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ROLE OF HERBAL TRANSDERMAL PATCHES IN ALZHEIMER'S DISEASE

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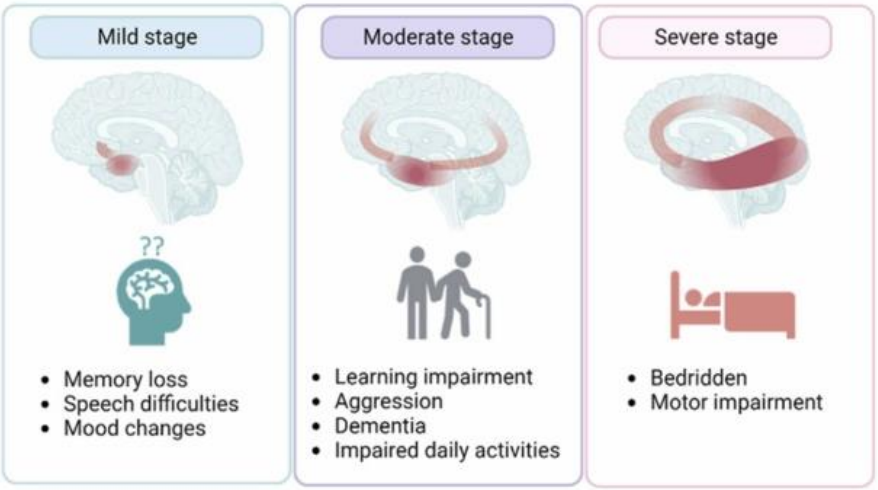
ABSTRACT

Alzheimer's disease (AD) is a progressive chronic neurodegenerative disease of the brain named after German physician Aloes Alzheimer, who first described it in 1906.[22] Alzheimer's is the most common form of dementia and affects an estimated 10 million people worldwide. It play an increasingly important role both socially and financially in the aging populations. It is a neurological disease where amyloid-beta (Aβ) plaques and neurofibrillary tangles are formed inside the brain. It is also characterized by progressive memory loss, depression, neuroinflammation, and derangement of other neurotransmitters.[22] The most common form of dementia is AD, which demolishes the vital brain cells, causing trouble with memory, thinking, and behavior, brutal enough to affect work, lifelong hobbies, and social life. Recognized factors in Alzheimer's disease include acetylcholine deficiency, free radicals, and inflammation of the brain tissue. Many of the current drugs taken to treat the disease, such as, donepezil, have unpleasant side effects and doctors are keen to find alternatives. There is no cure for Alzheimer's disease, but symptomatic treatment may improve the memory and other dementia related problems. The objective here is to provide a systematic review of the ongoing evidence pertaining to the use of medicinal herbs in the treatment of Alzheimer's disease (AD) and its associated symptoms.[22] Traditional medicine is practiced worldwide as memory enhancer since ancient times. Natural therapy including herbs and medicinal plants has been used in the treatment since a long time. Natural compounds have been investigated as an alternative therapy for their ability to treat Alzheimer's disease (AD). Traditional herbs and formulations which are used in the Indian ayurvedic system are rich sources of antioxidant, anti-amyloidogenic, neuroprotective, and anti-inflammatory compounds. They promote quality of life by improving cognitive memory and rejuvenating brain functioning through neurogenesis. A rich knowledge base of traditional herbal plants (Turmeric, Gingko, Ashwagandha, Shankhpushpi, Giloy, Gotu kola, Garlic, Tulsi, Ginger, and Cinnamon) combined with modern science could suggest new functional leads for Alzheimer's drug discovery. The oral administration of treating AD has had some drawbacks that decrease the medication adherence and efficacy of the therapy. Transdermal drugs are proposed as an alternative remedy to overcome the disadvantages of current pharmaceutical dosage options for this chronic disorder. They could have different strengths, such as offering a stable diffusion of active substance, avoiding the first pass metabolism, and reducing system adverse reactions. In this article Ayurveda, the ancient Indian herbal medicine system based on multiple clinical and experimental, evidence have been reviewed for treating AD and improving brain functioning. The main objective of this research is to provide a systematic review of herbal drugs that are easily accessible and effective for the treatment of AD and also reviews the technical principles, novel techniques of transdermal delivery drug, and prospects for future development for the management of cognitive and behavioral dysfunctions in AD patients.

KEYWORDS: Alzheimer's disease, Pathogenesis of Alzheimer's Disease, Transdermal patches, Herbal transdermal patches, Ashwagandha *(Withania somnifera),* Praparation and Extraction methods.

INTRODUCTION

Alzheimer's disease (AD) causes permanent damage to neurons. The hallmark features of Alzheimer's disease includes the formation of intracellular neurofibrillary tangles, senile plaques, and loss of neuronal synapses and pyramidal neurons inside the brain.[1] These changes lead to the emergence of the characteristic Alzheimer's disease symptoms, which include progressive and gross cognitive impairment and frequent behavioral disorders like depression, anxiety, aggression, and wandering.[2] The most common early symptom is complexity in remembering recent events (short term memory loss). As the disease advances, symptoms can include: problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self-care, and behavioural issues. As a person's condition declines they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. The entorhinal cortex and hippocampus are the foremost areas of the brain where Alzheimer's disease damages neuronal connections. Later on, it affects areas of the cerebral cortex that controls social interaction, language, and logic.Every part of cerebral cortex is involved, the occipital pole may be less affected in the great majority of patients. The cortical ribbon could be thinned, and the temporal horn shows obvious signs of ventricular dilatation due to atrophy of the amygdala and hippocampus.



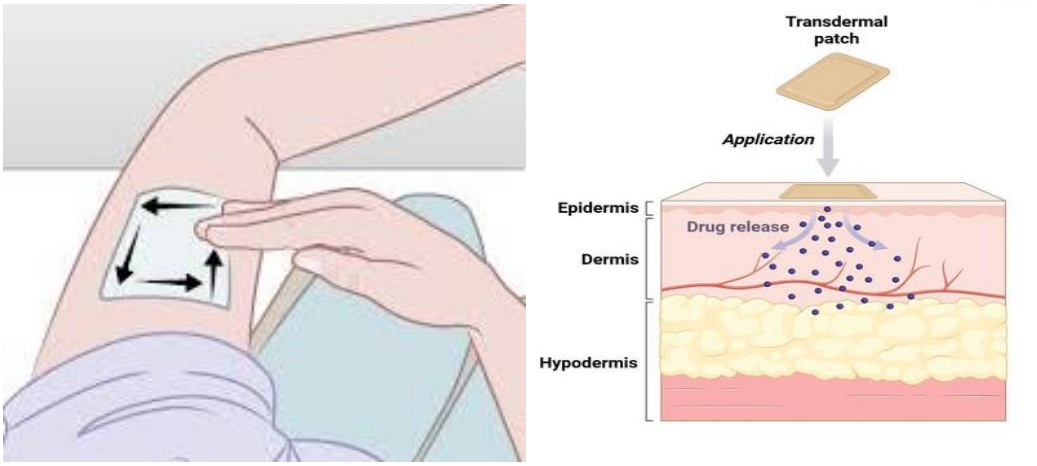
The main neuropathological hallmarks are the extraneuronal senile plaques and intraneuronal neurofibrillary tangles. Loss of neuronal synapses and neuronal death results due to decrease in acetylcholine and other neurotransmitters. Amyloid plaques and neurofibrillary tangles are both clearly visible under the microscope. AD can be characterized by gross diffuse atrophy of the brain, along with the loss of neurons, neuronal processes, and synapses in the cerebral cortex and certain subcortical regions, resulting in degeneration of the temporal lobes, parietal lobes, parts of the frontal cortex, and cingulated gyrus. Levels of some neurotransmitters, such as acetylcholine, serotonin, norepinephrine, somatostatin, and corticotropin-releasing factors, are reduced while the glutamate level is usually elevated. Accordingly, the affected people suffer from cognitive decline, memory impairment, difficulties in decision-making, and behavioral changes.

Dementia is often associated with progressive deterioration of intellectual function. It affects individuals over a gradual period of time followed by their lost ability to live and function independently.[2-3] AD is one of the most common neurodegenerative disorders observed in more than 80% dementia patients in geriatric population.[8-9] Because of increasing of life standards over the next decades, the number of Alzheimer victims will grow up from 47 million

patients now to 130 million by 2050. Due to the report of World Alzheimer, $818 billion was the social and economic cost for dementia in 2015, and it was estimated to rise to 1 trillion by 2018.[10-11]

Approximately 5 million new cases of dementia are diagnosed every year, affecting more than 25 million people worldwide, the majority of whom have AD.[4-5] Since AD is age-specific and is directly correlated with age its prevalence doubles by 5 years after the age of 65. In the past few years, a lot of interest has been shown in the epidemiologic study of dementia and AD in underdeveloped and developing nations. In Europe, the combined incidence rate of AD among those 65 and older was 19.4 per 1000 person-years. In the US, according to the combined data from two large, community-based studies, the incidence rate for AD was 15 per 1000 person-years for people aged 65+.[6-7]

Currently, There are five drugs which were approved by the Food and Drug Administration (FDA) for of AD: Tacrine, rivastigmine ,donepezil, and galantamine as cholinesterase inhibitors therapy and memantine as noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist.[12] These substances are mostly available in oral administration. Many disadvantages were reported, for example, the current dosage forms as high doses cause adverse reactions such as abdominal pain, nausea, vomiting, anorexia, and abdominal pain,[13] the poor medication adherence due to characteristics of disease with the age group,[14] low compliance because of high incidence of dysphagia and memory loss,[15-16] and variation of blood levels of drugs. Besides, other effects such as hepatotoxicity, renal failure, asthenia, or malaise often lead to discontinuation of treatment in affected people.[17]



Fortunately, transdermal delivery systems could be the solution for these drawbacks, and it could be an advantage as a novel therapeutic approach. Transdermal patches are an attractive alternative to conventional dosage forms based on oral and parenteral routes. They can control the concentration of the drug in plasma, reduce the frequency of drug administration, improve the bioavailability of the drug, and be easily applied to the skin and is particularly useful for patients with discomfort in swallowing.

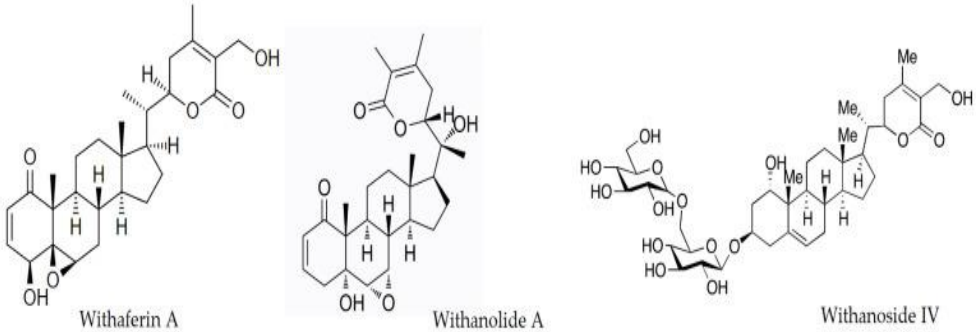
Transdermal patches would improve patient compliance as well as the benefit in prolonged use of drugs and preferred by caregiver during long-term treatment of disease. In addition, transdermal patches avoid the first-pass metabolism because drugs are absorbed directly into the blood through the skin to enable use at low doses and circadian cholinergic rhythms would be unaffected. Drug uptake into blood circulation can be easily stopped by removing the patches from the skin. Thus, transdermal patches are more accepted nowadays than oral and parenteral administration.

Numerous herbs with advantageous neurochemical constituents have also been discovered, such as plant molecules with anti-neurodegenerative or neuroprotective properties.[18] Studies have shown that Indian ayurveda had used medicinal plants for improving memory and rejuvenating brain cells since very ancient times. These herbs improve brain activity by enhancing anti-inflammatory and anti-amyloidogenic properties. Several well-known medicinal plants that have been extensively researched by scientists for their nootropic benefits are *Curcuma longa* (Turmeric), *Ginkgo biloba*, *Withania somnifera* (Ashwagandha), *Convolvulus pluricaulis* (Shankhpushpi), *Tinospora cordifolia* (Giloy), *Centella asiatica* (Gotu kola), *Allium sativum Linn* (Garlic), *Ocimum sanctum Linn* (Tulsi), *Zingiber officinale* (Ginger), *Cinnamon zeylanicum* (Cinnamon) *and Azadirachta indica* (Neem).

Ashwagandha *(Withania somnifera)*

The first aim of this study was to prepare herbal extracts from one of the traditional well-known Indian medicinal plant is Ashwagandha *(Withania somnifera)* which is a common ingredient of several Ayurvedic formulations marketed for the treatment of neurological disorders and to explore and evaluate the literature pertaining to the role of Ashwagandha in neurological disorders.

Ashwagandha belongs to the family Solanaceae. Other common names of Ashwagandha are Indian ginseng, poison gooseberry and winter cherry. Ashwagandha is cultivated in North western and central part of India. In India Madhya Pradesh, Gujarat, Haryana, Maharashtra, Punjab, Rajasthan and Uttar Pradesh are the main producing state of Ashwagandha. It is also found in Nepal, China and Yemen. The climatic conditions required for the cultivation of Ashwagandha include an altitude of 1500 m above the sea level. The semi tropical regions which receive about 500–800 mm annual rainfall are the best suited for its cultivation. The crops require dry condition during growing periods and optimum temperature required for its cultivation is 20–38 °C. The sandy loam or light red soil and partial shade sun are other suitable factors for its growth. The extract of roots contains steroidal lactones with ergostane, which contain withanone, withaferin, withanolides, sitoindosides and about 0.2% alkaloids.



Chemical structures of the main active compounds present in Ashwagandha *(Withania somnifera)* root.[21]

Various studies have been conducted on active phytoconstituents which helps in providing a rationale background for drug design with upgraded and better pharmacological properties. Ashwagandha modulates the brain oxidative stress makers, such as superoxide dismutase (SOD), catalase, lipid peroxidation (LPO), and non-enzymatic antioxidants like glutathione (GSH). The roots and its extract induce axon and dendrite outgrowth, proposing its possible effect on neuronal regeneration. Ashwagandha on the basis of phyto-pharmacological studies proved potential as anti-inflammatory, anti-oxidant, anti-cancer, anti-microbial, anti-malarial, diuretic, sedative, immumonodulatory and cardioprotective properties.

Therefore, it is envisaged that transdermal patches bearing Ashwagandha can overcome most of demerits of conventional delivery and will be able to release the drug at predetermined rate into systemic circulation for a prolong period of time, thereby minimizing its adverse effect and improving patient compliance.

Key potential advantages and mechanisms include

- Reduced Amyloid-Beta (Aβ) Plaques: Ashwagandha extracts have been shown in animal models to reduce the burden of Aβ plaques in the brain. One proposed mechanism involves increasing a protein in the liver (low-density lipoprotein receptor-related protein, or LRP) which helps clear Aβ from the brain into the periphery.
- Anti-Inflammatory Effects: Ashwagandha's active compounds, particularly withaferin A, exhibit potent anti-inflammatory properties by modulating immune responses and
  lowering pro-inflammatory markers. This helps to counter chronic neuroinflammation, a major contributor to AD progression and cognitive decline.
- Antioxidant Activity: Ashwagandha is a powerful antioxidant, scavenging free radicals that cause cellular damage and contribute to oxidative stress in the brain. This protective effect shields neurons and helps maintain mitochondrial function.
- Inhibition of Acetylcholinesterase (AChE): Some compounds in Ashwagandha, such as withanolide-A, have been shown to inhibit the AChE enzyme, a mechanism similar to some conventional AD medications. This action increases levels of acetylcholine, a neurotransmitter important for memory and cognition.

Key Disadvantages and Risks

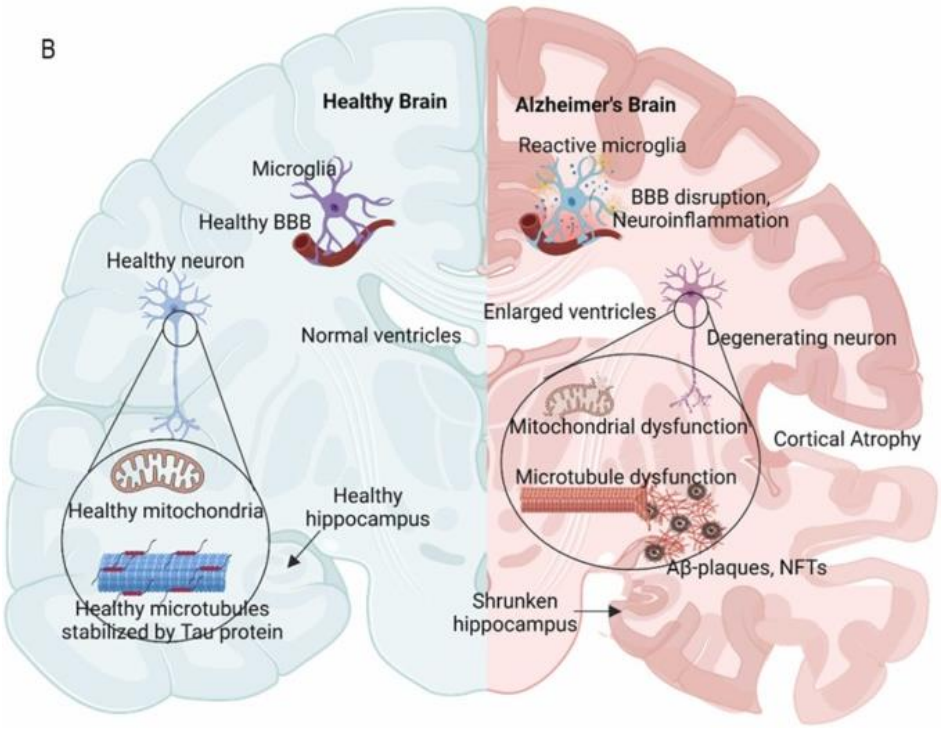
- Drug Interactions: Ashwagandha can interact with several types of medications commonly prescribed for older adults, including those that may be used by Alzheimer's patients:
  - Sedatives/Anti-anxiety medications: Ashwagandha has mild sedative properties and can intensify the effects of central nervous system (CNS) depressants, leading to excessive drowsiness or breathing problems.
  - Medications for high blood pressure: It may lower blood pressure, which can be risky if taken with antihypertensive drugs, potentially causing blood pressure to drop too low.
  - Medications for diabetes: Ashwagandha may lower blood sugar levels, increasing the risk of hypoglycemia if combined with diabetes medications.
  - Thyroid hormone medications: It can increase thyroid hormone levels, which could lead to too much hormone in the body if taken with thyroid supplements.
  - Immunosuppressants: Ashwagandha might cause the immune system to become more active, potentially decreasing the effects of medications used to suppress the immune system.

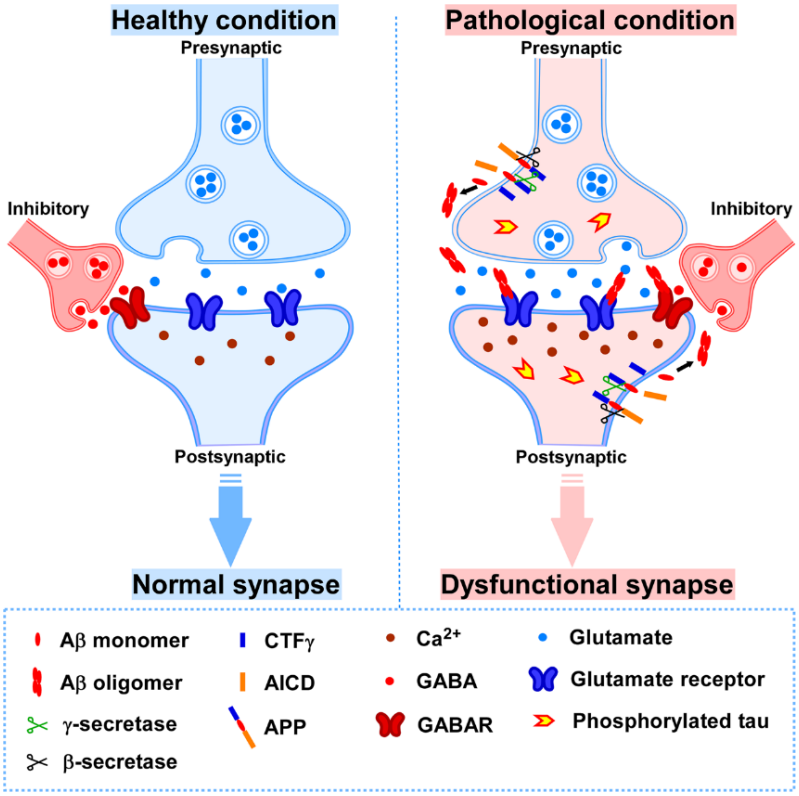
- Common Side Effects: Potential side effects, particularly at high doses, could be problematic for an elderly person with cognitive impairment:
  - Gastrointestinal Issues: Nausea, stomach upset, diarrhea, and vomiting are possible, which could exacerbate existing digestive problems or lead to dehydration.
  - Drowsiness/Dizziness: Its calming effect can cause excessive sleepiness, which might increase the risk of falls or interfere with daily activities and monitoring.
- Lack of Human Clinical Evidence: While animal and in vitro studies on ashwagandha's effect on beta-amyloid plaques (a hallmark of Alzheimer's) are promising, there is currently insufficient data from human clinical trials to confirm its safety or efficacy for preventing or treating Alzheimer's disease or dementia in people. The long-term safety of ashwagandha use in humans is not well-known beyond short-term (up to 3 months) use.
- Potential Liver Damage: Although rare, cases of liver injury have been linked to ashwagandha supplements, a risk factor to consider, especially if the individual has pre-existing liver conditions or takes other medications metabolized by the liver.
- Quality Control Issues: The supplement market is not strictly regulated by the FDA, meaning product quality and the presence of potential contaminants (like heavy metals) can vary, posing an additional risk.

  Therefore, it is envisaged that transdermal patches bearing Ashwagandha can overcome most of demerits of conventional delivery and will be able to release the drug at predetermined rate into systemic circulation for a prolong period of time, thereby minimizing its adverse effect and improving patient compliance

Pathogenesis of Alzheimer's Disease

Alzheimer's disease results from the accumulation of amyloid-β plaques and neurofibrillary tangles, particularly in the hippocampus. It is classified into familial AD (FAD), caused by mutations in **APP, PSEN1, and PSEN2**, and sporadic AD (SAD), which arises from a complex interaction of aging, genetic, metabolic, and environmental factors. Multiple hypotheses and mechanisms have been proposed to explain AD pathology, reflecting its multifactorial nature.



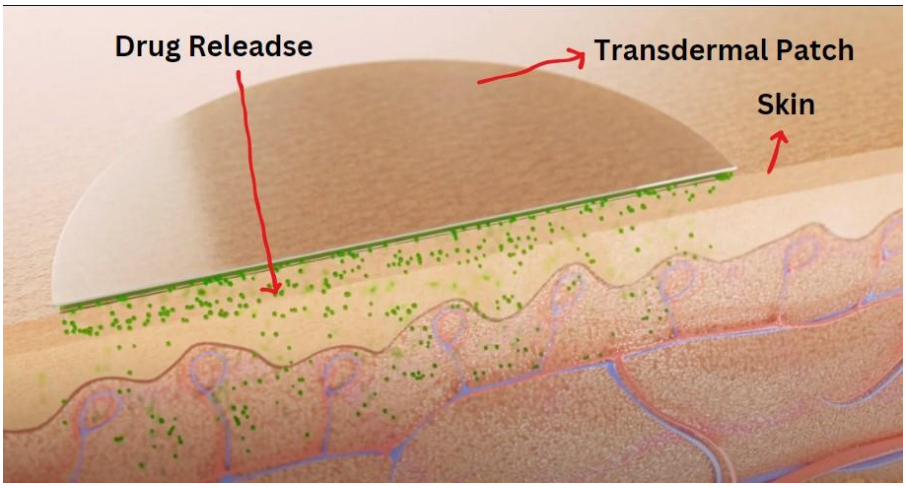


Transdermal delivery systems offer an effective solution to the limitations of oral and parenteral therapies. Transdermal patches provide controlled drug release, improve bioavailability, reduce dosing frequency, and are easy to use—especially for patients with swallowing difficulties. They also bypass first-pass metabolism, allow rapid discontinuation by removing the patch, and improve long-term patient compliance, making them a preferred option in chronic conditions like Alzheimer's disease.

Many medicinal herbs with neuroprotective and anti-neurodegenerative properties have been traditionally used in Ayurveda to enhance memory and support brain function. Key plants studied for their nootropic, anti-inflammatory, and anti-amyloidogenic effects include Turmeric, Ginkgo biloba, Ashwagandha, Shankhpushpi, Giloy, Gotu Kola, Garlic, Tulsi, Ginger, Cinnamon, and Neem.

PLAN OF WORK

Herbal transdermal patches are being used as an interesting alternative to provide controlled release of active compounds when applied to the skin. When natural herbal ingredients are used in their formula, herbal transdermal patches can help to maintain youthful and healthy skin. The human skin acts as a partition membrane to create a barrier that controls the release and absorption of a drug when it is accumulated on the skin; the drug in a topical or dermal patch shows only limited penetration of the tissue below the skin, whereas the drug in a transdermal patch enters into the circulatory system through the skin. Natural products have been broadly exploited as an important source for medicine. A large number of medicines are derived from plant-based extractions and fractionation and, have great importance for humans. Nowadays, medical practitioners are more inclined towards natural medicines for a trustworthy treatment with cost effectiveness and lower incidence of side effect. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.



Transdermal Patch Design

Transportation of drug across the skin is affected by various factors, such as skin permeability, area, and duration of application, as well as metabolic activity of the skin (i.e., first pass metabolism). In fact, every drug has its unique properties, which can affect transdermal delivery. To achieve adequate skin absorption and penetration, the drug should be non-ionic and relatively lipophilic to cross the skin barrier. Molecules larger than 500 Daltons make it difficult to cross the stratum corneum, and ideally the therapeutic dose of the drug should also be less than 10 mg per day.

Choosing the Right Transdermal Patch

The factor that is required to keep in mind while choosing the Right Transdermal patch is there drug's properties, dosage requirements, duration of treatment, and patient-specific considerations.

How to Apply Transdermal Patches

Stepwise procedures for applying these Patches are as Follow:

- The skin should be dry, clean, and Hair free
- Appling on the affected area i.e. back, chest (not over the heart), side of the waist, or upper arms.
- Read all the applying instructions provided on patches.
- Apply it by slightly pressing on the skin, and ensure proper adhesion.

Precaution: To prevent any skin irritation, rotate the site or apply near the previous area.

Potential Side Effects

While transdermal patches are the safest method. But sometimes it may cause side effects like; skin irritation, redness, or itching the skin. In some cases, the patient may feel an allergic reaction. So it is recommended to meet with your doctor/Pharmacist before applying itself on the skin.

Precautions and Safety Considerations

Following Precautions and Safety Considerations shall be kept in mind before it uses:

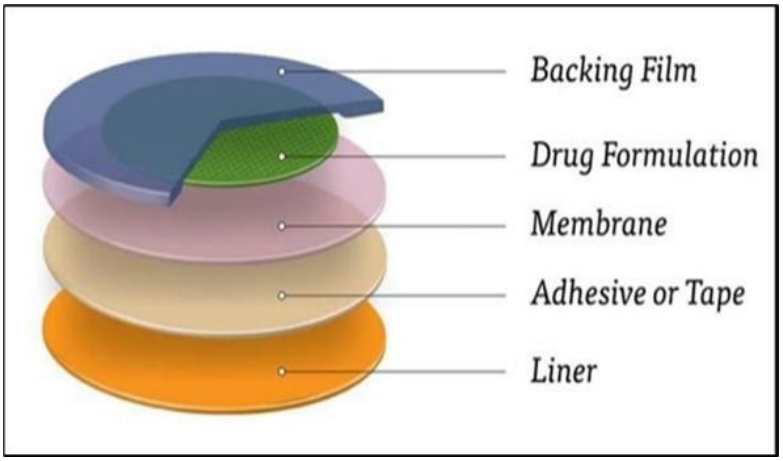
- Avoid applying patches to broken, damaged, or irritated skin.
- Inform a doctor about any allergies, medical conditions, or medications.
- Store patches properly, as per the storage instruction on the label.

Transdermal Patches vs. Other Delivery Methods

Transdermal patches have lots of advantages compared to other drug delivery methods. If you take oral medications that undergo digestion and may be affected by stomach acid, But in the case of transdermal patches, They by pass the gastrointestinal system, hence overall it improved drug bioavailability. Patches also help in the controlled release of drugs in the body, eliminating the need for frequent dosing or injections. They also help in reducing pain and discomfort for patients.

MATERIALS AND METHODS

The main components to a transdermal patch are polymer matrix, drug, permeation enhancers, adhesive, backing laminates, release liner, other excipients like plasticizers and solvents. The backing layer is the outermost layer of the patch and serves to protect the other layers from the environment. This layer is usually made of a flexible, waterproof material such as polyethylene or polypropylene. The adhesive layer serves to attach the patch to the skin and keep it in place. It usually consists of a strong, hypoallergenic adhesive that is gentle on the skin. The drug layer contains drugs that are delivered through the skin. It is formulated to release the drugs at a constant rate over a period of time. The rate-controlling membrane serves to control the rate at which the drugs are released from the patch. Membranes are usually made of semi-permeable materials that allow the drugs to pass through the membrane at a controlled rate. Linen acts as a protector for the patch and adhesive. The patch must be removed before being applied to the skin surface.



Basic Components of TDDS

- Polymer matrix/drug reservoir
- Membrane
- Drug Permeation enhancers
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

1. Polymer matrix/drug reservoir[20]

- Polymers are the backbone of TDDS, which control the release of the drug from the device. A polymer matrix can be prepared by dispersion of drug in a liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system, such as

penetration enhancers and PSAs. Additionally, they should provide consistent and effective delivery of a drug throughout the product's intended shelf-life, and should be safe. The following criteria should be preferred in selecting the polymer to be used in the transdermal system

(i) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it

(ii) The polymer should be stable, nonreactive with the drug, easily manufactured and fabricated into the desired product, and should be inexpensive.

(iii) The polymer and its degradation products must be nontoxic or non antagonistic to the host.

(iv) The mechanical properties of the polymer should not deteriorate excessively when large amounts of active ingredients are incorporated into it.

2. Membrane

- A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin. For example, ethylene vinyl acetate, silicone rubber, polyurethrane, etc. are used as a rate-controlling membrane.

3. Drug

- For successfully developing a TDDS, the drug should be chosen with great care. Transdermal patches offer many advantages to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic window or drugs with a short half-life, which cause noncompliance due to frequent dosing.

4. Permeation enhancers

- One long-standing approach for improving TDD uses penetration enhancers (also called sorption promoters or accelerants), which increase the permeability of the SC so as to attain higher therapeutic levels of the drug candidate. Penetration enhancers interact with structural components of the SC thus modifying the barrier functions, leading to increased permeability.[20] Three pathways are suggested for drug penetration through the skin: polar, nonpolar and polar/nonpolar. The enhancers act by altering one of these pathways
- The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the SC. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as
  (1) Chemical
  (2) Physical methods of enhancement.

5. Backing membrane

- Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyethylene, polypropylene , or polyesters . Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester.

Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability.

- In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate. Examples of some backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Ethylene-vinyl acetate, Aluminized plastic laminate.

6. Release Liner

- Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically,[20] it consists of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer of silicon.

7. Other excipients

- Various solvents such as water, ethanol, isopropylmy-ristate, isopropyl alcohol, and dichloromethane are used alone or in combination to prepare the drug reservoir Propylene glycol, ethanol are used as co solvents along with the permeation en-hancer. Plasticizers like diethyl phthalate, dibutylpthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudraflex and propylene glycol provide plasticity to the trans-dermal patch.[20]

Basic Component of Transdermal Patch

Transdermal patches typically consist of several layers that are designed to deliver the medication through the skin and into the bloodstream. illustrates the basic component of a medicated patch. The specific composition and structure of the patch may vary depending on the drug being delivered and the desired rate of drug release.

Types of Transdermal Patches

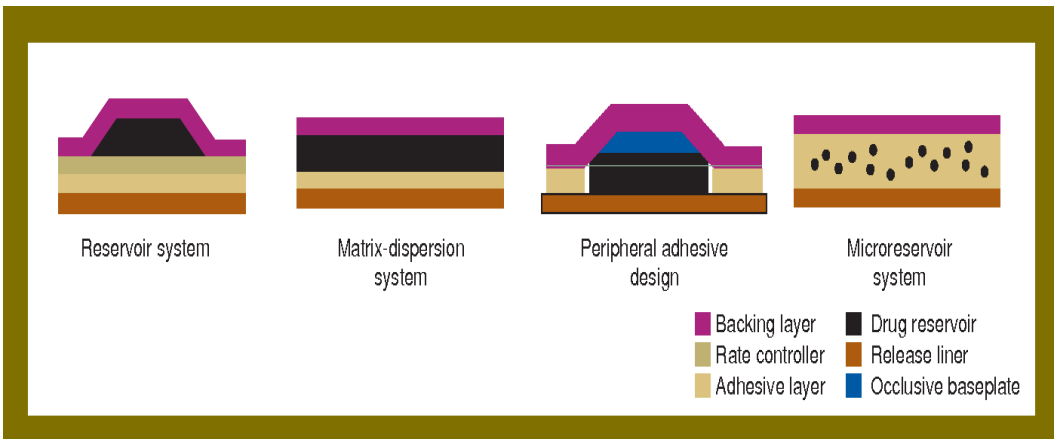
In general, there are four main type of transdermal medical patches. Most commercially available patches are categorized as reservoir or matrix systems.

(A) drug-in adhesive system

(B) Reservoir system

(C) matrix system

(D) Micro-reservoir system.



1. Drug-in-Adhesive System

This is the simplest form of membrane permeation control system. The adhesive layer in this system contains drugs and serves to glue the different layers together. The drug mixture is sandwiched between the liner and backing.

2. Reservoir System

In this system, the drug reservoir is held between the backing layer and the rate-controlling membrane, and the drug is released through the microporous rate-controlling membrane. The drug can be in solution, suspension, or gel form, or can be dispersed in a solid polymer matrix within the reservoir chamber.

3. Matrix System

Drugs are uniformly dispersed in hydrophilic or lipophilic polymer matrices. The resulting drug-containing polymer is affixed to drug-containing discs of controlled thickness and surface area.

4. Micro-Reservoir System

This system is a combination of reservoir and matrix dispersion system. Here, the drug is prepared by first suspending drug solids in an aqueous solution of a water-soluble liquid polymer and then uniformly dispersing the solution in a lipophilic polymer to create thousands of non-leaching microscopic drug reservoirs.

5. Microneedle-Based Patches

There are several types of microneedles, each with unique features and characteristics. Overall, four major types of microneedle-based patches have been developed, namely solid, hollow, dissolving, and coated microneedle. The choice of microneedle type depends on the specific application and requirements of the user.

The herbal transdermal patches by incorporating an extract of the plant in the matrix layer of polymer film. The polymer matrix film is an important constituent of herbal transdermal patches because it may be used to control the release behavior of the drug. Its ideal characteristics are ease of film formation, biocompatibility, and biodegradability; in particular, it must be compatible with the drug and safe for humans. A previous study prepared and optimized a polymer matrix film and predicted its properties, such as thickness, weight variable, folding endurance, swelling ratio, and moisture content.

METHOD[19]

Part 1: Preparation of Ashwagandha Extract

The most effective method for topical application involves a hydroalcoholic extraction to obtain the active compounds (withanolides and alkaloids).

Ingredients

- Dried Ashwagandha roots (powdered)
- Ethanol or methanol
- Distilled water

Method (Maceration)

1. **Powder the Roots:** Grind dried Ashwagandha roots into a fine powder.

2. **Maceration:** Soak the powder in a hydroalcoholic solvent mixture . A mixture of ashwagandha and methanol in ratio 1:2 (w/v).
3. **Soak:** Place the mixture in a sealed container (100gm of crushed ashwagandha root was soaked in 200ml of methanol). let it stand at room temperature for 7 days, shaking it frequently to ensure the soluble matter dissolves.
4. **Filter:** After 7 Days Filter the mixture using a muslin cloth or filter paper to separate the liquid extract from the solid residue.
5. **Evaporate Solvent:** Gently evaporate the solvent (using a low-heat method like a water bath to avoid damaging the active ingredients) to obtain a concentrated, semi-solid, or powdered extract. This is your active ingredient for the cream or gel.[19]

Part 2: Formulation of the Gel

The following methods outline how to incorporate the extract into a base. A typical effective concentration of Ashwagandha extract in the final product is around **10%**.

Method A: Ashwagandha Gel

Ingredients

- Ashwagandha extract (prepared in Part 1)
- Carbopol 940 (a common gelling agent): 0.5–1% w/w
- Distilled water: q.s. (quantity sufficient)
- Glycerin and/or Propylene glycol (humectants and extract solvents)
- Triethanolamine (TEA) (for pH adjustment and gelling)
- Preservatives(e.g. Methylparaben, Propylparaben, or a natural alternative)

Procedure

1. **Prepare Gel Base:** Disperse the Carbopol 940 in distilled water and stir continuously. Allow it to swell and hydrate for 1-2 hours (or overnight) until a homogenous mass forms.
2. **Add Humectants:** Mix in the glycerin and propylene glycol gently.
3. **Incorporate Extract and Preservatives:** Dissolve your Ashwagandha extract and preservatives in a small amount of propylene glycol or ethanol first. Slowly add this solution to the gel base with continuous stirring.
4. **Adjust pH and Gel:** Gradually add Triethanolamine (drop by drop) to adjust the pH to a skin-compatible range of **5.5–6.0**. This step also causes the Carbopol to gel, forming the final product consistency.
5. **Packaging:** Transfer the finished gel to a clean container and store at room temperature.

Formulation Table[19]

Sr.no	Ingredients	Quantity	%percentage	Function
1	Ashwagandha	0.30 g	2.0%	Antibacterial, antioxidant
2	Carbopol 943	0.15 g	1.0%	Gelling agent
3	Methyl paraben	0.03 g	0.2%	Preservative
4	Propyleneglycol	0.75 ml	5.0%	Moisturize
5	Triethanolamine	1-2 drops	q.s	pH adjuster
6	Glycerine	0.75 ml	5.0%	Humactant
7	Distilled water	13.02 ml	q.s to 100%	Vehicle

Key Characteristics of the API for TDDS

Not all APIs are suitable for transdermal delivery. Ideal APIs typically possess specific physicochemical properties:

- **Low Molecular Weight:** Ideally less than 500 Daltons, to effectively permeate the stratum corneum (the skin's primary barrier).
- **Potency:** Effective in small doses, generally less than 10-20 mg per day.
- **Balanced Solubility:** Sufficiently soluble in both lipid and water to pass through the various skin layers. The optimal log partition coefficient (logP) is typically between 1 and 3.
- **Short Half-Life:** Useful for APIs with a short half-life, as the TDDS provides prolonged, consistent administration, avoiding peaks and troughs in blood concentration.

RESULT AND DISCUSSION

This review evaluates the existing evidence on the role of **herbal medicines** and **transdermal drug delivery systems (TDDS)** in the management of Alzheimer's disease (AD). The combined analysis of traditional medicinal plants, modern phytochemical research, and transdermal technologies suggests that herbal transdermal patches hold substantial promise as an alternative therapeutic strategy. The findings indicate improvements in cognitive function, reduced neuroinflammation, enhanced antioxidant activity, minimized hepatic metabolism, increased patient compliance, and sustained drug release. Additionally, integrating Ayurveda-based herbs with modern transdermal technologies may provide a synergistic approach for managing AD.

Herbal Approaches in AD Management

1. Evidence from Traditional Medicine

Ayurvedic and traditional medicine systems have long emphasized the use of herbs for improving memory, focus, cognitive clarity, and brain rejuvenation. Herbs such as Curcuma longa, Ginkgo biloba, Ashwagandha, Shankhpushpi, Gotu Kola, Giloy, Tulsi, Ginger, Garlic, Cinnamon, and Neem are repeatedly mentioned in ancient texts like Charaka Samhita and Sushruta Samhita for their role in enhancing mental faculties and slowing age-related cognitive decline.

A narrative review of classical Ayurvedic literature shows that these plants are categorized under medhya rasayana, meaning cognitive enhancers. They work through multiple mechanisms such as antioxidant action, enhancement of synaptic function, restoration of cholinergic signaling, and reduction of neuroinflammation. These traditional claims align with modern pharmacological findings, suggesting a convergence between ancient knowledge and contemporary scientific validation.

2. Scientific Findings on Herbal Neuroprotection

A systematic review of modern research data reveals that many herbs contain active phytoconstituents that directly target the pathological events of AD. Systematic evidence from in vitro and in vivo studies demonstrates that these herbs collectively reduce oxidative stress markers (MDA), lower inflammatory cytokines (TNF-α, IL-6), and increase antioxidant enzyme activity (SOD, CAT, GPx). These findings support their potential role in preventing neuronal degeneration.

3. Limitations of Oral Herbal Therapy

Although herbs are effective, oral administration presents challenges:

- Low bioavailability due to poor solubility and first-pass metabolism.

- Slow absorption and inconsistent plasma concentration.
- Gastrointestinal degradation of active compounds.
- High pill burden, especially for elderly AD patients with swallowing difficulties.

These limitations emphasize the need for alternative delivery methods such as transdermal patches, which can enhance herbal efficacy.

Role of Transdermal Drug Delivery Systems (TDDS)

1. Advantages of Transdermal Delivery

- **Bypasses first-pass metabolism**, increasing active drug availability.
- **Provides controlled and sustained drug release**, maintaining consistent therapeutic levels.
- **Non-invasive and user-friendly**, ideal for long-term therapy.
- **Reduces systemic side effects** often seen with oral medications.
- **Improves patient compliance**, especially in AD patients who struggle with oral dosing.
- **Caregiver-friendly**, enabling easy application and removal.

Studies comparing oral vs. transdermal administration of synthetic AD drugs (e.g., rivastigmine) show significantly improved tolerability and adherence when delivered via patches.

2. Mechanistic Insights

Transdermal patches enhance herbal delivery by:

- Increasing skin penetration via permeation enhancers.
- Allowing lipophilic phytochemicals to diffuse efficiently into systemic circulation.
- Providing prolonged exposure to active molecules, thereby improving therapeutic outcomes.
- Reducing the dose required due to bypass of hepatic metabolism.

3. Combined Role of Herbal Transdermal Patches in AD Management

1) Synergistic Therapeutic Potential

The systematic examination suggests a **synergistic model**:

- Herbs provide **neuroprotective, anti-amyloidogenic, and antioxidant effects**.
- Transdermal patches provide **controlled release, better absorption, and improved patient compliance**.

  Together, they create a novel therapeutic strategy that may overcome the limitations of both oral herbs and conventional drugs.

2) Evidence from Experimental and Clinical Studies

Although research specifically on herbal transdermal patches for AD is limited, initial studies provide encouraging results:

- Herbal patches containing **curcumin** show improved plasma concentration compared to oral curcumin.
- Ginkgo biloba transdermal formulations demonstrate enhanced cognitive function in animal models.
- Ashwagandha transdermal gels increase neuronal regeneration markers.
- Polyherbal formulations used transdermally show reduced oxidative stress and improved learning behavior in rodents.

More clinical trials are needed, but preclinical evidence strongly supports the potential of herbal TDDS.

4. Challenges and Future Directions

1) Challenges

- Limited clinical data on herbal transdermal patches for AD.
- Need for optimizing patch compositions and permeation enhancers.
- Stability issues with certain phytoconstituents.
- Regulatory challenges in herbal-based transdermal products.

2) Future Research Directions

Future work should focus on:

- Conducting large-scale clinical trials.
- Developing standardized extraction techniques for herbal molecules.
- Formulating optimized transdermal systems using nanotechnology.
- Exploring polyherbal combinations for synergistic effects.
- Studying long-term safety and pharmacokinetics.

This combined narrative and systematic discussion indicates that herbal transdermal patches represent a promising advancement for Alzheimer's disease management. Herbs provide strong neuroprotective and cognitive-enhancing properties, while transdermal systems improve bioavailability, patient compliance, and therapeutic outcomes. Although more clinical research is needed, current evidence supports the integration of these two approaches as an innovative and effective strategy for managing AD

SUMMARY AND CONCLUSION

The present review aimed to explore and critically analyze the combined role of herbal therapeutics and transdermal drug delivery systems (TDDS) in the management of Alzheimer's disease (AD). AD is a multifactorial neurodegenerative disorder characterized by amyloid-β plaque deposition, neurofibrillary tangle formation, oxidative stress, neuroinflammation, and progressive cognitive decline. Conventional pharmacological therapies provide only symptomatic relief and are associated with limitations such as poor tolerability, adverse effects, and reduced patient compliance. These challenges highlight the need for alternative and complementary therapeutic strategies that are safer, more effective, and capable of targeting multiple pathological mechanisms.

A comprehensive evaluation of traditional literature, preclinical studies, and emerging scientific evidence reveals that herbal medicines possess significant neuroprotective potential. Medicinal plants such as *Curcuma longa*, *Ginkgo biloba*, *Withania somnifera*, *Convolvulus pluricaulis*, *Centella asiatica*, *Tinospora cordifolia*, *Ocimum sanctum*, *Zingiber officinale*, *Cinnamomum zeylanicum*, and *Azadirachta indica* contain active phytoconstituents that demonstrate antioxidant, anti-inflammatory, anti-amyloidogenic, anti-tau, and nootropic activities. These multi-targeted mechanisms make herbal formulations highly relevant in the context of AD management.

Despite the therapeutic potential of herbs, oral administration remains a key limitation due to poor bioavailability, first-pass metabolism, gastrointestinal degradation, and difficulties with patient adherence. Transdermal drug delivery systems overcome these limitations by enabling controlled drug release, avoiding hepatic metabolism, maintaining

steady plasma concentrations, and improving patient convenience. TDDS is particularly advantageous for individuals with cognitive impairment who may struggle with frequent oral dosing.

Integrating phytochemicals into transdermal patches offers a novel, synergistic approach that combines the pharmacological benefits of herbal molecules with the technological advantages of transdermal drug delivery. Evidence from preclinical and early clinical investigations indicates improved therapeutic outcomes with herbal TDDS, including enhanced cognitive performance, reduced oxidative stress, improved neuronal survival, and better bioavailability compared to oral formulations. These findings support the potential of herbal transdermal patches as an emerging, patient-friendly therapeutic tool for AD.

Alzheimer's disease (AD) is a global health concern due to its rising cases. It causes cognitive impairment and neurodegeneration. A number of evidence collected through clinical, animal, and *in vitro* studies indicates that the herbal plants reviewed in this research article help in neurogenesis and have many other therapeutic benefits. Traditional medicines with a strong knowledge base combined with modern science and techniques, help in improving the formulations that may be employed in drug development against AD and other neurogenerative diseases.

The review concludes the results of recent studies on Ashwagandha suggesting its extensive potential as neuroprotective in various brain disorders as supported by preclinical studies, clinical trials and published patents. However vague understanding of the mechanistic pathways involved in imparting the neuroprotective effect of Ashwagandha warrants further study to promote it as a promising drug candidate.

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