulation and increased vulnerability to infections and inflammatory diseases.[89]

e) Other Pharmacological Activities

Beyond its neuropharmacological profile, *Argyreia nervosa* exhibits several other pharmacological effects that support its medicinal use:

1. **Antimicrobial activity:** Extracts show inhibitory effects against a range of bacterial and fungal pathogens, suggesting potential use in infectious diseases.[90]
2. **Analgesic and anti-inflammatory effects:** The plant's extracts reduce pain and inflammation in animal models, likely due to triterpenoids and flavonoids.[91]
3. **Hepatoprotective effects:** Some studies indicate protection against chemical-induced liver damage, attributable to antioxidant and anti-inflammatory mechanisms.[92]
4. **Cognitive enhancement:** By promoting neurogenesis and synaptic plasticity, *A. nervosa* may improve learning and memory functions.[93]

f) Safety and Toxicological Profile

While *Argyreia nervosa* has many beneficial effects, it contains bioactive alkaloids with potential toxicity at high doses. Toxicological studies in rodents show that acute administration of seed extracts is relatively safe at moderate doses, but excessive intake may cause gastrointestinal and neurological adverse effects.[94] Careful standardization of extracts and controlled dosing is essential to maximize therapeutic benefits while minimizing risks.[95]

The pharmacological basis of *Argyreia nervosa* is deeply rooted in its complex phytochemical composition. Ergoline alkaloids, flavonoids, and polyphenols act synergistically to exert antidepressant, anxiolytic, neuroprotective, anti-inflammatory, antioxidant, and adaptogenic effects. These mechanisms validate the plant's traditional use in treating neuropsychiatric and inflammatory disorders. Ongoing research continues to explore the therapeutic potential of *A. nervosa*, with a focus on safety, efficacy, and clinical application in modern medicine.

V. EXPERIMENTAL MODELS AND METHODS

To comprehensively evaluate the pharmacological effects of *Argyreia nervosa*, a range of **experimental models and methods** are employed. These models allow researchers to elucidate the mechanisms behind its neuropharmacological, antioxidant, anti-inflammatory, and adaptogenic activities. Both **in vivo** (animal-based) and **in vitro** (cell-based) experimental techniques are commonly utilized, providing a multi-dimensional approach to understanding the therapeutic potential and safety profile of this medicinal plant.

1. In Vivo Experimental Models

In vivo studies predominantly use rodents, such as mice and rats, due to their physiological similarity to humans and ease of handling. These models are essential for behavioral, biochemical, and toxicological assessments.

1.1 Behavioral Models for Antidepressant and Anxiolytic Activity

1.1.1. Forced Swim Test (FST): One of the most widely used models to assess antidepressant activity. Rodents are placed in an inescapable container of water, and their immobility time is recorded. Decreased immobility reflects antidepressant-like effects.[101] *Argyreia nervosa* extracts have been shown to significantly reduce immobility time, indicating mood-enhancing properties.

1.1.2. Tail Suspension Test (TST): Similar in principle to FST, mice are suspended by the tail, and immobility duration is measured. This test complements FST in antidepressant screening.[102]

1.2 Neuroprotective and Cognitive Models

1.2.1. Passive Avoidance Test: This test evaluates learning and memory by conditioning rodents to avoid an environment where they previously received a mild shock. Improved retention time in *Argyreia nervosa*-treated animals indicates cognitive enhancement.[105]

1.2.2. Morris Water Maze (MWM): Assesses spatial learning and memory by training rodents to locate a hidden platform in a pool. Seed extract administration has shown improved learning curves and reduced escape latency.[106]

1.3 Models for Oxidative Stress and Inflammation

1.3.1. Lipopolysaccharide (LPS)-Induced Neuroinflammation: Injection of LPS stimulates systemic inflammation, increasing pro-inflammatory cytokines and oxidative stress markers. Treatment with *A. nervosa* seed extracts reduces these markers, demonstrating anti-inflammatory and antioxidant effects in vivo.[107]

1.3.2. Carrageenan-Induced Paw Edema: This model assesses anti-inflammatory potential by inducing localized inflammation in rodent paws. Reduction in paw swelling after *Argyreia nervosa* administration is indicative of anti-inflammatory activity.[108]

1.4 Stress and Adaptogenic Models

1.4.1. Chronic Mild Stress (CMS) Model: Rodents are subjected to mild, unpredictable stressors over several weeks, inducing depression-like behavior and elevated corticosterone levels. Treatment with *A. nervosa* reverses behavioral deficits and normalizes HPA axis function, validating adaptogenic effects.[109]

1.4.2. Restraint Stress Model: Animals are physically restrained for a defined period to induce acute stress. Seed extracts reduce stress-induced physiological and behavioral changes.[110]

2. In Vitro Experimental Methods

In vitro models complement in vivo studies by providing mechanistic insights at the cellular and molecular levels.

2.1 Antioxidant Assays

2.1.1. DPPH Radical Scavenging Assay: Measures the ability of *A. nervosa* extracts to donate hydrogen atoms or electrons to neutralize free radicals, quantified by a colorimetric change.[111]

2.1.2. Ferric Reducing Antioxidant Power (FRAP) Assay: Evaluates the reducing potential of extracts by measuring the reduction of ferric ions to ferrous form.[112]

2.1.3. Lipid Peroxidation Inhibition: Assesses protection against oxidative degradation of lipids, a marker of cellular oxidative damage.[113]

2.2 Anti-inflammatory Assays

2.2.1. Enzyme-Linked Immunosorbent Assay (ELISA): Quantifies pro-inflammatory cytokines (e.g., TNF-α, IL-6) in cultured macrophages or microglial cells treated with *A. nervosa* extracts after inflammatory stimulation.[114]

2.2.2. Nitric Oxide (NO) Production Assay: Measures NO levels in LPS-stimulated macrophages; inhibition indicates anti-inflammatory action.[115]

2.3 Neuroprotective Assays

2.3.1. Cell Viability and Cytotoxicity (MTT Assay): Evaluates neuronal cell survival following oxidative or toxic insult, with or without *A. nervosa* treatment.[116]

2.3.2. Reactive Oxygen Species (ROS) Measurement: Fluorescent probes quantify intracellular ROS levels to assess antioxidant protection.[117]

2.3.3. Apoptosis Assays: Techniques such as Annexin V staining and caspase activity measure anti-apoptotic effects of the extracts.[118]

3. Phytochemical Analysis Methods

Standardized phytochemical investigations ensure reproducibility and identification of active constituents.

3.1 High Performance Liquid Chromatography (HPLC): Separates and quantifies alkaloids, flavonoids, and phenolics.[119]

3.2 Gas Chromatography-Mass Spectrometry (GC-MS): Used to identify volatile and semi-volatile phytochemicals in seed extracts.[120]

3.3 Fourier Transform Infrared Spectroscopy (FTIR): Characterizes functional groups of bioactive compounds.[121]

4. Toxicological Evaluations

Toxicity studies determine the safety margin of *Argyreia nervosa* extracts.

4.1 Acute Toxicity Tests: Single high-dose administration with observation for mortality and behavioral abnormalities over 14 days.[122]

4.2 Sub-chronic Toxicity: Repeated dosing for 28-90 days to assess long-term safety, examining hematological, biochemical, and histopathological parameters.[123]

VI. RESULT AND DISCUSSION

The pharmacological evaluation of *Argyreia nervosa* seeds reveals significant promise as a natural antidepressant agent, supported by a convergence of behavioral, biochemical, and mechanistic data derived from preclinical models. This discussion synthesizes key findings, explores underlying mechanisms, and highlights future research directions.

1. Behavioral Evidence of Antidepressant Activity

Rodent behavioral paradigms consistently demonstrate that *Argyreia nervosa* seed extracts exhibit antidepressant-like effects. Reduced immobility in the Forced Swim Test (FST) and Tail Suspension Test (TST) strongly indicates a reversal of behavioral despair commonly linked to depressive states in humans[124]. Such findings corroborate the traditional use of *A. nervosa* in Ayurveda for mood disorders[125]. It suggest a broader spectrum of central nervous system (CNS) modulation beyond depression, potentially addressing comorbid anxiety symptoms often accompanying depression[126].

The cognitive-enhancing properties demonstrated through improved performance in the Morris Water Maze (MWM) and Passive Avoidance Test further emphasize the neuroprotective role of *Argyreia nervosa*. Depression is frequently associated with impaired memory and cognitive deficits, possibly mediated by hippocampal dysfunction[127]. The ability of *A. nervosa* to improve spatial and associative learning underscores its therapeutic potential in mitigating cognitive decline linked to depressive disorders.

2. Mechanistic Insights: Neurotransmitter Modulation

The antidepressant effects of *Argyreia nervosa* are hypothesized to stem from its influence on key neurotransmitter systems. Monoaminergic pathways, including serotonergic, dopaminergic, and noradrenergic systems, play central roles in mood regulation[128]. Several studies demonstrate that *Argyreia nervosa* seed extracts increase brain levels of serotonin (5-HT), dopamine, and norepinephrine, paralleling the pharmacodynamics of conventional antidepressants[129]. This monoamine reuptake inhibition or enhanced neurotransmitter release could explain the behavioral outcomes observed.

Moreover, the presence of bioactive alkaloids and flavonoids, such as ergoline derivatives, may contribute to serotonin receptor modulation, particularly 5-HT1A receptor agonism, which is implicated in anxiolytic and antidepressant effects[130]. These phytoconstituents might also inhibit monoamine oxidase enzymes, preventing neurotransmitter breakdown and enhancing synaptic availability[131].

3. Antioxidant and Anti-inflammatory Contributions

Increasing evidence links oxidative stress and neuroinflammation to the pathophysiology of depression[132]. Excessive reactive oxygen species (ROS) generation and pro-inflammatory cytokine release can impair neurogenesis, synaptic plasticity, and neurotransmitter function[133]. In this context, the potent antioxidant activity of *Argyreia nervosa* seed extracts, demonstrated by DPPH radical scavenging, FRAP assays, and lipid peroxidation inhibition, likely protects neuronal integrity[134].

Furthermore, the observed suppression of pro-inflammatory cytokines such as TNF-α and IL-6 in both in vitro and in vivo models indicates significant anti-inflammatory potential[135]. By mitigating neuroinflammation, *Argyreia nervosa* may alleviate depressive symptoms linked to chronic inflammatory states. This dual antioxidant and anti-inflammatory mechanism aligns with emerging paradigms that view depression as a neuroimmune disorder[136].

4. Adaptogenic Effects and Stress Response Modulation

Chronic stress is a well-known precipitant of depression, primarily through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis[137]. The ability of *Argyreia nervosa* to normalize corticosterone levels and reverse stress-induced behavioral deficits in chronic mild stress and restraint stress models supports its adaptogenic properties[138]. Adaptogens enhance the body's resistance to physical, chemical, and biological stressors, thereby restoring homeostasis[139].

By modulating the HPA axis, *Argyreia nervosa* may prevent the maladaptive responses that contribute to depression onset and progression. This property complements its direct neurotransmitter effects, providing a holistic approach to mood regulation.

5. Safety and Toxicological Considerations

Toxicological evaluations show that *Argyreia nervosa* seed extracts possess a wide safety margin in acute and sub-chronic administration[140]. No significant alterations in hematological, biochemical, or histopathological parameters were observed at therapeutic doses, indicating low systemic toxicity. However, careful dose optimization is necessary given the presence of potent bioactive alkaloids, some of which may have central nervous system stimulant effects at high doses[141].

6. Limitations and Future Directions

While preclinical data are encouraging, several limitations must be addressed. Most studies utilize crude extracts with variable phytochemical profiles, which complicates standardization and reproducibility[142]. Isolation and characterization of specific active compounds, followed by elucidation of their precise molecular targets, remain necessary. Additionally, long-term safety and efficacy studies, including chronic administration and withdrawal effects, are lacking.

Translation to human clinical trials is the ultimate goal. Investigating *Argyreia nervosa* in well-designed randomized controlled trials will confirm its therapeutic potential and inform dosing strategies. Furthermore, exploring synergistic effects with existing antidepressants could optimize treatment regimens.

VII. CONCLUSION AND FUTURE ASPECTS

The present review highlights the preclinical evidence supporting the antidepressant potential of *Argyreia nervosa* seeds, a traditional medicinal plant with deep roots in Ayurveda and ethnomedicine. Findings from multiple animal models, pharmacological assessments, and biochemical investigations underscore its relevance as a natural therapeutic agent in managing depression and related neurobehavioral disorders.

The psychotropic properties of *Argyreia nervosa* are largely attributed to its diverse phytochemical profile, particularly ergoline alkaloids, flavonoids, glycosides, and phenolic compounds. These constituents act through multifaceted mechanisms—modulation of monoaminergic neurotransmitters, inhibition of oxidative stress, attenuation of neuroinflammation, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis[143]. Behavioral tests in male Swiss albino mice consistently show improvements in depression-like and anxiety-like symptoms when treated with standardized extracts of *A. nervosa*, validating its adaptogenic and CNS-acting effects[144].

Moreover, studies suggest that the plant enhances cognition and memory, which may be beneficial in treating depression-related cognitive deficits^[145]. This effect, combined with its antioxidant and anti-inflammatory properties, places *Argyreia nervosa* in a unique position among herbal remedies, potentially offering broad-spectrum neurotherapeutic benefits[146].

Despite these encouraging findings, current research is largely limited to preclinical studies using crude extracts. This restricts reproducibility and hinders our ability to attribute observed effects to specific bioactive compounds. Furthermore, the exact molecular targets, pharmacokinetics, and long-term safety of these extracts remain inadequately explored[147].

To ensure clinical translation and therapeutic utility, future research should prioritize the following aspects:

1. **Isolation and Characterization of Active Constituents:**
   Rigorous phytochemical investigations are required to isolate the specific alkaloids, flavonoids, or phenolic compounds responsible for the antidepressant effects. These isolated compounds can be subjected to in vitro receptor-binding studies and in vivo pharmacological testing[148]
2. **Mechanistic and Molecular Studies:**
   Detailed mechanistic studies at the cellular and molecular level—including gene expression analyses, receptor affinity profiling, and neurotransmitter quantification—are essential to fully understand how *Argyreia nervosa* influences brain function and mood regulation[149]
3. **Standardization of Extracts and Dosage Forms:**
   Standardizing the composition and dosage of extracts is crucial for ensuring reproducibility across studies. Development of standardized extracts with known concentrations of key constituents will support the preparation of consistent and effective herbal formulations[150]
4. **Chronic and Long-Term Toxicity Studies:**
   While acute and sub-acute toxicity data appear favorable, chronic administration and reproductive toxicity studies are necessary to evaluate long-term safety. This is particularly important if *Argyreia nervosa* is to be considered for long-term use in psychiatric settings[151]
5. **Clinical Trials:**
   Transitioning from animal models to human studies is a critical next step. Controlled clinical trials must be designed to assess efficacy, safety, and tolerability of *Argyreia nervosa* extracts in patients with major depressive disorder, mild-to-moderate depression, or treatment-resistant depression[152]
6. **Synergistic Potential with Existing Therapies:**
   Exploring synergistic effects of *Argyreia nervosa* in combination with conventional antidepressants may reveal additive or potentiating effects, potentially enabling lower doses of synthetic drugs and reducing side effects[153]
7. **Neuroprotective and Preventive Potential:**
   Given its antioxidant and anti-inflammatory effects, *Argyreia nervosa* may also have a role in neuroprotection and preventive psychiatry, especially in populations at risk of developing depression due to stress, neurodegenerative conditions, or chronic illness[154]

In conclusion, *Argyreia nervosa* seeds present a compelling case for further research and development as a natural antidepressant. With proper scientific validation and clinical evaluation, this traditional botanical could emerge as a safe and effective alternative or adjunctive therapy for managing depression and promoting mental well-being.

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