



(REVIEW ARTICLE)



A review on a selected *Ayurvedic* herbal formula in the management of *Kaphaja Unmada* (Major depressive disorder): A critical analysis

Samaranayaka Liyanage Gayani Sewwandi ^{1, *}, Maligaspe Korralage Dulani Nadeeka Korralage ² and Samarawickrama Bandaralage Chathurika Jeewanthi Jayasena ³

¹ Temporary Demonstrator, Department of Cikitsa, Faculty of Indigenous Medicine, Gampaha Wickramarachchi University of Indigenous Medicine, Yakkala, Sri Lanka.

² Senior Demonstrator, Department of Desheeya Cikitsa, Faculty of Indigenous Medicine, Gampaha Wickramarachchi University of Indigenous Medicine, Yakkala, Sri Lanka.

³ Senior Demonstrator, Department of Ayurveda Basic Principle, Faculty of Indigenous Medicine, Gampaha Wickramarachchi University of Indigenous Medicine, Yakkala, Sri Lanka.

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Abstract

The widespread psychiatric disease known as major depressive disorder (MDD) is associated with a high rate of morbidity and mortality with correlation to *Kaphaja Unmāda*. According to family, twin and adoption studies, genetic variables are crucial in the emergence of MDD and may provide crucial details regarding the disease's pathophysiology. *Bacopa monniera* (*Brāhmi*) and *Evolvulus alsinoides* (*Vishnukrānthi*) were the ingredients of a decoction from a traditional formula and this review's objective was to investigate how well the herbal formula of decoction effective to treat MDD. Information about MDD and *Kaphaja Unmāda* was acquired from *Ayurvedic* scriptures, contemporary texts and earlier research studies (from primary and secondary sources). A survey of the literature was done on those two herbs in the selected decoction and then examined for their *Pancha Padārtha* (5 elements of herb) and pharmacological qualities regarding in the management of MDD. *Ayurvedic Pancha Padārtha* study has revealed that selected herbal formula has anti-depressant qualities because of their compatibility with *Mēdhya* (nootropic action) *Prabhāva* (special action). The majority of studies have demonstrated the anti-depressant effects of herbal formula, but reviewed articles have also highlighted additional qualities that aid in lowering the symptoms of MDD. According to the literature review and *Pancha Padārtha* analysis, selected herbal formula is useful in the treatment of MDD.

Keywords: Anti-depressant; *Kaphaja Unmāda*; Major Depressive Disorder; *Mēdhya*

1. Introduction

Both the transient emotional condition known as depression—which almost everyone encounters at some point in their lives—and the clinical or bio behavioral syndrome known as Major Depressive Disorder (MDD) are included in the term. The symptoms of MDD include abnormalities of affect and mood, neurovegetative processes (such as disturbed sleep and hunger), cognition (such as unwarranted guilt and feelings of worthlessness) and psychomotor activity (such as agitation or retardation). Being explicitly mentioned in medical books from ancient Greece, it is one of the most ancient and well-known medical illnesses ^[1].

One in six persons will experience MDD at some point in their lifetime, with women experiencing it nearly twice as frequently as men. MDD has a complex etiology with a heritability of about 35%, according to estimates. Environmental variables such childhood sexual, physical or emotional abuse are very closely linked to the likelihood of having MDD ^[2].

* Corresponding author: Samaranayaka Liyanage Gayani Sewwandi

There are many clinical differences in this illness that cannot be explained by a single mechanism. Many of the effects of antidepressants can be explained by the monoamine oxidase theory, however depression is also influenced by genetic, stressful and psychological variables [3].

The premise that social threat and adversity experiences up-regulate immune system elements implicated in inflammation is at the heart of this social signal transduction theory of depression. Pro-inflammatory cytokines, the main mediators of this reaction, can also cause severe behavioral changes, such as the onset of depressive symptoms like melancholy, anhedonia, exhaustion, psychomotor slowness and social withdrawal. Treatment targeting inflammation can be used to treat and prevent MDD [4].

Unmāda is a serious mental ailment that is mentioned in all *Ayurvedic* texts and is characterized by abnormal mental functions. It is a general phrase that refers to a variety of psychiatric issues under one general heading. The definition of *Unmāda* according to etymology is "a state of disturbed mental functions." One of the five varieties of *Unmāda* that results from the aggravated *Kapha Dōsha* (body humor) is known as *Kaphaja Unmāda*. All traditional *Ayurvedic* books included a description of *Kaphaja Unmāda* and its symptomatology [5].

Unmāda is discussed in *Vruddhatraya* and *Laghutraya*, according to *Ayurveda*. *Charaka Samhitā*, *Susruta Samhitā* and *Ashtānga Hridaya Samhitā* (major classical texts) are examples of *Vruddhatraya*. Standing in one place, observing silence, little walking, oozing of saliva, swelling on face, white, moist and dirty eyes are the symptoms of *Kaphaja Unmāda* [6]. According to the *Susruta Samhitā* the patient has vomiting, weakness of digestive fire, debility, loss of taste and cough when suffering from *Kaphaja Unmāda* [7]. In *Kaphaja Unmāda* vomiting, desire for women, sleep, swelling of face are the symptoms and they strong during nights and soon after taking food [8].

Sārangadhara Samhitā, *Bhāvaprakāsha*, and *Mādhava Nidhāna* are all part of the *Laghutraya* (minor classical texts). According to *Mādhava Nidhāna Kapha* getting increased along with *Pitta* by indulgence in overeating, lack of physical exercises brings about derangement of intellect and memory and causes *Kaphaja Unmāda* [9]. *Bhāvaprakāsha* mentioned less speech, aversion for food, excessive sleep, vomiting and salivation present in *Kaphaja Unmāda* [10]. Globally, the use of herbal medicines to treat a variety of ailments is growing nowadays. Memory loss, cognitive deficiencies, poor mental function, etc. are frequently related with psychiatric and neurological illnesses. The multifactorial character of these disorders has limited the success of psychoactive medications in modern medicine. As a result, novel products that could target various pathways and enhance mental capacities are subject to a longer need. The current study based on an *Ayurvedic* medicinal formula that used in *Unmāda*. Herbal decoction chosen from a traditional formula which is used in traditional practice has the following ingredients: *Bacopa monniera* and *Evolvulus alsinoides*. The study critically analyzed the pharmacological activities of the ingredients in selected formula in the management of *Kaphaja Unmāda*

Aims and objectives

The study was created to determine the anti-depressant activity of the ingredients in selected herbal decoction in the management of *Kaphaja Unmāda*.

2. Research methodology

The literary review was referred through authentic *Ayurveda* classics such as *Charaka Samhitā*, *Susruta Samhitā*, *Ashtānga Samgraha*, *Mādhava Nidāna* also from *Bhāvaprakāshaya* and *Ayurveda Pharmacopiea*. The review on MDD was conducted through recent scientific explanations and findings which published in official websites and indexed journals, articles, books, reports of WHO and encyclopedias. The gathered information was compared with traditional and modern scientific explanations using based on pharmacological characteristics, *Rasa (taste)*, *Guna (quality)*, *Veerya (potency)*, *Vipāka (last taste)* and *Prabhāva (specific action)*.

2.1. Review

Decoction chosen from a traditional formula has two ingredients: (Table 1).

Table 1 Review of selected herbs

Ingredients	<i>Bacopa monniera</i>	<i>Evolvulus alsinoides</i>
Family	Scrophulariaceae	Convolvulaceae
Sanskrit name	<i>Brāhmi</i>	<i>Vishnukrān̄thi</i>
Part used	Whole plant	Whole plant

2.1.1. *Bacopa monniera* (Brāhmi)

Herb *Bacopa monniera* is not fragrant. This plant has oblong, succulent leaves that are 4-6 mm (0.16-0.24 in) thick. Oblanceolate leaves are oppositely placed on the stalk. The actinomorphic, white, tiny blooms have four to five petals. Even mildly brackish conditions can support its growth. Cuttings are a common method for achieving propagation. The bacosides, which are triterpenoid saponins of the dammarane type and include jujubogenin or pseudo-jujubogenin moieties as aglycone units, are the phytochemicals in *Bacopa monniera* that have been most thoroughly studied. There are 12 recognized analogs in the family of bacosides. There are other saponins known as bacopasides I–XII. The plantainoside B, D-mannitol, apigenin, hersaponin, monnierasides I–III, cucurbitacin, and the alkaloids brahmine, nicotine, and herpestine have all been categorized. *Brāhmi* has *Kashāya* (astringent) *Tikta* (bitter) *Rasa*, *Laghu* (light) *Guna*, *Sheeta* (cold) *Virya*, *Madhura* (sweet) *Vipāka* balances *Vāta Kapha Doshā* (body humors) and *Mēdhya* in *Prabhāva*

The anti-depressant activity, nootropic property, anti-neuro-inflammatory activity, anti-oxidant activity, anxiolytic activity and neuro-protective activity of *Brāhmi* helps to reduce MDD and *Unmāda*. *Brāhmi's* bioactive components, which also have neuro-protective qualities, boost cognition and learning processes by reducing neuro-inflammation, and amyloid- aggregation [11]. Research on animals has shown that *Bacopa monniera* extracts act on neuro humoral mechanisms in the brain, which may have a good impact on mental performance. According to reports, *Bacopa monniera* improves kinase activity, restores synaptic activity, and eventually improves nerve impulse transmission in the brain to repair injured neurons [12]. In a cognitive study, it was found that rats given either dose of *Brāhmi Ghrita* (*Ayurvedic* medicine) (400 or 800 mg/kg body weight) had improved cognitive function compared to rats in the control group and on Day 1 of every experimental procedure [13].

The neuro-protective and memory-improving activities of the bioactive phyto-constituents, such as the dammarane-type triterpenoid saponins such as bacosides A, B, and C, were primarily documented. *Bacopa monniera* also functions naturally as an antioxidant, which helps lessen morphine dependence [14]. The current discovery showed that *Bacopa monniera* methanol extract has antidepressant effects and experiments displayed longer immobility times in depression models after receiving various dosages of methanol extracts (50, 100, and 200 mg/kg) [15] [16] [17] [18] [19] [20].

It has been demonstrated that *Mēdhya Rasāyana*, a nootropic medicine made from extract of *Bacopa monniera*, encourages free radical scavenger mechanisms and guards prefrontal cortex, hippocampus and striatum cells from cytotoxicity [21] [22] [23] [24] [25] [26]. The anxiolytic effects of *Bacopa monniera* at dosages of 100, 200, and 400 mg/kg in rats suffering from anxiety brought on effectively by ethanol withdrawal [27].

Bacopa participants had improved Auditory Verbal Learning exam delayed word recall memory scores compared to placebo when baseline cognitive deficiency was controlled for using the Blessed Orientation-Memory-Concentration exam. Stroop results showed that the *Bacopa* group improved while the placebo group remained stable. Epidemiologic Studies Center Heart rate, combined state plus trait anxiety scores and depression scale depression scores all dropped with time for the *Bacopa* group but went up for the placebo group [28]. The research study assess the neuro-protective and neuro-trophic effects of *Bacopa monniera* extract (BME) on behavioral depression caused by chronic unpredictable stress in rats. In order to investigate if BME had antidepressant-like effects, behavioral tests were used. Potential mechanisms were evaluated by assessing neuro-trophin levels and hippocampal neurogenesis [29]. A well-known *Ayurvedic* remedy called *Bacopa monniera* has potent antidepressant and anti-nociceptive effects that are equivalent to morphine's effects via adenosinergic, opioidergic, and adrenergic processes. The effectiveness of BM in treating neuropathic pain has also been reported. It also has a potent anti-inflammatory action that is mediated by a COX-2 inhibitory mechanism [30].

2.1.2. *Evolvulus alsinoides* (Vishnukrān̄thi)

It is an herbaceous plant with multiple prostrate or ascending stems that is annual or perennial and has spreading and appressed hairs. The petiolate or sessile leaves range in length from 5 to 10 mm and 0.7 to 2.5 cm. The pauciflorous cymes or single blooms are carried on filiform peduncles that are 2.5 to 3.5 cm long. The fruit is a globular capsule with

four valves and often has four smooth, black seeds inside. Scopoletin, umbelliferone, scopolin, and 2-methyl-1,2,3,4-butanetetrol are among the chemical substances identified from *Evolvulus alsinoides*. *Vishnukrānthi* has *Katu* (pungent) *Tikta Rasa*, *Laghu Singdha* (Unctous) *Guna*, *Katu Vipāka*, *Sheetha Virya*, balance *Kapha Vāta Dosha* and *Mēdhya* in *Prabhāva*

The anti-depressant activity, nootropic property, anti-neuro-inflammatory activity, anti-oxidant activity, anxiolytic activity and neuro-protective activity of *Vishnukrānthi* helps to reduce MDD and *Unmāda*. The forced swim despair test, which was used to assess the anti-depressant activity of *Evolvulus alsinoides*, revealed a reduction in the immobility period compared to the animals in the control group. Significant action was produced at dosages of 50 and 100 mg/kg, and larger doses resulted in an extension of the mobility time [31] [32] [33]. *Evolvulus alsinoides* is a nootropic substance that is used to improve memory, heal injured neurons and operate on neuro humoral systems [34] [35] [36]. Plant extracts have powerful antioxidant properties because they are high in alkaloids and flavonoids [37] [38]. The elevated plus-maze test, open field exploratory behavior, and rotarod performance trials all evaluated ethanol extract of the plant's aerial portions. A dose of 100, 200, and 400 mg/kg of ethanolic extract in the elevated plus-maze demonstrated an anxiolytic effect [39].

The enormous potential of plant-derived bioactive compounds has been shown in a large number of in vitro and in vivo investigations, as evidenced by their ability to modulate the expression and activity of several proteins involved in oxidative stress, neuro-inflammation, apoptosis and aggregation. Therefore, the main focus of this review was on *Evolvulus alsinoides* protective antioxidant, anti-inflammatory, anti-aggregation, anti-cholinesterase, and anti-apoptotic effects [40].

Popular *Ayurvedic* medicinal plant *Vishnukrānthi* has antioxidant, anti-inflammatory, anti-amyloidogenic, nutritional, and immune-supportive effects in addition to slowing down brain aging, reducing stress, improving memory, and aiding in neural tissue regeneration [41]. The review emphasizes on how neuro-inflammation affects neuro-protection and the molecular mechanisms through which various natural compounds or phytochemicals, of the *Evolvulus alsinoides* are employed in various signaling pathways. Currently, scientists are concentrating on naturally occurring substances that have the potential to reduce inflammation in the brain [42].

Since *Evolvulus alsinoides* has been proven to have potential benefits on inflammatory illnesses, wound healing and immune-modulatory activity, it is already employed in traditional Indian medicine as a neuro-protective agent. The acetylcholine esterase activity was thought to be inhibited by plant extracts, which enhanced the establishment of spatial memory and had a neuro-protective impact [43]. In the traditional Indian medical system, Ayurveda, *Evolvulus alsinoides* is widely known for its memory-improving, antiepileptic and immune-modulatory qualities. *Evolvulus alsinoides* crude ethanolic extract is being tested for its adaptogenic and memory-improving effects in mice in light of the growing interest in plants that provide generalized resistance (adaptogens) to stress [44].

3. Results and Discussion

Unmāda is a serious mental ailment that is mentioned in all *Ayurvedic* texts. *Charaka Samhitā*, *Susruta Samhitā* and *Ashtānga Hrdaya Samhitā* described various symptoms of *Kaphaja Unmāda* while *Laghutraya* described symptoms and pathogenesis of *Kaphaja Unmāda*. Modern research articles mentioned the etiology, prevalence, pathogenesis, symptoms and treatment of MDD. Both plants share *Tikta Rasa* as well as additionally shared by the two plants is *Laghu Guna*. Both are *Sheeta Veerya* and *Kapha Vāta Shāmaka*. Both plants share *Mēdhya Prabhāva*. *Katu*, *Tikta* and *Kashāya Rasa* pacify *Kapha Dōsha* so can be used in *Kaphaja Unmāda*. Due to excessive food intake and inactivity *Kapha* is vitiated in *Rasa Dhātu* (tissue). As seat of *Rasa* is *Hrdaya* (heart) *Kapha* increases in *Hrdaya*. *Kapha* increases *Tama Guna* (quality of mind) in *Manas* (mind) and *Mana* become depressed, finally cause *Kaphaja Unmāda*. According to this pathway When *Tikta Rasa* is prominent it favours normal functioning of *Dhātavāgni* (metabolic state) facilitating increased nutrition from *Rasa Dhātu* to subsequent *Dhātu* and prevent the vitiation of *Kapha* in *Rasa Dhātu*. *Laghu Guna* seen in brain, works as *Kapha Shāmaka* so can apply to *Kaphaja Unmāda*. *Laghu Guna* helps easy digestion and kindling digestive fire. It accounts for normal functioning of *Pitta* and *Vāta* in *Kōshtha*. Then proper *Rasa Dhātu* is formed from *Āhara Rasa* (essence of food) and prevents vitiation of *Kapha* in *Rasa Dhātu*. So, it is effective in the management of *Kaphaja Unmāda*. *Snigdha Guna* reduce irritability, depression and increase sleep which is beneficial in the insomnia of depressed patients. *Katu Vipāka* helps to pacify aggravated *Kapha Dōsha* seen in symptom like social withdrawal of MDD. *Sheeta Virya* gives cooling, happiness, comfort mind and pacify anger. Both *Madhura Vipāka* and *Sheeta Virya* act as *Mēdhya*. (nootropic action)

Mēdhya Prabhāva increase intelligent, boost memory and reduce depression. The *Mēdhya* effect improves mental strength thus resist pathogenesis of depression. As the both plants have *Mēdhya Prabhāva* it is highly significant in

patients suffering from depression. The *Mēdhya* property helps to get relief from loss of concentration, obsessional, irritational thoughts and lack of self-control in depression. According to reviewed articles, herbs in selected decoction are potential natural bioactive substances with a wide range of pharmacological effects. The literature review indicates that both herbs in the selected decoction are anti-depressant and nootropic. Nootropic means which improve higher integrative brain functions like memory learning, thinking and understanding. So highly effective in the management of *Kaphaja Unmāda* or MDD. Also selected decoction shows anti-oxidant, anti-neuro-inflammatory, neuro protective and anxiolytic actions. According to studies, diet and nutrition are crucial for both preventing depression and treating it clinically [45]. Consumption of dietary antioxidants such green tea polyphenols or isoflavones has been linked negatively to depression or depressed symptoms. It is commonly believed that stress, anxiety and depression are interrelated phenomena. So, anxiolytic action is beneficial in the management of depression. Depression is related to inflammation and treatment targeting inflammation can be used to treat and prevent MDD. Also neuro-protective action is suitable to manage MDD and hence, selected decoction is efficient in the treatment of MDD.

4. Conclusion

MDD is an important public health problem has been discussed in recent few decades worldwide. *Bacopa monniera* and *Evolvulus alsinoides* are useful in the control of MDD according to the review of the literature and the *Pancha Padārtha* examination. The previous studies of pharmacological effects have revealed that these herbs in the selected herbal formula have strong anti-depressant capabilities. There is an urgent need to reduce the prevalence of MDD among people worldwide.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

- [1] Fava M, Kendler KS. Major depressive disorder. *Neuron*. 2000 Nov 1; 28(2):335-41.
- [2] Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, Mohr DC, Schatzberg AF. Major depressive disorder. *Nature reviews Disease primers*. 2016 Sep 15; 2(1):1-20.
- [3] Belmaker RH, Agam G. Major depressive disorder. *New England Journal of Medicine*. 2008 Jan 3; 358(1):55-68.
- [4] Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin*. 2014 May; 140(3):774.
- [5] Gupta K, Mamidi P. Kaphaja unmada: Myxedema psychosis?. *International Journal of Yoga-Philosophy, Psychology and Parapsychology*. 2015 Jul 1; 3(2):31.
- [6] Sharma RK. *Charaka Samhita, Volume I, Chaukhamba Orientalis, Sanskrit series office: 2005. p. 289.*
- [7] Sharma PV. *Susruta Samhita, Volume I, Chaukhamba Orientalis, Varanasi: 2010. p. 4-411.*
- [8] Srikantha Murthy KR. *Ashtangahrdayam, Chowkhambhakrinadas Academy, Varanasi, India: 2009. p. 58.*
- [9] Murthy KR. *Madhava Nidana. 7th ed., Chaukhamba Orientalis: 2005. p. 72.*
- [10] Srikantha Murthy KR. *Bhavaprakasha, 1st ed., Volume 2, Chowkhambhakrinadas Academy, Varanasi, India: 2009. p. 272.*
- [11] Dubey T, Chinnathambi S. Brahmi (*Bacopa monnieri*): An ayurvedic herb against the Alzheimer's disease. *Archives of biochemistry and biophysics*. 2019 Nov 15; 676:108153.
- [12] Sarkar S, Mishra BR, Praharaj SK, Nizamie SH. Add-on effect of Brahmi in the management of schizophrenia. *Journal of Ayurveda and integrative medicine*. 2012 Oct; 3(4):223.
- [13] Yadav KD, Reddy KR, Gupta LN, Kumar V. Impact of Brahmi Ghrita on Cognition in Damaged Liver. *International Journal of Pharmacy and Life Sciences (IJPLS)*. 2014 May 1; 5(5):3507-11.

- [14] Nandy S, Mukherjee A, Pandey DK, Dey A. Bacopa monnieri: The neuroprotective elixir from the East—Phytochemistry, pharmacology, and biotechnological improvement. *Bioactive Natural products in Drug Discovery*. 2020:97-126.
- [15] Alkahtani J, Elshikh MS, Dwiningsih Y, Rathi MA, Sathya R, Vijayaraghavan P. In-vitro antidepressant property of methanol extract of Bacopa monnieri. *Journal of King Saud University-Science*. 2022 Nov 1; 34(8):102299.
- [16] Zhou Y, Shen YH, Zhang C, Su J, Liu RH, Zhang WD. Triterpene saponins from Bacopa monnieri and their antidepressant effects in two mice models. *Journal of natural products*. 2007 Apr 27; 70(4):652-5.
- [17] Brimson JM, Brimson S, Prasanth MI, Thitilertdecha P, Malar DS, Tencomnao T. The effectiveness of Bacopa monnieri (Linn.) Wettst. as a nootropic, neuroprotective, or antidepressant supplement: analysis of the available clinical data. *Scientific reports*. 2021 Jan 12; 11(1):596.
- [18] Shen YH, Zhou Y, Zhang C, Liu RH, Su J, Liu XH, Zhang WD. Antidepressant effects of methanol extract and fractions of Bacopa monnieri. *Pharmaceutical Biology*. 2009 Apr 1; 47(4):340-3.
- [19] Hazra S, Banerjee R, Das BK, Ghosh AK, Banerjee TK, Hazra US, Biswas SK, Mondal AC. Evaluation of antidepressant activity of Bacopa monnieri in rat: a study in animal model of depression. *Drug Discov*. 2012 Oct; 2(4):8-13.
- [20] Girish C, Oommen S, Vishnu R. Evidence for the involvement of the monoaminergic system in the antidepressant-like activity of methanolic extract of Bacopa monnieri in albino mice. *International Journal of Basic and Clinical Pharmacology*. 2016 May; 5(3):914-22.
- [21] Chaudhari KS, Tiwari NR, Tiwari RR, Sharma RS. Neurocognitive effect of nootropic drug Brahmi (Bacopa monnieri) in Alzheimer's disease. *Annals of neurosciences*. 2017 May 12; 24(2):111-22.
- [22] Kasture SB, Kasture VS, Joshua AJ, Damodaran A, Amit A. Nootropic activity of BacoMind, an enriched phytochemical composition from Bacopa monnieri. *Journal of Natural Remedies*. 2007 Jan 1; 7(1):166-73.
- [23] Rajani M. Bacopa monnieri, a nootropic drug. *Bioactive molecules and medicinal plants*. 2008 Oct 16:175-95.
- [24] Russo A, Borrelli F. Bacopa monnieri, a reputed nootropic plant: an overview. *Phytomedicine*. 2005 Apr 20; 12(4):305-17.
- [25] Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb Bacopa monnieri. *Rejuvenation research*. 2013 Aug 1; 16(4):313-26.
- [26] Sudheer WN, Thiruvengadam M, Nagella P. A comprehensive review on tissue culture studies and secondary metabolite production in Bacopa monnieri L. Pennell: A nootropic plant. *Critical Reviews in Biotechnology*. 2023 May 5:1-5.
- [27] Sudershan B, Chowta MN, Ullal SD, Rajeshwari S, Sayeli VK, Shivaprasad S, Srivastava P. Effect of Bacopa monnieri on ethanol-induced anxiolysis and withdrawal anxiety in wistar rats. *Indian J Physiol Pharmacol*. 2018 Jul 1; 62(3):339-46.
- [28] Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *The journal of alternative and complementary medicine*. 2008 Jul 1; 14(6):707-13.
- [29] Kumar S, Mondal AC. Neuroprotective, neurotrophic and anti-oxidative role of Bacopa monnieri on CUS induced model of depression in rat. *Neurochemical research*. 2016 Nov; 41:3083-94.
- [30] Rauf K, Subhan F, Al-Othman AM, Khan I, Zarrelli A, Shah MR. Preclinical profile of bacopasides from Bacopa monnieri (BM) as an emerging class of therapeutics for management of chronic pains. *Current medicinal chemistry*. 2013 Mar 1; 20(8):1028-37.
- [31] Chauhana D, Raman D, Dhobia M. The neuropharmacological potential and pharmacognosy of *evolvulus alsinoides* linn.; an overview. *International Journal of Pharmaceutical Research and Analysis*. 2018; 3(2):1-6.
- [32] Singh A. Review of Ethnomedicinal Uses and Pharmacology of *Evolvulus alsinoides* Linn. *Ethnobotanical leaflets*. 2008; 2008(1):100.
- [33] Yadav MK, Singh SK, Tripathi JS, Tripathi YB. Ethnopharmacological activities of traditional medicinal plant: *Evolvulus alsinoides*. *World journal of pharmacy and pharmaceutical sciences*. 2016 Feb 19; 5(4):2263-8.
- [34] Tabish M, Jawaid T. A traditional approach to herbal nootropic agents: An overview. *International journal of pharmaceutical sciences and research*. 2012 Mar 1; 3(3):630-6.

- [35] Gupta A, Singh Karchuli M, Upmanyu N. Comparative evaluation of ethanolic extracts of *Bacopa monnieri*, *Evolvulus alsinoides*, *Tinospora cordifolia* and their combinations on cognitive functions in rats. *Current Aging Science*. 2013 Dec 1; 6(3):239-43.
- [36] Nahata A, Patil UK, Dixit VK. Effect of *Evolvulus alsinoides* Linn. on learning behavior and memory enhancement activity in rodents. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 2010 Apr; 24(4):486-93.
- [37] Moghadam NS, Anil Kumar HV, Laksmikanth R, Muralidhar N, Talkad MS, Nagaraj M. Anti-bacterial and anti-oxidant activities of *Evolvulus alsinoides* Linn. *J Pharm Biol Sci*. 2017; 12(01):83-6.
- [38] Srinivasan J, Sundaramoorthy P, Packiam KK. *Evolvulus alsinoides* (Linn.) Linn.: A Revitalizer. In *Cytotoxicity-New Insights into Toxic Assessment* 2021 Sep 15. IntechOpen.
- [39] Sethiya NK, Nahata A, Dixit VK. Anxiolytic activity of *Canscora decussata* in albino rats. *Journal of Complementary and integrative medicine*. 2010 Jun 8; 7(1).
- [40] Shoaib S, Ansari MA, Fatease AA, Safhi AY, Hani U, Jahan R, Alomary MN, Ansari MN, Ahmed N, Wahab S, Ahmad W. Plant-Derived Bioactive Compounds in the Management of Neurodegenerative Disorders: Challenges, Future Directions and Molecular Mechanisms Involved in Neuroprotection. *Pharmaceutics*. 2023 Feb 23; 15(3):749.
- [41] Farooqui AA, Farooqui T, Madan A, Ong JH, Ong WY. Ayurvedic medicine for the treatment of dementia: mechanistic aspects. *Evidence-Based Complementary and Alternative Medicine*. 2018 Oct; 2018.
- [42] Chakraborty B, Mukerjee N, Maitra S, Zehravi M, Mukherjee D, Ghosh A, Massoud EE, Rahman MH. Therapeutic potential of different natural products for the treatment of Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity*. 2022 Jul 22; 2022.
- [43] Yadav MK, Singh SK, Singh M, Mishra SS, Singh AK, Tripathi JS, Tripathi YB. Neuroprotective activity of *Evolvulus alsinoides* & *Centella asiatica* Ethanolic extracts in scopolamine-induced amnesia in Swiss albino mice. *Open Access Macedonian Journal of Medical Sciences*. 2019 Apr 4;7(7):1059.
- [44] Siripurapu KB, Gupta P, Bhatia G, Maurya R, Nath C, Palit G. Adaptogenic and anti-amnesic properties of *Evolvulus alsinoides* in rodents. *Pharmacology Biochemistry and Behavior*. 2005 Jul 1; 81(3):424-32.
- [45] Huang Q, Liu H, Suzuki K, Ma S, Liu C. Linking what we eat to our mood: a review of diet, dietary antioxidants, and depression. *Antioxidants*. 2019 Sep 5; 8(9):376.