Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681 | Vol. 03, Issue-09, September-2026 | pp.-76-87

ORIGINALARTICLE https://jprims.in/

Combined Antidepressant Potential of *Trigonella Foenum- Graecum* and *Asparagus Racemosus*: A Comprehensive Review

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Abstract:

Methanolic extract of *Trigonella foenum- graecum* (seed) and *Asparagus racemosus*(root) were studied in the mice and rat both. The study applied the Force Swim Test (FST) and Tail Suspension Test (TST). Poor mood, low energy, oxidative stress, diminished motivation, and compromised emotional functioning are the main symptoms of depression. Depression is the common neuropsychiatric illness. Medicinal plants like *T. foenum- graecum* and *A. racemosus* have possible neuroprotective and mood- modulating qualities which has been prompted by the drawbacks of traditional antidepressant medication. Both *T.foenum- graecum* and *A.racemosus* have no of physiologically active components and have been shown to have neuropharmacological and adaptogenic effects. The goal of the current investigation was to assess the antidepressant activity of *T. foenum- graecum*(seed) and *A. racem*osus (root) using the FST and TST. The purpose of the study was to evaluate the combination formulation behavioral reaction to that of the control and conventional treatment groups. *A. racemosus* has shown antidepressant like action which is linked to noradrenergic and serotonergic systems, previous experimental research suggest that flavonoids produced from fenugreek can Affect monoaminergic pathways. Therefore, by modifying neurotransmitter function and associated stress- response pathways, the combination formulations may offer a supplementary pharmaceutical strategy. The outcome of this study may offer initial scientific proof in favor of this herbal combination's further investigation and mechanistic assessment as a viable antidepressant formulation.

Keywords: *Asparagus racemosus*; Antidepressant action; *Trigonella foenum- graecum*; Tail Suspension Test; Herbal formulation; Oxidative stress; Monoaminergic route; Forced swim test; Neurotransmitter

Received: June 08, 2026 **Revised: July 29, 2026** **Accepted: August 18, 2026** **Published: September 08, 2026**

DOI: https://doi.org/10.64063/3049-1681.vol3.issue9.000299

1. INTRODUCTION

Mood, mental peace, cognition, conduct, and quality of life are all impacted by depression. Depression is very complex and common illness. Low mood, sleep and appetite disorder, exhaustion, mental illness, difficult to concentrate anything, feeling very low and hope less are directly connected to the depression [1]. Change in dysregulation of the hypothalamic pituitary-

adrenal (HPA), neuroinflammation, monoaminergic neurotransmission, oxidative stress, and impaired neuroplasticity all are related to pathophysiology of depression, which cannot describe by the single mechanism [2,3]. A research indicates that cell activation and present inflammatory signaling may disrupt the neurotransmitter function and neural plasticity, which may exacerbate the depression symptoms [4]. Depression is also a brain derived neurotrophic factor, which is crucial regulator of neuronal survival and plasticity, with elevated levels seen after successful antidepressant treatment decreased levels are reported in people with major depressive disorder [5]. Need for new and alternative approaches is highlighted by delayed therapeutic response, side effect, and insufficient response in some patients, even though traditional antidepressant medications are crucial part of treatment [6]. According to estimates from the World Health Organization, depression affects about 5.7% of adults globally, or hundreds of millions of people.

A single neurotransmitter system's malfunction cannot fully account for the complicated pathophysiology of depression. According to available data, a number of interrelated mechanisms are involved, such as disruption in monoaminergic neurotransmission, oxidative stress, neuroinflammation, neurotrophic signaling, hypothalamic-pituitary-adrenal axis control, neurotrophic signaling, and synaptic plasticity [7]. Interest in therapeutic strategies that can affect several biological pathways has grown as a result of its multifactorial character. Evidence from extensive comparative assessments supports the effectiveness of a number of traditional antidepressant medications, and pharmacological antidepressants continue to play a significant role in the treatment of depressive disorder.

Recently medicinal plants increasing attention to the possible sources of targeting therapeutic medicines for depression. Methi, or *T. foenum- graecum* is a traditional ayurvedic medicinal herb which contain some bioactive compounds like alkaloids, saponins, flavonoids, and polyphenols that is linked to antioxidant and neuroprotective properties and also as well as claimed antidepressant like effects [8,9]. Many of researches can show that the *Asparagus racemosus* (Shatavari) which is also ayurvedic medicinal plant which can show neuroprotective, adaptogenic, antioxidant, and antidepressant related properties and also contain saponins, and other bioactive compounds. After knowing the pharmacological properties of both plants may offer a viable multi target strategy for investigating antidepressant efficacy.

2. BOTNICAL, PHYTOCHEMICAL, PHARMACOLOGICAL PROFILE OF TRIGONELLA FOENUM- GRAECUM

Due to their pharmacological activities and various phytochemical compounds both *T. foenum-graecum* and *A. racemosus* medicinal plants have lot of interest as possible sources of antidepressant drugs. Through modulation of monoaminergic neurotransmitter like norepinephrine, dopamine, serotonin's, regulation of HPA axis, decrease of oxidative stress, neuroinflammation and improved of neuroprotective pathways, both plants and its constituent have showed antidepressant like effect in preclinical research and these pathways signal that the both medical plants can offer interesting techniques for treating depression. *Asparagus racemosu*s and *Trigonella foenum- graecum* are the plants that can catch attention due to their good phytochemical features and neuropharmacological and adaptogenic qualities [10,11].

2.1 *Trigonella foenum- graecum* (methi)

Fenugreek, or *Trigonella foenum- graecum* L. (Fabaceae), is a significant medicinal herb that has long been utilized for a variety of therapeutic uses. Steroidal saponins, flavonoids, alkaloids, phenolic compounds, and other bioactive chemicals are among the many phytoconstituents found in its seeds [12]. *Trigonella foenum- graecum L*. also called Methi or Fenugreek. It comes under the Fabaceae family. Fenugreek is annual herb that is commonly grown throughout the Mediterranean region, Asia, and India. The plant's height is around 20 to 50 cm, with trifoliate leaves and tiny white to yellowish blooms. Its fruits are thin, slander carving pods that contain many solid, aromatic, yellowish- brown seeds. Seeds are the most extensively used as medicinal portion and it have many bioactive ingredients such saponins, dietary fiber, proteins, alkaloid, flavonoids and volatile chemicals [13,14].

FIG: 1.1 *TRIGONELLA FOENUM- GRAECUM* (SEEDS)

These compounds have been linked to metabolic, anti- inflammatory, antioxidant, and other pharmacological effects, which justifies more research on fenugreek in conditions involving oxidative and neurological dysfunction [15]. Crucially, research has shown that *T. foenum-graecum* seed extract has antidepressant- like effects in mice. Additional research, 4-hydroxyisoleucine and flavonoids produced from fenugreek may influence monoaminergic pathways and MAO-A activity to provide antidepressant- like effects and evaluated the Tail Suspension Test (TST) and Forced Swim Test (FST) to examine a fenugreek seed methanolic extract. In all models, the extract significantly reduced immobility, and its stated activity was similar to that of imipramine [16]. The authors hypothesized that the seeds saponin glycosides and flavonoids might interact with the adrenergic, dopaminergic, serotonergic, and GABAergic systems to produce the observed activity.

***Asparagus racemosus* (Shatavari)**

Another medicinal plant with a long history of traditional use *Asparagus racemosus* Wild, also referred to as Shatavari. Steroidal saponins and other phytoconstituents found in its roots have been studied for their neuropharmacological, antioxidant, and adaptogenic qualities. *Asparagus racemosus* is a good medicinal plant it comes under the Asparagaceae family. It is woody, thorny, perennial climber and it is mostly found in India's tropical and subtropical regions. Its branches are stems and slender and developed as climbing shrub. Its leaves are reduced and modified into tiny, green, and needle like cladodes and it perform like photosynthetic function. Its flowers fragrant, tiny and their white flowers are grouped in branching clusters. Its fruits are tiny, globular berries that grow from dark purple to black. Most important part of the plant is fascicled tuberous root system, it is made up of many long, fleshy roots, it is very medicinally significant feature. These roots are contained various bioactive compounds and it is the major source of the medicinal ayurvedic preparation [17].

FIG: 1.2 *ASPARAGUS RACEMOSUS* (ROOTS)

Methanolic root extract of *A. racemosus* dramatically decreased immobility in mice in both the TST and FST in a dose- dependent manner. According to reports, the effects were similar to those of the reference antidepressants imipramine and fluoxetine [18]. The neurobehavioral potential of this medicinal plant was further supported by Singh et al.'s evaluation of a standardized methanolic root extract *of A. racemosus* in mouse models, which reveled antidepressant efficacy. *A. racemosus* may have an impact on behavioral and neurochemical changes associated with depression, according to additional experimental data [19].

Table 1. Comparative phytochemicals and pharmacological profile of *Trigonella foenum-graecum* and *Asparagus racemosus* with related antidepressant activity.

Plant	Part used	Phytoconstituents	Pharmacological activities	Antidepressant related evidence
Trigonella foenum-graecum	Seed	Trigonelline, Diosgenin, 4-hydroxyisoleucine, steroidal saponins, flavonoids, phenolic compounds, alkaloids, flavonoids, polysaccharides and dietary fibre	Antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, hepatoprotective, neuroprotective and immunomodulatory activities	Bioactive constituents such as trigonelline, flavonoids and steroidal compounds provide a pharmacological basis for investigating its potential in CNS- related disorders
Asparagus racemosus	Root	Steroidal saponins, racemosol, flavonoids, phenolic compounds, alkaloids, and polysaccharides	Antioxidant, adaptogenic, anti-inflammatory, immunomodulatory, neuroprotective, anti- stress and antidepressant activities	Root extract has demonstrated antidepressant like effects in Forced Swim Test and learned helplessness models, with proposed involvement of serotonergic systems

3.COMBINED ANTIDEPRESSANT POTENTIAL OF *TRIGONELLA FOENUM* GRAECUM AND ASPARAGUS RACEMOSUS

The combination of *Trigonella foenum- graecum* seed and *Asparagus racemosus* root may have a complimentary antidepressant effect. Fenugreek has shown antidepressant- like effects via inhibiting MAO-A activity and modifying monoaminergic neurotransmitters. Additionally, *Asparagus racemosus* has been shown to have neuroprotective and antidepressant properties, potentially by antioxidant pathways, monoaminergic and GABAergic neurotransmission, and HPA axis modulation. As a result, mixing the two extracts could have a wider pharmacological effect and be investigated as a possible herbal treatment for depression [20].

3.1 Possible mechanism of combined:

Complementary mechanisms including monoaminergic neurotransmission, antioxidant defense, and modulation of stress- related pathways maybe how the combined extracts work. According to reports, herbal antidepressant drugs affect neurotransmitters, oxidative stress, inflammation,

and neuroendocrine pathways; this suggests that their antidepressant potential may be attributed to multi- target activity.

3.2 Phytochemical basis:

Various phytoconstituents found in both plants may be responsible for the combined formulation's pharmacological effects. *Asparagus racemosus* is highly rich in steroidal saponins, while fenugreek has flavonoids and other bioactive compounds. These Components may have neuroprotective, depressive, and antioxidant characteristics.

3.3 Research gap:

While isolated extract of *Asparagus racemosus* and *Trigonella foenum- graecum* have demonstrated encouraging antidepressant- like effects in experiments, there is little data on their particular combination. As a result, assessment of the combined extracts might offer helpful proof of their possible complimentary or synergistic antidepressant action [21,22].

4. EXPERIMENTAL MODEL FOR ANTIDEPRESSANT EVALUATION

For the first assessment of possible antidepressant, animal behavioral models are frequently utilized. Among these, the Tail Suspension Test (TST) and Forced Swim Test (FST) are frequently utilized screening techniques because they offer a quick and affordable evaluation of antidepressant- like effects. In the TST, mice are suspended by their tails, but animals in the FST are forced to swim. Conduct rodents to assess various facts of depression various no of additional behavioral models are employed in addition to the Forced Swim Test (FST) and Tail Suspension Test (TST). LH model assesses deficiencies in escape- directed behavior after exposure to unmanageable stress, while the sucrose desire test is frequently used to measure anhedonia, which indicated decreased desire for a pleasant sucrose solution. Another very popular paradigm is chronic modest stress. In which animals are subjected to a range of modest, erratic stressors and may exhibit changes in behavior by including decreased reward responsiveness. Anxiety, exploratory behavior, and locomotor activity can be obtained during Novelty- Suppressed Feeding and Open Field experiment. Combined various behavioral assessments can offer a more evaluation of antidepressant like activity because no single model can replicate complicated clinical aspects of human depression [23,24].

5.PHARMACOLOGICAL MECHANISMS OF ANTIDEPRESSANT ACTIVITY AND PRECLINICAL EVIDENCE

Preclinical research has shown that *Asparagus racemosus* and *Trigonella foenum- graecum* exhibit antidepressant- like properties. Flavonoids extracted from fenugreek seeds corrected changes in monoamine neurotransmitters and MAO-A activity in stressed mice and decreased stress- included immobility in the Forced Swim Test (FST) and Tail Suspension Test (TST). *Trigonella foenum- graecum* capacity to regulate monoaminergic neurotransmission it can be linked to its antidepressant- like properties. According to researches, *T. foenum graecum* flavonoids can lower MAO-A activity and can affect the serotonin, norepinephrine, and dopamine levels, it may help to explain its antidepressant like effects. In experimental animal model researches, *Asparagus racemosus* has also shown various antidepressant like effects, mainly by altering noradrenergic neurotransmission, serotonergic and decreasing immobility in FST [25]. Its neuroprotective and stress- modulating benefits may also supported its antioxidant qualities. Reported pharmacological profile of both plants may be attributed to the presence of

flavonoids, steroidal saponins and other bioactive components. All things can be considered for our preclinical results justification for examining possible antidepressant efficacy of combining both *T. foenum- graecum* and *A. racemosus*.

In a rat model of diabetic depression produced by streptozotocin, examined the antidepressant efficacy of an ethanolic root extract of *Asparagus racemosus*. Fluoxetine was utilized as the usual medication, and the extract was given orally at 100 and 200 mg/kg for a week. The extract treatment increased exploratory behavior in the Open Field Test, decreased escape failures in the Learned Helplessness Test, and considerably decreased immobility in the Forced Swim Test [26]. According to the results, *A. racemosus* root may helpful for depressive-like behavior linked to diabetes.

Table 2. *Asparagus racemosus* and *Trigonella foenum- graecum* bioactive components, molecular targets, and antidepressant mechanism

Plant	Evidence/ active compounds	Target/pathway	Reported effect	Antidepressant relevance
T. foenum-graecum	Seed flavonoids	Monoaminergic system; MAO-A	Increased 5-HT and DA; inhibition of MAO-A	May enhance monoamine availability and reduce depressive- like behavior
T. foenum-graecum	4-Hydroxyisoleucine(4-HI)	Serotonergic neurotransmission	Reduced immobility and enhanced 5-HT-induced head-twitch response	Suggest involvement of serotonergic mechanism
Asparagus racemosus	Root extract	Serotonergic and noradrenergic pathways	Reduced behavioral immobility with changes in monoaminergic activity	Supports antidepressant-like activity
Asparagus racemosus	Root bioactive constituents	HPA axis and neuroplasticity	Reported modulation of stress- related pathways and BDNF	May improve stress adaption and neuronal resilience
Asparagus racemosus	Root extract	Oxidative- stress pathways	Increased antioxidant defense	May reduce oxidative stress

6.SAFETY, TOXICOLOGICAL CONSIDERATION AND THERAPEUTIC EFFECTS

Various preclinical studies have examined the safety profile of both medicinal plants *Asparagus racemosus* and *Trigonella foenum- graecum* but the evidence that is now available it varies depending on the plant part, extract type, dose, and period of exposure. *Asparagus racemosus* has shown a comparatively acceptable acute safety profile in experimental animals. They show

a very good margin of acute safety because its oral administration of roots extract at doses up 3200mg/kg did not cause major immediate toxic effects and did not result in fatality [27]. In similar an acute toxicity evaluation of an ethanolic root extract at an oral dose of 200mg/kg revealed no mortality [28]. Fenugreek has also show wide range of safety in preclinical and clinical trials. A study of *T. foenum- graecum* seed toxicity identify multiple valid toxicological studies confirming the absence of substantial acute or repeated- doer toxicity and supporting the safety standardized fenugreek seed extracts [29]. In 28- day sub- chronic toxicity investigation, fenugreek seed extract can not show any kind of toxicity, adverse effect in treatment [30]. Clinical data can also show that fenugreek is well tolerated with majority of reported side effects being moderate temporary, such as nausea, gastrointestinal distress, dizziness, and sporadic hypoglycemia effects [31].

Although both *T. foenum- graecum* and *Asparagus racemosus* have good safety profiles, their therapeutic uses should be the proper dosage, extract standardization, length of administration, and potential herb- drug interactions. When used with antidiabetic medication fenugreek may show hypoglycemic effects and can alter the absorption of medication [32]. *Asparagus racemosus* contain various properties like adaptogenic, anti- stress and neuroprotective that why it can be most widely use, which can suggest its potential therapeutic role in diseases related to mood and stress. Dose selection, treatment duration, extract standardization can guarantee consistent therapeutic result and safety [33].

7. RESEARCH GAP AND FUTURE PROSPECTIVE

7.1 Research gap:

There are still considerable research gaps even though *Trigonella foenum- graecum* and *Asparagus racemosus* each showed promising neuropharmacological and antidepressant-like effects in preclinical research. While *Asparagus racemosus* has showed antidepressant- related effects connected to monoaminergic signaling, HPX-axis modulation, BDNF and antioxidant mechanisms, fenugreek- derived, flavonoids have been demonstrated to alleviate depression-like behavioral changes by regulation of monoaminergic neurotransmission and the KLF11/SIRT1/MAO-A pathway. Nevertheless, there is little systematic data assessing the combined antidepressant potential of *A. racemosus* roots and *T. foenum-graecum* seeds in a standardized formulation [34].

7.2 Future prospective:

Further studies should be directed toward the development and standardization of the combination formulations of *T. foenum-graecum* seed and *A. racemosus* root with specific phytochemical profile and ideal dose ratio [35]. In addition to the quantification of monoamine neurotransmitters, MAO-A, BDNF, HPA-axis activity, oxidative stress and inflammatory biomarkers, future studies should investigate the antidepressant activity of these compounds using complementary behavioral models. Recent preclinical depression research highlights the role of strain, model validity, sex, species and diverse behavioral paradigms which should be explored in future studies to improve repeatability and translation relevance long term toxicity and pharmacokinetic investigations, herb- drug interaction future effort should be devoted at enhancing the bioavailability of potent phytoconstituents and determining the individual chemicals responsible for the antidepressant effects of both herbs. Research into the gut- brain axis, molecular targets and neuroplasticity can provide further insight into the therapeutic

potential of the combination formulation. These researches may be beneficial to create a more accurate pharmacological basis for treating depression with *Trigonella foenum- graecum* and *Asparagus racemosus.*

Table-3. Research gaps and future study requirements for *Asparagus racemosus* and *Trigonella foenum- graecum*

Current evidence	Major limitation	Future research requirement
Individual plant pharmacological evidence available	Direct combination evidence limited	Combination- specific animal studies
Different phytoconstituents identified	Active antidepressant constituents not clearly established	Bioactivity- guided isolation
Preclinical evidence exists	Standardized extract/ dose is not fully established	Extract standardization and dose- response studies
Proposed mechanisms available	Molecular mechanisms need confirmation	Neurotransmitter, oxidative- stress and molecular pathway studies
Traditional use reported	Clinical antidepressant evidence remains limited	Well- designed clinical trials

8. CONCLUSION

Review suggest that that the *Asparagus racemosus* and *Trigonella foenum- graecum* can have neuroprotective, neurotransmission and antidepressant- like characteristics especially in preclinical model. Fenugreek have some bioactive compounds like 4- hydroxyisoleucine, saponins, and flavonoids, MAO-A activity, monoaminergic neuro- transmission that has shown antidepressant- like effects. *Asparagus racemosus* root extract can decreases the immobility in the FST and TST, with data pointing to the participation of the GABAergic, serotonergic, dopaminergic, and adrenergic systems as well as inhibition of MAO-A and MAO-B. These can be offered a pharmacological foundation for seeing both two plants Fenugreek and *Asparagus racemosus* as complimentary options for a combined antidepressant strategy. However, direct information about the efficacy, appropriate ratio, pharmacological interaction and long-term term safety of their combination remains scarce. Therefore, to determine whether their combined use offers an advantage over individual extracts, well- designed studies utilizing standardized extracts, validated animal model, mechanistic biomarkers, and appropriately controlled clinical trials are needed. All things considered, the evidence that is currently available encourages more research into *T. foenum- graecum* and *A. racemosus* as possible complementary botanical candidates in the creation of safer and more targeted depression treatments.

9. ACKNOWLEDGEMENT

I would like to convey my sincere gratitude to my esteemed guide, Dr. Arpan Kumar Tripathi, for his important advice, consistent support, constructive comments, and encouragement throughout the writing of this review article. I am also thankful to the Kamla Institute of Pharmaceutical Science (SSPU), Junwani, Bhilai, Chhattisgarh, for providing the essential academic environment and facilities for finishing this study. I genuinely value the support and encouragement received from the academic members and my coworkers.

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