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Review article

Adaptogenic property of *Asparagus racemosus*: Future trends and prospects

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ABSTRACT

Major depressive disorder (MDD) is a multimodal neuropsychiatric and neurodegenerative illness characterized by anhedonia, continued melancholy, dysfunctional circadian rhythm and many other behavioral infirmities. Depression is also associated with somatic ailments such as cardiometabolic diseases. The existing and upcoming hypotheses have succeeded in explaining the pathophysiology of depression. Only a few of the most validated theories, such as hyperactivity of the HPA axis, activated inflammatory-immune response, and monoaminergic and GABAergic deficit hypotheses, have been discussed in this review. So, an effective and safer alternative approach beyond symptomatic relief has been desired. Therefore, botanical products have steadily been probed to strengthen the modern medicinal system as a promising medicament. In this line, *Asparagus racemosus* Willd. belongs to Asparagaceae family is the well-documented adaptogen cited in the ancient texts namely, Ayurvedic, Greek, and Chinese medicine system. The whole plant possesses pleiotropic therapeutic activity, antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, nootropic, antidepressant, etc., without showing any remarkable side effects. The literature review has also suggested that *A. racemosus* administration at varied levels alleviates depression by modulating the HPA axis, increasing BDNF levels, and monoaminergic and GABAergic neurotransmission.

Alongside, spikes the level of antioxidant enzymes, SOD, GSH peroxidase, GSH, and catalase in distinct brain regions (i.e., hippocampus, prefrontal cortex, amygdala, and hypothalamus) and promote neurogenesis and neuroplasticity. Thus, it could be a new generation antidepressant that provides relief from both behavioral and somatic illness. The review first describes the plant characteristics, then discusses the hypotheses associated with the pathogenesis of depression, and gives an insight into *A. racemosus antidepressant* properties and the underlying mechanism.

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1. Introduction

Mental health is not merely the absence of mental disorders or disabilities. It is the state of well-being where a person can recognize their potential, subsist daily stress of life, performs tasks productively, and contributes to society. However, in the contemporary era, mental health is getting worsen day by day. Most importantly, the coronavirus outbreak has long-lasting implications for mental health. For instance, isolation from the external environment and family has disrupted their daily routines and restricted their activities and livelihoods. This consequently leads to anxiety, insomnia, drug abuse, depression, and many others (WHO 2020c). Recently a survey conducted by the Indian Psychiatric Society interpreted a 20% rose in mental disorders in India since this deadly pandemic outbreak [1]. Almost half of the global population has been lived with one of the mental disorders. There are myriad mental disorders varying in presentation, but they are usually distinguished by interweaving unusual thoughts, ideas, beliefs, emotions, perceptions, behaviors, and relations with others. The facts and figures of the Global Burden of diseases 2019 study delineated that between 1990 and 2019, the global number of disability-adjusted life–years (DALYs) attributable to mental disorders has an upsurge from 80.8 million to 125.3 million [2]. The proportion to global DALYs due to mental disorders elevated from 3.1% to 4.9%. Hence, mental illnesses are in the list of top ten leading causes of burden globally, among which depression and anxiety are more frequently prevailing worldwide, afflicted around 264 million people, and are the predominant cause of disability in the world [2].

As per WHO, depression is generally characterized by an array of symptoms such as continued melancholy, lack of interest or delight in performing activities, poor concentration, anhedonia, altered sleep and appetite, fatigue feeling, low mood, and relative cognitive, emotional, behavioral and physical imbalance. Moreover, depression has several detrimental effects on all aspects of life that can persist for a prolonged period or recurrent and can influence the individual's ability to work and live a rewarding life. It is caused by a complex interplay of psycho-social and biological factors. Nevertheless, childhood trauma, microbial infection, loss and unemployment, environmental stress, neurological abnormalities, and inheritance are some causal factors associated with the manifestation of depression [3]. The epidemiological data has also stipulated a comorbidity between depression and other physiological conditions such as diabetes, chronic lung disease, arthritis, angina, stroke, obesity, hypertension, and metabolic dysregulation [4,5] and coronary heart disease likely to be caused by interleukin-6, C-reactive proteins (CRP) and triglycerides [6]. Apart from this, clinical data have also evinced the coexistence of depression and other neurological disorders. For instance, a large cohort study in the elderly suggested that individuals with a history of depression and severity of depression have increased the incidence of Alzheimer's disease [7].

Conventionally, dysregulation of the HPA axis, deficiency of monoamines in the central nervous system (CNS), alteration in GABAergic neurotransmission, and dwindling of brain-derived neurotropic factors have been explained as causal factors in the development of depression. However, deepening research in this domain breakthrough new pathways and proteins involved in depression pathophysiology. A review scrutinized that the newly discovered protein, High-mobility group box (1) (HMGB1) is involved in producing depressive-like behaviors by acting as pro-inflammatory cytokines through binding to the specific receptors particularly, a receptor for the advanced glycation end product (RAGE) and Toll-like receptors 2 and 4 (TLR 2 and 4). Thereby, releasing inflammatory markers from microglia (brain immune cells) and responsible for other neuroinflammatory disorders. Usually, depressive subjects have increased levels of proinflammatory cytokines in the glial cells, microglia, and serum [8]. In a similar fashion, upregulation of unfolding protein response (UPR) [9], calpains (calcium stimulated cysteine protease) [10], and CAPN2 expression [11] tend to produce depressive-like conditions. The activation of unfolding protein response (UPR) due to perturbed homeostasis of the endoplasmic reticulum leads to protein misfolding which consequently results in the upregulation of TLR expression and synthesis of inflammatory cytokines [9] thus inducing depressive-like behaviors. In spite, of the exhaustive discovery of proteins, genes, epigenetic factors, and signaling pathways associated to produce depressive-like behaviors, the scrupulous details behind depression pathophysiology need to be probed beyond what we know presently.

Though psychotherapy, antidepressant drugs, and electroconvulsive therapy have been widely used to treat depression, phytoconstituents as alternative therapy are also progressing. The phytoconstituents are the copious source of polyphenols that impede the expression of signaling pathways triggered by oxidative stress, thereby exhibiting anti-inflammatory and antioxidant abilities [12]. The phytoconstituents are plant adaptogens that play a major role in alleviating depression.

The phytoadaptogens (i.e., adaptogens from plant origin) are the vital medicaments since human existence, as these therapeutic agents aid in coping stress response in the alarm phase or thwart the exhaustion phase and consequentially provide some degree of non-specific resistance from chronic/long-term stress. Moreover, they tend to exhibit pleiotropic actions on the neuroendocrine-immunological system. Hence in the contemporary era, the rationale use of adaptogens is linked chiefly to counteract stress-induced fatigue, anxiety, depression, cognitive impairment, and other neurodegenerative ailments.

Plant-adaptogens also impart multivariate pharmacological effects against metabolic disorders, cancer, chronic inflammation, atherosclerosis, and many other age-related diseases. *Bacopa monnieri*, *Rhodiola rosea*, *Panax ginseng*, *Asparagus racemosus*, *Glycyrrhiza glabra*, *Tinospora cordifolia*, *Ocimum sanctum*, *Emblica officinalis*, *and Withania somnifera* are some of the well-acclaimed adaptogens that attenuate psychological stress and stress-induced somatic disorders [13–15]. Robust scientific data suggested that botanical adaptogens modulate perturbed homeostasis via acting on several signaling pathways such as HPA-axis, monoaminergic system, and key biochemical mediators or receptors, namely, corticosteroids, mineralocorticoid receptors, estrogen receptors, nitric oxide, cholesterol, triglycerides, and among others [16].

Asparagus racemosus is one of the well-documented plant adaptogens in Traditional Medicinal Systems such as Siddha, Ayurveda, and Unani. Alongside, their biological properties have already been published in Indian and British Pharmacopeias [17]. In Ayurveda, it is a tonic having several therapeutic applications, usually, anti-dyspepsia, alleviating neuronal disorders, liver diseases, anti-inflammatory, and certain other infectious and non-infectious ailments [18]. It has also been inferred as a Rasayana or rejuvenator herb which augments body's defense systems by rendering immunoadjuvant potential. The immunostimulant action of the plant has

been coherently supported by certain trials where *Asparagus* have been found to upregulate the Th1 (IL-2, IFN-g) and Th2 (IL-4) cytokines that, in turn, activate the cellular and humoral immune response along with suppression of pro-inflammatory cytokines (IL-6 and TNF). Therefore, it could be worked as a potent immunomodulator in unfavorable conditions [19,20]. A literature review also suggested that plant is a copious source of biologically active compounds which elicit polyvalent pharmacological properties notably, galactagogue, anti-tussive, immunomodulatory, neuroprotective, anti-cancer, anti-diabetic, anti-aging, cardioprotective and many other properties [21]. A plethora of clinical and preclinical models show that *A. racemosus* possesses neuro-nutraceutical activities such as nootropic, anti-inflammatory, antioxidant, and neuroprotective potential without causing any remarkable adverse reactions [22]. Additionally, recent research stipulated the neuromodulatory effect of *Asparagus racemosus* Extract (ARE) and its ubiquitously present therapeutic compound (shatavarin IV). They significantly ameliorate cholinergic transmission by increasing the synaptic acetylcholine level and nicotinic acetylcholine receptors (nAChR) through inhibition of acetylcholinesterase enzyme and up-regulation of transcription factors, primarily, cha-1, cho-1, unc-38, and unc-50. However, cholinergic dysfunction has been recognized as a biomarker of various neurological maladies. Thus, ARE and steroidal saponin, Shatavarin IV could be effectively reverse the neuronal damage caused by reactive oxygen species [23]. Above all, an experiment has suggested that Methanolic Extract of *Asparagus racemosus* (MEAR) is perhaps a possible cerebroprotective agent to recondition an impaired physiological balance caused by oxidative stress. The study results specified that MEAR administered at a dosage of 200 mg/kg in rodents were significantly attenuated the glutathione, superoxide dismutase, and catalase levels in the brain and reduced the nitric oxide, malondialdehyde, and cytokine synthesis in the brain [24].

Several previous and latest studies performed on multiple cell lines depicted that *A. racemosus* comprises phytoestrogens, particularly shatavarin IV and rutin, which show anti-proliferative activity by effectively binding to the targeted estrogen receptor (ERα). Henceforth, it could be a powerful new generation therapy against breast cancer [25,26]. Likewise, an investigation inferred that estrogen deficiency in postmenopausal women may also lead to sarcopenia and osteoporosis which can be reversed by Shatavari supplementation, which restores muscle functioning and contractility by mimicking estrogen-like effects. The efficacy of shatavari supplementation was proved by a randomized double-blind experiment conducted in 20 postmenopausal women who were on shatavari supplementation (1000 mg/d) and a placebo for six weeks. Wherein, the obtained results displayed an improvement in handgrip strength, Aktser473 and Myosine modulated light chain phosphorylation in Vastus lateralis. But certain parameters remained unaltered such as knee extensor strength, and plasma markers of bone turnover. The improvement in muscle functioning might be due to the binding of phytoestrogen components of shatavari to the estradiol receptor [27]. However, an in-depth analysis related to components responsible for improving the muscle condition still needs to be explored. Furthermore, animal and clinical examinations have consistently cited that Shatavari supplementation proffer galactagogue/lactagogue effect by potentiating the prolactin hormone production [28,29], thus augmenting the milk production in case of lactational inadequacy. Conclusively, *Asparagus* is defined as a potent female tonic because it is found to be beneficial in improving reproductive, muscle, and eye health, potentiates breast milk production, and aid in revitalizing vigor and vitality.

Apart from this, the plant was found to exhibit ergogenic effects, as demonstrated by a study where *Asparagus* supplementation at 500 mg/d expedited the training load during eight weeks of bench press training, enhancing muscle strength and endurance. Thus, it could be employed as an ergogenic aid to improve sports/exercise performance [30].

Indeed, ethanopharmacological investigations of root extracts of *Asparagus racemosus* reported multivalent therapeutic actions, for instance, anticandidal activity [31], antiurolithiatic activity [32], larvicidal, adulticidal and ovicidal action against virulent vector mosquitoes [33] and antihepatotoxicity [34].

Nevertheless, the functionality of the *Asparagus* plant is not limited to its therapeutic property but can also be applied to diverse domains such as in the food industry, packaging industry, and others. In the food arena, the addition of Shatavari root powder in a range of 3–3.5% in bread has been found to improve functionality and nutraceutical profile of the product optimally due to the presence of essential bioactive components, namely, saponins, steroids, alkaloids, and terpenoids. So, it can be a promising nutraceutical agent or fortificant to enhance the nutritional profile of bakery products [35]. Besides, until now, only one study has reported the application of *Asparagus* as a preservative where meat product (chevon sausages) packed in edible films integrated with *A. racemosus* root extract (at 1% and 2% levels) were found to maintain the functional aspects of the products by reducing the microbial growth, free fatty acid content and TBARS and consequently increased lipid oxidative stability and shelf life of the product. All of these properties are exhibited due to the presence of bioactive agents that bestow antioxidant and antimicrobial properties to edible films [36]. The phytoconstituents reported in root extract were tannin, vanillin, triterpene saponins, alkaloids, diosgenin, coniferin, mucilage, starch, proteins, and sarsasaponin [37]. Thus, it could be a powerful preservative agent and pave the way for the new generation of active packaging material.

So, the present manuscript has attempted to provide a detailed description of the anti-depressant potential attributed to *A.racemosus* plant. As of now, there is no literature review present on the anti-depressant potential of the plant. The present manuscript tried to interlink the underlying mechanism of action of *A. racemosus* to attenuate the depressive-like symptoms according to suggested depression hypothesis.

2. Botanical description: morphology, bioactive compounds and their pharmacological potential

Asparagus racemosus Willd. (Shatavari) is an epitome of love and devotion, implying its potential to facilitate fertility and vitality. Therefore, Shatavari may also be symbolized as "who possesses 100 spouses or acceptable to many". In Ayurvedic text, it is renowned as "Queen of Herbs" due to its rejuvenating properties thus, promoting general well-being or support in counterbalancing day-to-day environmental stress. Moreover, it is well-reckoned as a female tonic because it partly contributes to various herbal formulations

Fig. 1. Different parts of plant *Asparagus racemosus* (shatavari).

designed to treat or ameliorate women's health ailments. Globally, the genus *Asparagus* is comprised of about 300 species, among 22 species has been reported in India alone. Of these, *A. racemosus* is ubiquitously disseminated worldwide means stretched throughout tropical and sub-tropical areas. However, it is majorly cultivated in India (Assam, Kashmir, Odisha, Maharashtra, and Kerala), Bhutan, Myanmar, and Thailand [38].

2.1. Morphology

It is a small annual climber approximately 1–3 m in height, and vastly scandent spinous, mostly branched under-shrub. The root part of the plant is distributed abundantly, which are wedged, succulent and tuberous in nature, having a diameter of around 0.5–1.5 cm. It emerges as a bundle from the stem's proximal tip. Generally, the stem is woody, partly surrounded by convoluted spines. Leaves are known as cladode due to their reduced small scales. They are clustered in 2–6 in a node, finely acuminate. Flowers appear in June–October, which are clustered racemes, whitish in color, and sweet-smelling. However, the fruiting is initiated from October month, and the ripe fruits are red hue berries, globose, and 3–6 seeds enclosed in it, which are black and hard [39]. Fig. 1. Illustrated different parts of plant *Asparagus racemosus* (shatavari).

Taxonomy.

Root	Root
Kingdom	Plantae
Phylum	Tracheophyta
Class	Liliopsida
Order	Asparagales
Family	Asparagaceae
genus	*Asparagus*
Species	*Asparagus racemosus* willd

Vernacular names.

Hindi	Satavar, shatavir, satawari
Sanskrit	Abhiru, shatavari, hiranyasringi
English	Asparagus, wild asparagus
Assamese	Satmuli, shatmul, satomul
Bengali	Satamuli, satamul
Kannada	Aheruballi, ashadhi, halarru-makkal
Malayalam	Chathavalli, sathavali, satavali, thalicheria, thaliperiya etc.
Telugu	Challagadda, ethavaludutige, challa-gaddalu
Manipuri	Nunggarei

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(*continued*)

Hindi	Satavar, shatavir, satawari
Marathi	Asvel, satavari-mul
Oriya	Vari
Urdu	Satawar, shaqaqul misri
Other	Hundred roots, asparagus roots, wild asparagus etc.

2.2. *Bioactive compounds and their pharmacological activity*

Data repository on screening of bioactive constituents of *Asparagus racemosus* extracts confirms the presence of phenolic compounds, flavonoids, alkaloids, tannins, steroids, saponins, terpenes, and carbohydrate in different solvents. Amongst various phytoconstituents, steroidal saponins have been majorly reported in *Asparagus* Species. Notably, asparoside B, shatavarin V, asparanin A, asparinin B, asparoside B, filiasparoside C, and immunoside were few major steroidal saponins that have been found in the *A. racemosus* roots [40,41]. Alongside, three more steroidal saponins such as racemoside A, B, and C have also been isolated in its fruit part [42]. The clinical and pre-clinical evidence displayed that steroidal saponins possess potent therapeutic effects, viz., immunostimulant (shatavaroside A and shatavaroside B, at low concentration 5 ng/ml), improve female reproductive health, and have anti-stress, anxiolytic, and lactogenic properties [28,44]. Some of the vital saponin components have been shown in Fig. 2.

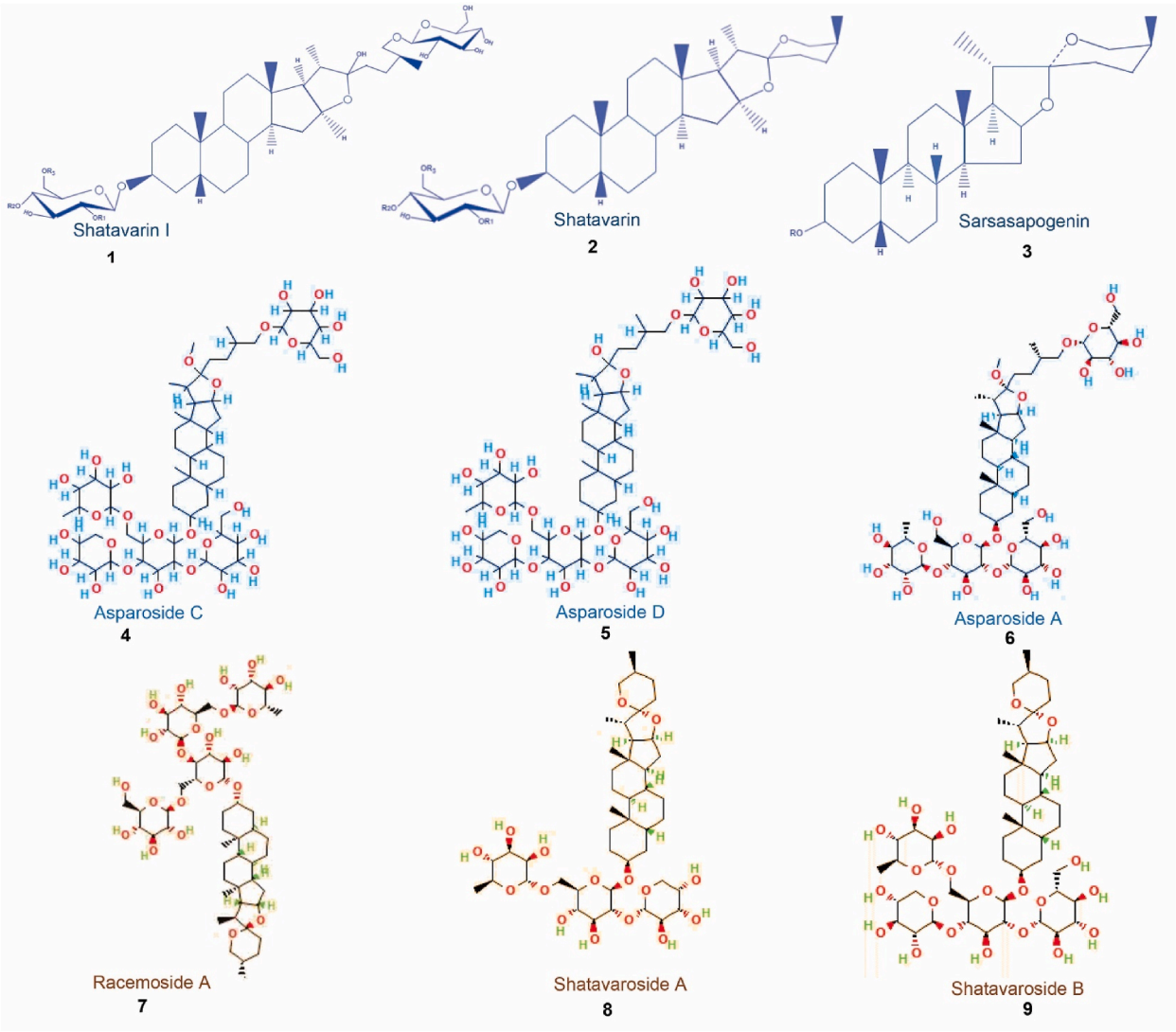

Fig. 2. Presenting vital saponin components possessing neuroprotective properties/antidepressant-like behavior [44–50].

Similarly, studies have also elucidated that not only steroidal saponins but polysaccharides (fructans) isolated from AR root encompass immunostimulatory property too [43].

The recent in-vitro and in-vivo investigation revealed the role of *Asparagus* polysaccharide (ASP) in impeding the proliferation, migration, and invasion of hepatocellular carcinoma (HCC) partly by repressing HIF-1/VEGF expression mediated via knockdown of PI3K and MAPK signaling route without causing any cytotoxic effects on normal liver cells. Hence, it could be a promising alternative strategy for liver cancer but needs further research for robust knowledge [51]. Further, Gas Chromatography -Mass Spectroscopy (GC-MS) investigation showed the presence of biologically active compounds such as Oleic acid, Tetradecanic acid, 9, 12-Octadecadienoic acid, 4H Pyran- 4 One, n-Hexadecanic acid, Tetranorlipoic acid, 1,6-Anhydro-β-D-talopyranase, 2- Furancarboxaldehyde, and 2,3 dihydro – 3,5 dihydroxy – 6 methyl [52]. In addition, recent studies have discovered new bioactive compounds, acemosin, spirosteroids (asparacemosones (A-D), and spiro-21-norsteroid), and norlignans (nyasol and asparenydiol), from *A. racemosus* roots which exhibit modest cytotoxic property upon HepG2 cancer cell line and normalize blood glucose level [53,54]. The literature has also suggested that roots of the plant also contain mucilage, vitamins (A, B1, B2, C, E), and minerals (calcium, iron, magnesium, phosphorus, and folic acid). Other vital chemical components of plants are arginine, asparagine, tyrosine, resin, flavonoids (rutin, quercetin, and Kaempferol), and tannin [55].

Beyond that, chemical derivatization of different extracts of *A. racemosus* (aerial parts) unveiled that methanolic extract contained highest content of polyphenolic compounds (p-Coumaric acid and caffeic acid) and flavonoids (Myricetin and quercetin), which possesses multiple pharmacological properties such as anti-inflammatory, antioxidant, immunomodulatory, neuroprotective, hepatoprotective, and antidiabetic [56]. For the first time, research conducted by Ahmad et al. extracted a novel bioactive agent, *β*-glucogallin from *A. racemosus* roots [57]. The compound manifested advanced glycation end products (AGEs) inhibitory potential, thereby implicated in reducing pathogenesis of AGEs associated metabolic infirmity, including aging, neurological disorders, chronic inflammation, diabetes-related complications, and atherosclerosis. Lastly, a former investigation has isolated several chemical constituents from the *A. racemosus* roots: racemoside A, stigmasterol, shatavrin IV, furostanol steroidal saponin (shatavaroside C), shatavarol, ursolic acid, and beta-sitosterol. Table 1 outlined the diversity of phytoconstituents isolated from *Asparagus racemosus* with their therapeutic value and underlying mechanisms.

Conclusively, *Asparagus racemosus* comprise of vital bioactive constituents which impart multiple pharmacological activity such as anticancer, neuroprotective, immunomodulatory, cardiometabolic diseases and many more. However, data analysis of existing investigations directing dearth of human clinical trials and other in-vivo model in proving their clinical efficacy. Hence, the plant needs to be probed more deeply to proven the mechanistic pathway of reported bioactive agents exhibiting clinical activity.

Table 1
Diversity of phytoconstituents isolated from *Asparagus racemosus* with their therapeutic value and underlying mechanisms.

Plant Part	Extract	Subjects (In-vitro and in-vivo)	Phytoconstituents	Therapeutic effect/Mode of action	References
Roots	Crude extract	In-vitro	Spiorosteroids and norlignans	Anti-diabetic potential by inhibiting α-glucosidase, but norlignans showed inhibition greater than (5×10^4 fold) standard acarbose.	[54]
Roots	Hydroalcoholic and aqueous extracts	Rats	–	Aphrodisiac activity	[58]
Root	Aqueous root extract	In-vitro (PC12 cell lines)	Sarsasapogenin	Attenuate the symptoms of Alzheimer's diseases by suppressing multiple enzymes such as BuChE, MAO-B, AChE, BACE-1 and Aβ42 fibrillization.	[59]
Root	AR root extracts	In-vitro	Saponins	Antifungal activity (against *Malassezia furfur and M. globosa*) and anti-inflammatory activity.	[60]
Root	Aqueous extract of AR	In-vitro (P388 cell line)	2 → 1 linked fructo-oligosaccharides (FOS)	Immunomodulatory activity via stimulation of natural killer cells action.	[61]
Root	AR extracts	In-vitro (Splenocytes) and Balb/c mice	Sarsasapogenin glycoside (immunoside)	Anti-HBsAg effect mediated via stimulating Th1/Th2 immunity in a dose dependent manner.	[62]
Root	Root powder (5% and 10% levels)	Male albino rats	Phytosterol, ascorbic acid, flavonoids, saponins, and polyphenols	Anti-hyperlipidemic/hypercholestermic effect exhibited by removal of excess cholesterol, boosts hepatic antioxidant profile, and increased bile acid synthesis	[63]
Leaves	Ethanol, hexane, and chloroform leaf extracts	In-vitro	Flavonoids	Antimicrobial property	[64]
Leaves	–	In-silico molecular docking and dynamic studies	Asparoside-C, D and F	Antiviral activity (against SARS-CoV-2)	[65]
Fruit	–	Parasite culture (promastigotes from two L. donovani strains (AG83 and GE1F8R)	Steroidal saponin (Racemoside A)	Anti-leishmanial activity via initiation of programmed cell death directed by damaged plasma membrane integrity, imbalance in mitochondrial membrane potential, and DNA nicking	[66]

AChE: acetylcholinesterase; BuChE: butyrylcholinesterase, MAO-B: monoamineoxidase-B; HBsAg: hepatitis B surface antigen.

3. Pathophysiology of depression and mechanism of action of *Asparagus racemosus* as antidepressant

3.1. Background

The innumerable factors or hypotheses have been implicated in the pathogenesis of depression. But in this literature, we have mentioned a few of the most studied or validated theories. However, the credibility of one single hypothesis to explain the etiopathogenesis of depression is insufficient due to its heterogeneous nature. Still, there are some scientifically relevant neurobiological theories that may explain the pathological cause of major depressive disorders (MDD). These include dysfunctional hypothalamic-pituitary-adrenal (HPA) axis, systemic inflammation, monoamines deficiency, impairment of GABAergic and glutamate neurotransmission, and disturbed circadian rhythm [67].

Thereby integration and linkage of all the plausible mechanism/causal factors would provide a holistic knowledge of the pathogenesis of depression. This correspondingly, aid in developing a novel antidepressant strategy. Multiple pharmacological antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, and selective noradrenaline reuptake inhibitors (SNRIs) have long been recognized to alleviate depression. But, the findings from clinical trials implied that conventional antidepressant regimens show a 60–70% response rate while remission has prevailed in approximately 30% of depressed patients (also known as Treatment Resistant Depression) [68]. Indeed, multidisciplinary approach is needed that cover all the aspects of depression. Accordingly, phytotherapy is one of the alternative strategies against standard pharmacological antidepressant drugs because its usage is perhaps related to several challenges, viz. refractoriness, remission, dry mouth, lower tolerability, hepatotoxicity, cardiac and gastrointestinal episodes, and seizures [69] On top of that, synthetic antidepressants targets either one or two molecular mechanisms, plant therapy may show antidepressant response via acting on multiple molecular systems—named a few, ginseng, *Withania somnifera*, St. john wort, ginkgo, asparagus, etc. *Asparagus racemosus* is one herb amongst them. It is categorized as a pivotal adaptogen that profoundly maintains the homeostasis of daily environmental stress. Because of its excellent therapeutic potential, it could be an emerging nutraceutical ingredient or functional food in the modern era, i.e., one herb with a multipronged therapeutic response. So, first we discuss existing literature on pathophysiology of depression and then explaining the clinical efficacy and mechanism of action of *A. racemosus* in ameliorating depression.

3.2. Glimpse of depression theories in its etiopathogenesis

3.2.1. HPA axis theory

The overactive hypothalamic-pituitary-adrenal (HPA) axis in response to psychological stress has been interlinked to the etiology of depression and anxiety [70]. The activity of HPA axis is controlled by hippocampus region of the brain, which regulate the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, and subsequently CRH stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH), which further signals the adrenal cortex to secrete glucocorticoids (i.e., cortisol) into plasma. Afterward, the circulating endogenous glucocorticoid elicits feedback inhibition of HPA axis activity, which is mediated by binding to the glucocorticoids (GR) and mineralocorticoids (MR) receptors inside (hippocampus and hypothalamus) and outside (pituitary) the brain regions. Thereby, impede the synthesis and release of hormones, CRH and ACTH, thus this GR-mediated feedback inhibition loop sustains the low level of glucocorticoid under normal physiological state. Albeit, evidence accommodated in the review strongly highlighted that impairment of GR-regulated feedback inhibition system on HPA axis have been involved in depression which correspondingly result in compromised neurogenesis and neuroplasticity, specifically in hippocampus. Accordingly, the preclinical studies mentioned in the review have postulated the effect of antidepressant in modulating the GR function. Thereby, pointing out the key role of receptor in the etiology and symptomatology of depression. Hence, targeting the GR more effectively could provide a new strategy to alleviate the depression symptoms and other related neurobiological illness [71].

The meta-analytic study has suggested that depressed subjects are likely to have a higher cortisol level and adrenocorticotropic hormones [72]. Additionally, the findings from a large cohort study have also conveyed a significant relationship between MDD and specific HPA axis indicators, where increased cortisol awakening response (CAR) was seen among patients with both current MDD and remitted MDD. Additionally, higher CAR was observed in depressed subjects with comorbid anxiety instead of other depressive traits (symptoms severity, chronicity, and childhood trauma). Thus, perhaps indicating increased susceptibility to depression [73].

Besides, cumulative evidence has also demonstrated an implication of activated inflammatory response system and immune system (innate immunity) in the pathogenesis of depression where a greater level of pro-inflammatory cytokines, particularly interleukin-6, C-reactive proteins, tumor necrosis factor (TNF)-α have detected in MDD patients than healthy controls [74,75] Accordingly, several study outcomes have shown a profound effect of HPA activity and increased immune-inflammatory response in the prognosis of somatic disorders, namely, cardiovascular diseases, diabetes, adiposity, and neural disorders [76–78]. Also, a literature review has described the idiosyncratic role of depression heterogeneity, where the interface between metabolic dysregulation and up-regulation of inflammatory markers was found to be more specific to atypical depression. In contrast, hypercortisolemia could be more specific to melancholic depression [79].

3.2.2. Monoamine theory of depression

The following hypothesis on the ladder of the pathophysiology of depression is the "historical catecholamine theory of affective disorder" that describes most of the depression that occurred due to the deficiency of noradrenergic and dopaminergic neurotransmission at the adrenergic receptor site [80]. Later, when the action of tryptophan in the antidepressant treatment was revealed [81], the "monoaminergic theory of depression" was come into effect that accounts for the depletion of the neurotransmitters serotonin,

norepinephrine, and dopamine in the central nervous system [82] The majority of the monoaminergic neurons (i.e., serotonergic, dopaminergic, and noradrenergic) are extended from the midbrain and brain stem nuclei to the broader region of the entire brain. This monoaminergic system has been believed to be engaged in synchronizing various brain activities such as sleep, appetite, behavioral, emotional, and cognitive functions. For that reason, standard antidepressant treatments were emphasized to inhibit monoamine re-uptake and elevate the level of these biogenic amines in the central nervous system (i.e., in synaptic cleft). Interestingly, a review of studies has also postulated that functional polymorphism of genes coded for Type A monoamine oxidase (MAOA) and serotonin signaling pathways are involved in major depression or psychiatric disorders. However, this relation has been explained by various MAOA-deficient humans and MAO knockout animal experiments where both MAOA and serotonin modulate the development of brain structure and neurocircuits [83].

In fact, a meta-analysis of 101 studies has scrutinized that in depression, tryptophan metabolism switches from serotonin to the kynurenine pathway, which further preferentially metabolizes into neurotoxic quinolinic acid rather than neuroprotective kynurenic acid [84]. Furthermore, array studies have analyzed that stimulation of inflammatory cytokines induces the upregulation of transcripts code for enzymes indoleamine-2,3-dioxygenase (IDO), Kynureninase, and kynurenine-3-monooxygenase (KMO) located in microglia, and astrocytes. These enzymes directed the tryptophan catabolism towards kynurenine production, which consequently restrained the tryptophan availability for the synthesis of serotonin [85,86]. The plethora of studies have investigated that serotonergic dysfunction

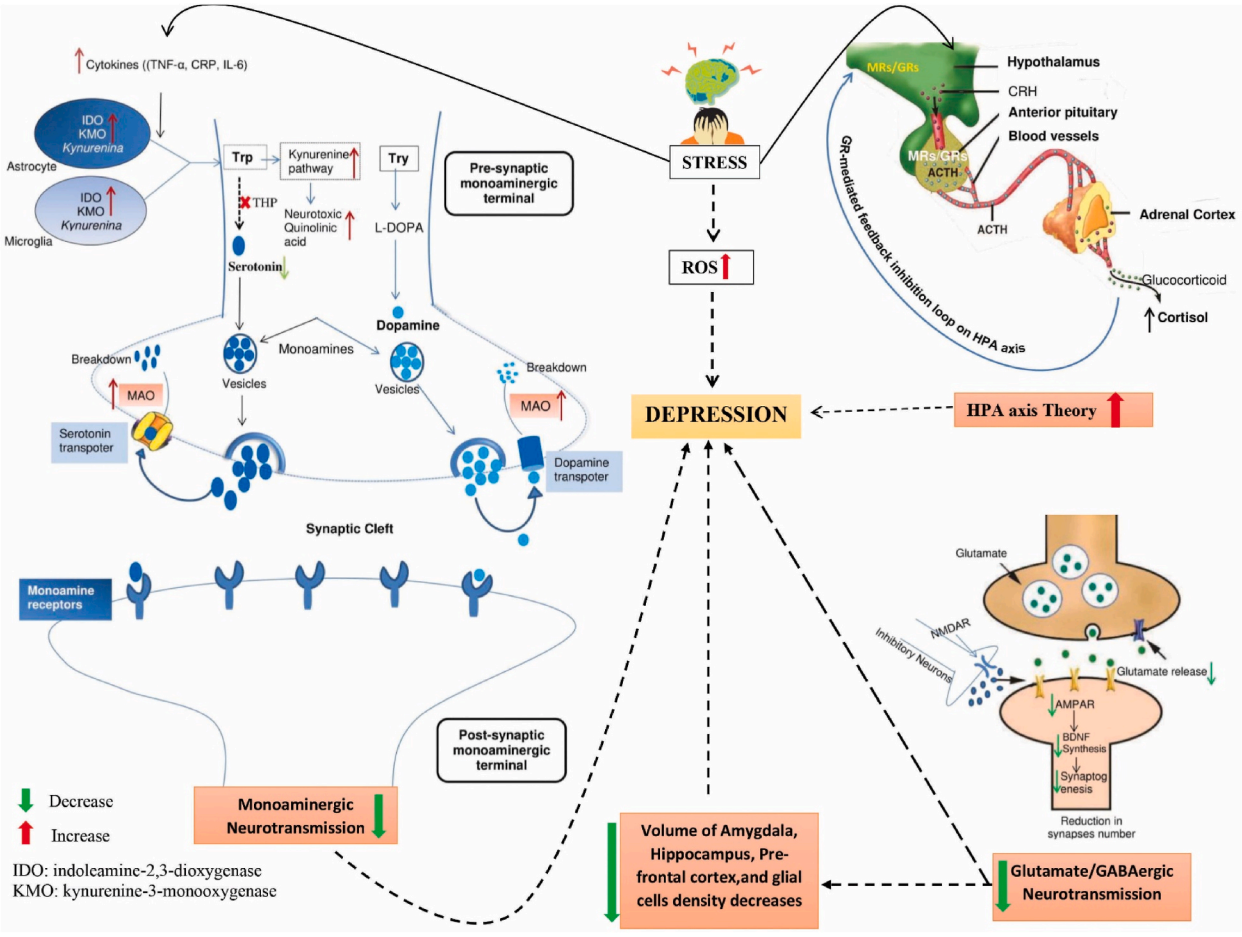

Fig. 3. The partial schematic diagram elucidated the most studied hypothesis linked to the pathophysiology of depression/MDD. The numerous pathways are involved in MDD, but only a few of them are represented in the figure. (a) Monoaminergic theory where deficiency of monoamines in the CNS implicates MDD. In particular, increased concentration of monoamine oxidase (MAO) enzymes and pro-inflammatory cytokines (IL-6, CRP, TNF-α) shifted the tryptophan (Trp) route from serotonin synthesis to neurotoxic quinolinic acid. Additionally, dopamine is synthesized from tyrosine (Try) released in the synaptic cleft, where instead of binding to the dopamine receptor on the post-synaptic terminal, it binds to the re-uptake channels and is oxidized by the MAO enzyme. Hence, upregulation of MAO enzymes has been implicated in MDD by making monoamines neurotransmitter unavailable in different brain regions. (b) Representing an alteration in the GR-mediated negative feedback system on the HPA axis causes hyperactivity of the HPA system, thus increasing the cortisol concentration in various tissues. (c)Depict that dysregulation of glutamate/GABAergic neurotransmission has been involved in MDD, where upregulation of NMDA receptor on GABAergic interneurons interferes with the glutamate release and decreases the glutamate level in the synaptic cleft. Thereby resulting in downregulation of glutamate neurotransmission and reduces the number of synapses and functions.

may be involved in the etiology of neuropsychiatric disorders such as depression, schizophrenia, Alzheimer's, autism, anxiety, eating disorders, and many others [87]. Indeed, a review of animal studies has anticipated that multiple serotonin receptors (most studied 5-HT 1A and 5-HT 1B receptors) and 5-HT membrane transport protein (SERT) that modulates serotonergic transmission may have been involved in MDD and primary targets of antidepressant treatment [88,89]. The extensive literature is present on the role of 5-HT in neuropsychiatric illness, yet the definite function needs to be investigated further.

Emerging animal and human investigations based on pharmacological, neuroimaging, and electrophysiological techniques surmised that dysregulation of dopaminergic mesolimbic and mesocortical systems is allied with depressive symptoms and majorly anhedonia [90]. Notably, the converging results have suggested a strong relationship between depressive symptoms (anhedonia) and decreased striatal expression to reward [91]. This is supported by previous PET imaging studies, where a chronic decline in mesolimbic DA signaling causes down-regulation of the dopamine transporter, consistent with reduced striatal DAT BP expression [92,93].

3.2.3. GABAergic theory of depression

Following the previous theories, the latest GABAergic theory of depression proposed that deficiency in GABAergic neurotransmission is also linked to depressive disorders. In matured brain, both γ-aminobutyric acid (GABA) and glutamate are principal inhibitory and excitatory neurotransmitters respectively [94].

Evidently, the dearth of inhibitory synaptic transmission on glutamatergic interneurons subtypes causes an imbalance in excitation/inhibition (E:I) in the prefrontal cortex. In this regard, Glutamate/GABA neural circuit is a prime target for synthesizing a new generation of fast-acting antidepressants, primarily hinged on $GABA_A$ receptors and N-methyl-D-aspartate (NMDA) [95]. Review of several clinical and preclinical indagations postulated that patients with MDD have low concentration of inhibitory neurotransmitter GABA and altered $GABA_A$ receptors directing GABAergic inhibition. Therefore, GABAergic transmission has been involved in the hippocampal neurogenesis and neural maturation [96]. Fig. 3 represents the network of most studied hypothesis linked to the pathophysiology of depression/MDD.

In summarizing, the mechanism of action discussed above explained the part of depression pathogenesis. However, numerous theories and mechanisms have made room to elucidate the depression etiopathogenesis more comprehensively. One such instance is the role of oxytocin in MDD, where oxytocin interact with different neurotransmitters, inflammatory markers, and neuroendocrine pathways that have described previously been involved in depression [97]. Nevertheless, all the molecular pathways discovered till date are connected from one another i.e., modification/mutation in one signaling pathway sequentially affect the other pathways that have previously been implicated in depression.

3.3. Mechanism of action of Asparagus racemosus on depression

Forced swim tests (FST) and learned helplessness tests (LH) are two validated animal models that are most frequently employed to assess the antidepressant activity of a drug or herb. Singh et al. have reported the antidepressant effect of Methanolic Extract of *Asparagus racemosus* (MAR) in rodents, where MAR was found to reduce the rat immobility in FST, decrease escape failure, and increase the avoidance response in LH. Further, MAR (at a dosage of 200 mg/kg body weight) was effective in reducing oxidative stress generated by an increased level of lipid peroxidation, alongside improved the antioxidant capacity by increasing the antioxidant enzyme in hippocampus and striatum regions [98]. Correspondingly, the antidepressant power of MAR may be due to its action on both serotonergic and noradrenergic systems but not effective on the dopaminergic pathway as per behavioral trial [98]. The knowledge of the underlying mechanism of AR as an antidepressant is lacking despite clinical and non-clinical experiments that have proved the anti-stress/antidepressant property of *Asparagus racemosus* (AR). However, one study has tried to bridge the gap between clinical mechanism and the anti-stress response of AR, where its activity was investigated on two salient neuroendocrine pathways attributed to the onset of depression, particularly the HPA axis and sympathetic-noradrenergic systems. Eventually, results inferred that MAR has the inherent ability to regulate the stress response by activating the monoaminergic system and reducing the HPA axis activity and the SNS system when MAR is administered at a level (50, 100, and 200 mg/kg, per oral) for 7 days in un-manipulated rodents. More importantly, the HPA axis and SNS activity were declined due to a decrease in plasma corticosterone (CORT) and norepinephrine (NE) levels, respectively, by MAR in a dose-dependent manner [99]. On the contrary, MAR has done significant region-specific amendments in monoamines and their metabolites levels and turnover in different brain regions (hippocampus, prefrontal cortex, nucleus accumbens, and hypothalamus) associated with memory, fear, and reward. Surprisingly, MAR showed ceiling effects at 100 mg/kg, where a change in monoaminergic level in several brain regions was independent of its dose [99]. A substantial body of evidence has reported that MAR also possessed nootropic and anti-amnestic potential in a tested behavioral model that may be apparently mediated via instigation of the cholinergic system as a result of its anti-cholinesterase response in distinct brain regions (hypothalamus, prefrontal cortex, and hippocampus) [100,101]. The clinical evidence also incites the anxiolytic effect of MAR via modulating GABA and serotonergic systems [102].

Indeed other factors, mainly lower level of brain-derived neurotrophic factors (BDNF) and decreased neurogenesis, are also ascribed to the depression etiology. The ubiquitously distributed plant-derived moiety saponins exhibit adaptogenic and neuroprotective effects by promoting neurogenesis, revitalizing monoaminergic neurotransmission, escalating neurotrophic factors (BDNF), impeding apoptosis, and intra-neuronal calcium dynamic [103]. Besides, rutin, a glycoside flavonoid, also exhibits antidepressant activity [104].

A series of short-term and long-term randomized, double-blind, placebo-controlled cross-over trials inferred that enzyme-treated asparagus extract (ETAS) at a dosage of 50 mg/d and 250 mg/d was found to enhance the ability to manage the daily psychological stress load and stabilize the sleep quality via anti-stress effect. Further, ETAS supplementation decreased the dysphoria and fatigue,

improved the performance during the stress period, and stimulated the stress response by elevating salivary sIgA [105,106]. The anti-stress effect of ETAS might be due to the induction of heat shock protein 70, a type of heat shock protein that protects cells from various stresses caused by inflammation, reactive oxygen species, fever, infection, hypoxia, UV-radiations, and so on [105,107]. Besides, acute toxicity study (2000 mg/d) and sub-chronic study (500, 1000, and 2000 mg/d for 90 days) and genotoxicity investigation in rats revealed that ETAS do not possess any adverse effects on body weight, food consumption, organ weight, necropsy, mortality etc. thus, could be a safe food and dietary supplement [105]. Similarly, the investigation has also reported the beneficial effect of ethanolic extract of *Asparagus racemosus* (EEAR) in alleviating stress in mice. The trial has suggested that EEAR in a dose-dependent manner was effective in diminishing the oxidative damage in mice brain by reducing the level of lipid peroxidation and nitric oxide. Concurrently, EEAR at a 400 mg/kg dosage significantly elevated the protein and glutathione levels [108]. Apparently, the research has also conveyed that dispensing ethanol root extract of *Asparagus racemosus* (AR) at a dose of 100 and 1000 mg/kg/b.w. in ovariectomized rodents for 90 days was effective in ameliorating the cognitive performance and promoting neuroprotective effects, via up-regulation of estrogen receptors (ERα and ERβ) and spiked level of BDNF in the hippocampus and frontal cortex [109,110]. Withal, all these studies mentioned above were conducted on small sample size and needed further investigation on larger samples.

The excitotoxicity and oxidative stress are key drivers that cause neuronal cell death in several neurodegenerative diseases. However, the study supervised by Parihar, & Hemnani, has manifested that acetone extract of AR (dosage-18 mg/kg/b.w) along with a

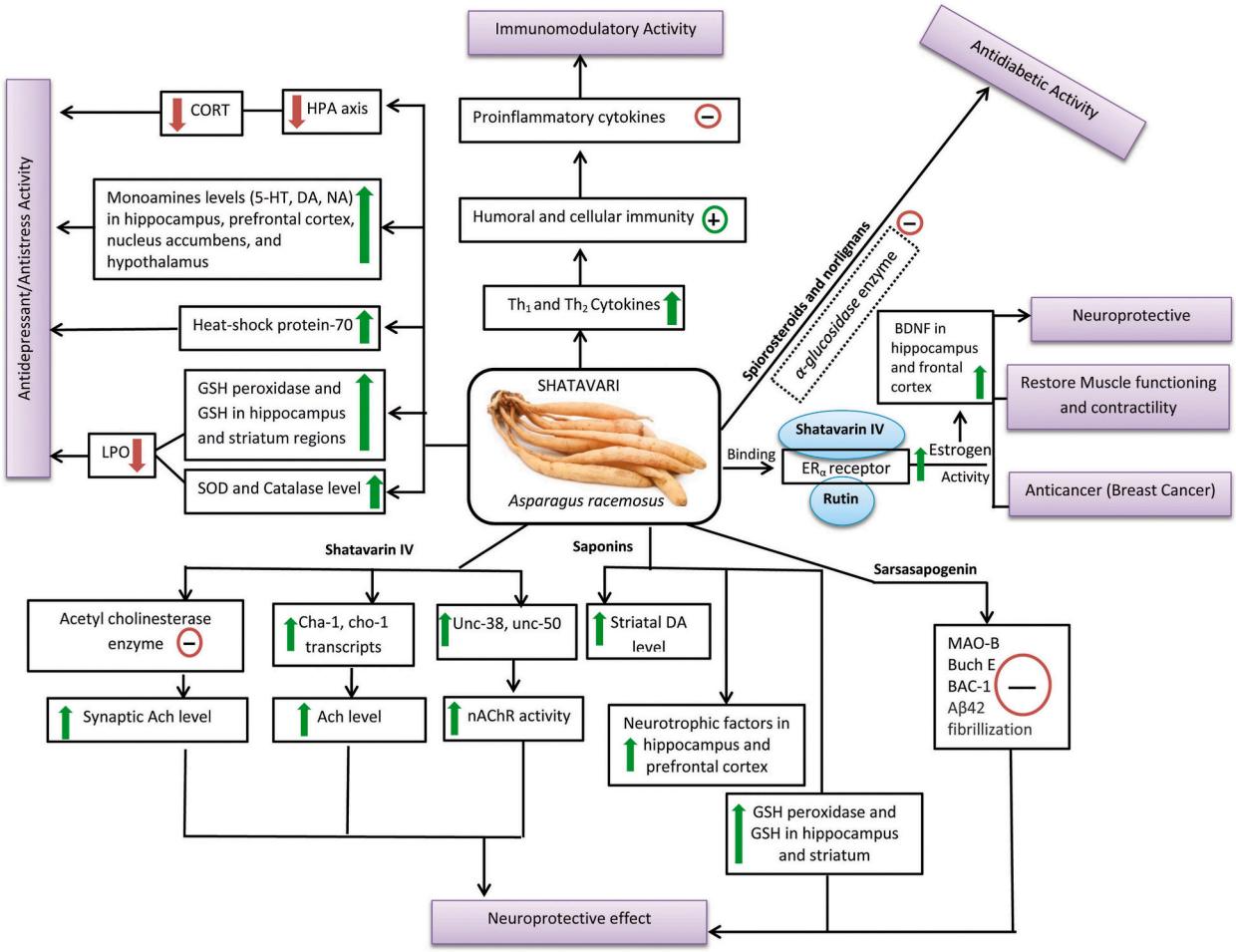

Fig. 4. Visual representation of therapeutic effects of *A. racemosus*, the plant possesses multipronged pharmacological properties by modulating various molecular routes. For instance, neuroprotective effects of plant perhaps due to the inhibition of acetyl cholinesterase enzyme, and upregulation of transcripts which subsequently increases the synaptic acetylcholine level and nicotinic acetylcholine receptors (nAChR) activity. Alongside, suppression of various enzymes such as MAO-B, Buch E, BAC-1, Aβ42 fibrillation and upregulation of antioxidant enzymes (GSH peroxidase, GSH, Catalase, and SOD) in different brain region promote antidepressant like effects and cerebroprotective properties. Apart from this, the antidepressant effects of Shatavari mediated via modulation of several neurotransmitters and neuronal circuits. Further, downregulation of proinflammatory cytokines improves immune response which delineate immunomodulatory efficacy of the plant. BDNF: Brain derived neurotropic factors; AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase, 5-HT: Serotonin; DA: Dopamine; NA: Norepinephrine; GSH: Glutathione; GSH peroxidase: Glutathione peroxidase; SOD: Superoxide dismutase; CORT: Cortisol; nAChR: Nicotinic acetylcholine receptor.

Table 2
Asparagus spp. contributes to alleviate neuropsychiatric illness.

Asparagus spp.	Extract/dosage/Time	Behavioral observation	Neuro-nutraceutical property	References
Asparagus adscendens	Hydroethanolic extract of *A. adscendens* root at a dosage of (25, 50, and 100 mg/kg/day) for 14 days in mice	Diminished immobility time in both FST and TST.	Showed anti-depressant effect by normalizing HPA axis, augmenting monoaminergic mechanism and alleviating oxidative stress by improving antioxidant activity.	[114]
Asparagus cochinchinensis (AC)	AC root extracts (1000 or 2000 mg/kg, PO) delivered to ovariectomized (OVX) rats and rested for two weeks to recover from post-surgical operation.	OVX rats exposed to CUMS treated with AC extract were effectively recovered sugar preferences to control level in SPT, normalize immobility time and swimming time in FST and restore open and closed arm time to control level in EPM, thus indicating anti-depressant like response	AC extracts inferred anti-depressant like behaviors and anxiolytic effects by decreasing corticosterone and pro-inflammatory cytokines and triggers BDNF-TrkB signaling route in an animal model of menopausal depression.	[115]
	Aqueous extract of AC root (AEAC) (100 mg/kg/day) administered to mice	–	Reduced the accumulation of Aβ-42 peptides and neuronal dead cells via stimulating nerve growth factor secretion and impede acetylcholinesesterase enzyme activity along with decreased oxidative damage.	[116]
Asparagus racemosus (AR)	Aqueous extract of AR	–	In vitro study elucidated that sarsasapogenin, a bioactive compound of AR could alleviate AD by suppressing major enzymes such as AChE, BuChE, BACE1 and MAO-B. It also manifested antioxidant, neuroprotective and amyloidogenic activity.	[59]
A. officinalis	Aqueous extract of *A.officinalis* stems (AEAS) administered at 1.6, 8, and 16 ml/kg in mice	Reduced the escaped latency in the Morris water maze test.	Enhance learning and memory ability by increasing cholinergic transmission, BDNF, acetylcholine level, and CREB expression.	[117]

SPT: Sugar preference test; FST: Forced swim test; TST: Tail suspension test; EPM: Elevated plus maze; OVX: Ovariectomized; CUMS: Chronic unpredictable mild stress; BDNF: Brain derived neurotropic factors; TrkB: Tropomyosin receptor kinase B; AD: Alzheimer's disease; AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase; MAO-B: Monoamineoxidase-B; CREB: cAMP response element-binding protein.

regular dietary regime for 2 weeks reversed the hippocampal and striatal neuronal death induced by kainic acid [111]. The diminishing effect of AR on oxidative damage was basically due to enhanced glutathione content and glutathione peroxidase action and lowering of membrane lipid peroxidation and protein carbonyl. Further, it has previously been reported that mice pretreated with hydroethanolic extract of AR root (ARE) at varying doses (i.e., 200, 400, and 800 mg/kg) were effective in lessening seizure severity and improving the depressive condition linked with kindling induced by pentylenetetrazol as well as enhance memory and learning ability. Furthermore, these behavioral changes were modulated by alteration in neurochemical compounds where ARE was significantly tweaked monoaminergic neurotransmission (dopamine, NE, and serotonin) in the hippocampus and cortex region [112]. Fig. 4 demonstrating visual representation of therapeutic effects of *A. racemosus*, the plant possesses multipronged pharmacological properties by modulating various molecular routes.

Indeed, *A. racemosus* root extracts reduce seizure incidence and associated depressive conditions by restoring progesterone, estradiol, corticosterone, and biogenic amines to a normal level, thus could be a promising adjunct treatment along with standard antiepileptic therapy for the management of catamenial epilepsy and associated depression [113]. Table 2 illustrated the other species (Spp.) of *Asparagus* contributes to alleviate neuropsychiatric illness.

Though several preclinical and clinical trials in rodents have successfully reported the antidepressant like-effect of *A. racemosus*, the molecular pathways involved and changes takes place at epigenetic level to alleviate depression have not been fully explored. Furthermore, human studies indicating neuropharmacological effects and dosage of *A. racemosus* is lacking. However, most of the antidepressant action and neuroprotective effects of plant were reported in animal models.

4. Potential toxicity of *Asparagus racemosus*

Insofar, as few clinical studies have proclaimed that *Asparagus racemosus* was safe at higher doses. For instance, Kumar et al. set up a clinical trial in a rat model to test the acute toxicity of aqueous root extract of *A. racemosus* at oral doses of 2000 mg, 4000 mg, 8000 mg, 16000 mg, and 32000 mg/kg for 14 days [118]. The results revealed no marked changes in certain aspects such as neuronal, behavioral, and autonomic alterations and no fatality at such high doses. Thereby, indicating the safety of extract even at a high dose of 32000 mg/kg [118]. An in-vivo experiment analyzed the acute toxicity of a few medicinal plants in mice wherein, aqueous plant extracts were given at two doses i.e., 2500 mg and 5000 mg/kg body weight (b.w.) for 14 days. All plants including *A. racemosus* root extract, *Fuerstia Africana*, and *Ekebergia capensis* were found to be safe at a dose of more than 5000 mg/kg but *H. abyssinica* exhibited 20% fatality at the same high dose [119]. In two other studies, no mortality and acute toxicity were observed in animal models (rats and mice) administered with ethanolic extract of *A. racemosus* and shatavari syrup at a dose of 2000 mg/kg [120,121]. Besides, enzyme-treated asparagus extract was also evaluated for its acute and sub-acute toxicity and genotoxicity in rats at doses of 500, 1000, and 2000 mg/kg b. w. for 90 days. Where, the dosage above 2000 mg/kg was found to be safe and did not cause any mutagenic changes as observed in *S. typhimurium* strains and *E. coli* [122]. However, as per our knowledge, only one study has reported the teratogenic effect of methanolic root extract of *A. racemosus* when administered in rats at a dose of 100 mg/kg/day for 60 days. A marked reduction in body weight and other deformities were also reported [123].

Though *A. racemosus* considered safe, long-term clinical trials need to be conducted to evaluate its chronic toxicity and to generate strong evidence on its safety profile. Moreover, limited studies have been available on the toxicity of the shatavari but the available evidence has significantly displayed that it is safe at consuming high doses.

5. Conclusive remark and future prospects

According to prehistoric texts and progressive pharmacological studies, *Asparagus racemosus* have an immense scope to become a new generation phyto-pharmaceutical agent due to its pleiotropic medicinal effects. As phytopharmaceutical it promotes neuroprotective, nootropic, antioxidant, lactogogue, anti-inflammatory, anticancer, adaptogenic effects and so on. The phytoconstituent, majorly steroidal saponins, of the plants are accountable to impart neuroprotective and other therapeutic effects. Furthermore, growing body of evidence delineated in the present manuscript has also proclaimed the promising anti-depressant properties of *A. racemosus* extracts isolated by using different solvents.

Despite this, further research is needed to bridge the gap between pre-existed literature and modern pharmacology regarding extracts standardization, its clinical efficacy, and mechanism of action of isolated phytoconstiuents as neuropharmaceutical. However, investigation on this herb is still at infancy stage due to dearth of knowledge about "how various bioactive constituents intricately influence the neurological circuit related depression". Indeed, series of preclinical and clinical trials have also elucidated "how this herbal cocktail" elicit antidepressant effects by modulating several biomolecular pathways. Yet, more unbiased long-term clinical studies with large sample size are needed for profound knowledge linked to its dosage, herb-herb/herb-drug interactions, and extract standardization for product uniformity. Henceforth, after passing all the requisite gateways, *A. racemosus* has a potential to be a new era FDA approved neuropharmaceutical drug or clinically advised nervine tonic for ever rising psychiatric illnesses.

CRediT author statement

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Declaration of competing interest

No conflict of interest.

Data availability

No data was used for the research described in the article.

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