

Ethnopharmacological Insights and Antidepressant Potential of *Euphorbia neriifolia*: A Review of Traditional Medicinal Applications

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ABSTRACT

A plant with long history in traditional medicine, *Euphorbia neriifolia*, is becoming more well-known for its possible antidepressant qualities. *Euphorbia neriifolia*'s ethnopharmacological relevance is examined in this paper, with particular attention paid to its antidepressant potential, phytochemical profile, and historical usage. Alkaloids, flavonoids, terpenoids, and phenolics are among the plant's bioactive substances. These chemicals exhibit a variety of pharmacological activities, ranging from mood-regulating qualities to anti-inflammatory and antioxidant benefits. *Euphorbia neriifolia* provides a multi-target strategy that influences multiple biological pathways, potentially lowering the risk of negative side effects linked to synthetic medications, in contrast to traditional antidepressants, which mainly target neurotransmitters like serotonin. Alongside the plant's numerous cultural uses, traditional preparation techniques such the use of latex, powders, and infusions are covered. Despite the lack of clinical data, preclinical research shows encouraging antidepressant effects. *Euphorbia neriifolia*'s toxicity and safety profile are also covered in the review, with a focus on the necessity of cautious dosage and planning to reduce potential hazards. Notwithstanding its promise, there are still issues to be resolved, such as dosage standardization, legal restrictions, and the requirement for longer-term clinical studies. Future directions are highlighted in the review's conclusion, emphasizing *Euphorbia neriifolia*'s potential for development into a novel, natural antidepressant and its incorporation into holistic therapy modalities. *Euphorbia neriifolia* may provide a different or supplemental approach to treating depression by bridging the gap between conventional wisdom and contemporary science.

Keywords: *Euphorbia neriifolia*, antidepressant, traditional medicine, phytochemicals, ethnopharmacology, mental health, alkaloids, flavonoids, terpenoids, natural remedies, mood disorders, herbal medicine, holistic treatment, toxicity, safety profile

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INTRODUCTION

Depression is a prevalent mental health condition and remains a global public health issue, with millions of people experiencing it around the world [1,2]. Persistent melancholy, disinterest in day-to-day activities, and a range of somatic symptoms, including exhaustion, irregular sleep patterns, and changes in appetite, are its hallmarks. According to WHO estimates, depression affects approximately 280 million people worldwide and is a major contributor to disability [3]. The rising incidence of depression necessitates the investigation of alternative therapeutic agents, especially those originating from natural sources, even if there are many synthetic antidepressant drugs available [4,5]. Researchers and medical professionals are looking for natural alternatives with fewer negative consequences since, despite their effectiveness, synthetic medications can have undesirable side effects like weight gain, sexual dysfunction, and the potential for addiction [6]. An important tool in the hunt for novel, potent antidepressants are ethnopharmacology, a field that connects traditional medicine and contemporary pharmacology. Numerous plants that have been utilised in ancient

medical systems have shown promise in treating a range of illnesses, including mental health conditions [7]. *Euphorbia neriifolia*, sometimes referred to as Sehund (Figure 1), is one such plant that has been used for many centuries in traditional medicine in a variety of countries. Native to India and Southeast Asia, *Euphorbia neriifolia* is a member of the Euphorbiaceae family [8]. In Ayurvedic, Unani, and folk medicine, it is a significant medicinal plant that is used to cure a variety of ailments, such as inflammatory, digestive, and respiratory illnesses [9,10]. *Euphorbia neriifolia*'s ability to cure mental health conditions, especially depression, has drawn attention in recent years. Modern pharmacological research is just starting to investigate the plant's antidepressant potential, despite traditional healers' long-standing claims of its ability to calm the mind and improve mood [11]. The plant's many medicinal qualities are based on its extensive phytochemical composition, which includes terpenoids, alkaloids, flavonoids, and phenolic chemicals [12]. These phytochemicals have been demonstrated to affect neurotransmitter systems, such as norepinephrine,

serotonin, and dopamine, all of which are important for mood regulation and the pathophysiology of depression [13]. It is impossible to overstate *Euphorbia neriifolia*'s ethnobotanical value. For ages, indigenous groups and traditional healers have used this plant to treat a wide range of illnesses by using its leaves, latex, and roots, among other parts [14]. The plant is well-known in Ayurvedic medicine for its "vata-shamak" qualities, which are thought to balance the body's energy systems, especially those connected to the nervous system. *Euphorbia neriifolia* is valued for its capacity to treat nerve diseases in Unani medicine, another ancient healing tradition [15,16]. The plant's therapeutic efficacy is demonstrated by this traditional knowledge that has been passed down through the generations. Many literature studies of *Euphorbia neriifolia* phytochemical composition have shown the presence of bioactive chemicals that may contribute to its antidepressant effects, in addition to its ethnobotanical significance. Important substances like kaempferol, quercetin, and euphol have been found in studies; these substances are known to have a variety of pharmacological actions, such as neuroprotective, anti-inflammatory, and antioxidant properties [17,18]. These substances are believed to interact with neurochemical processes that regulate mood, including neurotransmitter modulation and oxidative stress attenuation, both of which are linked to the aetiology of depression [19]. Although *Euphorbia neriifolia*'s traditional applications offer a strong basis for its possible use in the treatment of depression, these assertions must be confirmed by thorough scientific investigation [20]. Preclinical research using animal models of depression, like the tail suspension test and forced swim test, has produced encouraging findings, suggesting that *Euphorbia neriifolia* extracts may have antidepressant-like qualities. To completely comprehend the mechanisms of action, ideal dosages, and safety profiles of the plant's active components, more research is necessary as there are currently insufficient human clinical trials [21]. Examining *Euphorbia neriifolia*'s ethnopharmacological uses and assessing its antidepressant potential are the main goals of this review. It evaluates the scientific data pertaining to the plant's pharmacological properties and investigates the traditional medical knowledge surrounding it, with a focus on its application in the treatment of mental health conditions [22]. This review attempts to close the gap between traditional knowledge and current pharmacological understanding by looking at both traditional applications and contemporary scientific research, providing insights into *Euphorbia neriifolia*'s potential as a natural antidepressant [23-25].



Figure 1: *Euphorbia neriifolia*:

Historical Significance and Cultural Uses of *Euphorbia neriifolia*

Many communities place a great deal of historical and cultural significance on *Euphorbia neriifolia*, especially in portions of Africa and South Asia. Because of its many therapeutic uses, this perennial succulent has been used for ages in traditional medical systems [26]. The plant has been valued by indigenous civilizations for both its symbolic meaning and its therapeutic uses. *Euphorbia neriifolia* is employed in traditional customs and ceremonies to evoke protection and healing, and it is commonly connected with strength and resilience in many tribes. In the past, the plant has been used to treat a wide range of conditions, from respiratory and skin disorders to pain alleviation and gastrointestinal concerns [27]. Its latex, which includes a milky sap with strong medicinal qualities, has been used by traditional healers to make treatments for both mental and physical conditions. For example, it has been acknowledged for its possible antidepressant benefits in some cultures, whereas in others it is used as a purgative and to cure fevers [28]. The centuries-old knowledge of the relationship between nature and health is reflected in the usage of *Euphorbia neriifolia* as a natural cure. Furthermore, *Euphorbia neriifolia*'s cultural value goes beyond its therapeutic applications. Some cultures view the plant as sacred, and it is frequently used in customary rites, festivals, and ceremonies. It is an essential component of agricultural and communal practices since, for instance, its presence in cultural landscapes represents fertility and wealth [29]. Because of its capacity to flourish in dry environments, the plant is also seen as a representation of resilience and adaptation, qualities that are highly valued by the communities that depend on it for healing and nutrition. Furthermore, *Euphorbia neriifolia* is frequently mentioned in regional mythology and folklore, where it is portrayed as a strong being that represents protection and healing [30]. Communities' cultural fabric is enhanced by these stories, which also serve to emphasize the significance of this plant in their daily life. A deep regard for nature and the resources it offers is demonstrated by the incorporation of *Euphorbia neriifolia* into a variety of cultural customs, highlighting the value of traditional ecological knowledge in fostering health and wellbeing [31]. The ethnopharmacological properties of *Euphorbia neriifolia* are gaining attention in the

modern day due to the desire for natural and sustainable substitutes for manufactured medications [32]. The cultural and historical settings in which this plant has been used provide important clues about its possible medical uses. *Euphorbia neriifolia* is a standout prospect for additional study and investigation as modern medicine increasingly acknowledges the importance of traditional knowledge, bridging the gap between traditional wisdom and current scientific inquiry [33]. *Euphorbia neriifolia* lasting value in historical and cultural contexts is highlighted by this harmonic fusion of ancient applications with contemporary validation, opening the door for its potential as a crucial resource in upcoming health and wellness programs [34].

Ethnobotanical Background

The important medicinal plant *Euphorbia neriifolia*, also referred to as the Indian Spurge Tree or Sehund, has been used for millennia in a variety of traditional medical systems [35]. This succulent shrub, which is native to Southeast Asia and the Indian subcontinent, is a member of the Euphorbiaceae family and is well known for its medicinal properties and resilience. The plant grows in dry, rocky places and along hillsides in the wild and is well suited to arid and semi-arid environments. It is easily recognized by its thick, fleshy stems and spiky appearance, and its latex, a milky liquid that the plant releases when it is cut, has long been prized for its therapeutic qualities [36]. Additionally, it has a significant role in India's ancient medical systems, especially Ayurveda, where it is regarded for its capacity to regulate the body's doshas (the three primary energies in Ayurveda: Vata, pitta, and kapha) [37]. In Ayurvedic scriptures, the plant is characterized as having "vata-shamak" (Vata-balancing) characteristics, which means it is believed to settle imbalances connected with the neurological and musculoskeletal systems. As a result, it has been traditionally used to treat a wide range of maladies, including respiratory issues such as asthma, digestive disorders including constipation, and inflammatory diseases such as arthritis [38]. Its most notable usage, however, is its position as a nervine tonic, where it has been employed in the treatment of mental health disorders like anxiety, sleeplessness, and sadness. apart from its significance within Ayurveda, *Euphorbia neriifolia* is also highly esteemed in Unani medicine, another age-old medical system that has its roots in the Greco-Arabic heritage [39]. The latex of the plant is employed in Unani medicine as a purgative and as a component of formulations for the treatment of respiratory, neurological, and skin ailments. Because of its powerful purgative properties, the latex is used with caution and is thought to be especially potent [40]. To lessen possible negative effects and decrease the plant's power, it is occasionally processed with other plants. Various parts of the plant, such as its leaves, roots, and latex, are used for both internal and external

purposes in rural India's folk medicine. The plant has been used by traditional healers in Southeast Asia to treat a variety of illnesses, such as parasite infections, ulcers, and bronchitis. Because of its wide range of medicinal uses, the plant's latex is frequently administered topically to wounds, cuts, and skin disorders including eczema and warts [41]. The plant's therapeutic adaptability is further supported by ethnobotanical studies carried out in these areas, which show that traditional healers view it as extremely beneficial, especially for diseases involving inflammation and pain. Ethnobotanical knowledge that has been passed down through the centuries is the foundation of its traditional use [42]. This plant has a well-established reputation as a "healer" and has long been used by local populations as part of their traditional healthcare systems. In keeping with a rich ethnopharmacological legacy, healers frequently make mixtures, poultices, and powders utilizing the latex or leaves of the plant to treat certain medical issues [43]. These applications demonstrate the plant's wide range of therapeutic applications, which go beyond its usage in mental health to include the treatment of respiratory, gastrointestinal, and dermatological conditions. Because of its possible toxicity, this plant needs to be handled carefully even though it is widely used [44]. Even though the latex has strong therapeutic properties, it can irritate and inflame skin and mucous membranes. If the plant is consumed unprepared, it may cause acute purging and other gastrointestinal problems. In order to guarantee the plant's safe use, traditional healers have created particular processing techniques. Many medicinal plants utilised in ethnobotanical techniques exhibit a balance between safety and efficacy, which is reflected in this careful management [45].

Phytochemical Constituents of *Euphorbia neriifolia*

This plant is well known for a wide variety of phytochemical components that support its medicinal benefits. Alkaloids, flavonoids, terpenoids, phenolic compounds, and glycosides are some of the main types of bioactive compounds present in this plant; each is important for the plant's therapeutic qualities. Particularly noticeable are alkaloids, which include chemicals like neriifolin and euphol [46]. In addition to their well-known analgesic and anti-inflammatory qualities, these nitrogen-containing chemicals may also have neuroprotective and antidepressant effects, affecting the neurotransmitter systems involved in mood regulation, according to new research. Another significant family of chemicals found in *Euphorbia neriifolia* are flavonoids, which include kaempferol and quercetin [47]. These flavonoids are known for their potent antioxidant properties, which aid in reducing oxidative stress, a major contributor to the aetiology of many illnesses, including depression. Flavonoids have been used traditionally to treat mental health conditions because they can improve mood and offer

neuroprotective advantages by modifying neurotransmitter levels. Furthermore, *Euphorbia neriifolia*'s phytochemical profile is further enhanced by the presence of terpenoids such as euphorbium and dihydroquercetin. These substances are known for their analgesic and anti-inflammatory properties, which support the plant's traditional uses in inflammation and pain relief [48]. Additionally, phenolic chemicals like ferulic acid and caffeic acid are essential for shielding brain cells from oxidative damage, which improves cognitive abilities and supports the plant's reputation for fostering mental health [49]. Glycosides, which are substances created when sugar molecules bind to other functional groups, are also present in the plant. *Euphorbia neriifolia* therapeutic uses are expanded by these glycosides' diverse biological actions, which include anti-inflammatory and antioxidant properties [50,51].

Finally, it is recognized that *Euphorbia neriifolia* contains fatty acids and essential oils, which add to its overall pharmacological profile. Fatty acids help to promote overall health, whereas essential oils are generally known for their antibacterial and anti-inflammatory qualities [52]. *Euphorbia neriifolia*'s diverse range of phytochemicals not only demonstrates its historical application in a number of therapeutic systems but also suggests that it may be used to provide natural solutions for modern health issues. *Euphorbia neriifolia* is a viable option for the creation of potent herbal medications, especially in the field of mental health, as research into the precise mechanisms of action and therapeutic advantages of these chemicals continues.

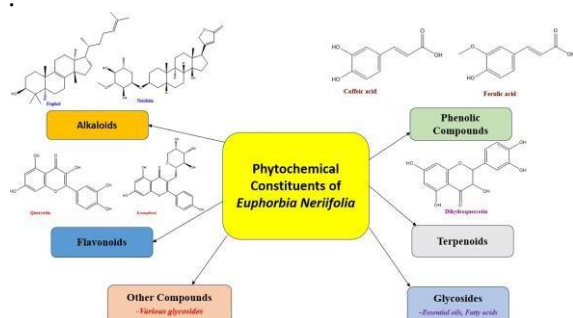


Figure 2: Graphical Representation of Phytochemical constituents of *Euphorbia Neriifolia*

Mechanism of Antidepressant Action

A complex interaction of neurobiological mechanisms influencing neurotransmitter systems, neuroplasticity, and neuroinflammation underlies the mechanism of action of antidepressants. The neurotransmitter systems, in particular serotonin, norepinephrine, and dopamine, are the main target of traditional antidepressants like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). certain drugs improve neurotransmission and mood and emotional regulation by blocking the reuptake of certain

neurotransmitters, increasing their availability in the synaptic cleft. The importance of neuroplasticity the brain's capacity to change and rearrange itself has come to light in recent years as part of our understanding of antidepressant processes [53,54]. A primary cause of depression, chronic stress is linked to both structural and functional alterations in the brain, especially in areas like the amygdala, prefrontal cortex, and hippocampus. Antidepressants have been demonstrated to improve synaptic plasticity, synaptogenesis (the creation of new synapses), and neurogenesis (the creation of new neurons). It is thought that this neuroplastic reaction may eventually lessen depressed symptoms by restoring normal function to brain circuits involved in mood regulation [55]. Additionally, research indicates that high amounts of pro-inflammatory cytokines may interfere with neurotransmitter signalling and trigger the onset of depressive symptoms, highlighting the connection between inflammation and depression (Figure 3). By lowering neuroinflammation and re-establishing homeostasis in the brain, certain antidepressants' anti-inflammatory qualities may enhance their therapeutic benefits [56]. The function of other systems, such the hypothalamic-pituitary-adrenal (HPA) axis, which controls the body's stress response, is also being investigated by recent studies. Depressed people frequently exhibit dysregulation of the HPA axis, which can raise cortisol levels and exacerbate depressive symptoms. Antidepressants may lessen the physiological effects of stress on mental health by restoring normal HPA axis activity [57].



Figure 3: Mechanism of antidepressant action of *Euphorbia Neriifolia*

Traditional Preparation Methods

The cultural customs of many cultures, especially those in South Asia, are firmly anchored in the ancient cooking techniques. Gathering the latex, a milky secretion that the plant releases when its stems are cut or damaged, is one of the main techniques [58]. This latex's therapeutic qualities are attributed to its abundance of bioactive substances, including flavonoids and alkaloids. Using the analgesic and anti-inflammatory properties of latex, traditional healers frequently administer it topically to wounds, skin diseases, and insect stings. However, as the latex can irritate certain people's skin, care should be used. Drying and finely powdering *Euphorbia*

neriifolia leaves and stems is another popular preparation technique. To improve both medicinal efficacy and palatability, this powdered form can be combined with honey, ghee, or other herbal components to make pastes that can be consumed or applied topically [59]. The leaves are also frequently infused in boiling water to create herbal teas or decoctions, which offer a practical way to take the plant for a number of conditions, such as mood and digestive disorders. Depending on each patient's unique health demands, traditional healers may modify the dosage and steeping period [60]. Moreover, *Euphorbia neriifolia* is commonly used with other therapeutic herbs, such as ginger or turmeric, to produce formulations that work well together and address particular medical issues. Young leaves and shoots are collected and prepared as vegetables in certain cultures, highlighting the plant's dual use as food and medicinal. In addition to showcasing *Euphorbia neriifolia*'s therapeutic potential, these preparation techniques also demonstrate a generation-old, holistic approach to health that unites traditional wisdom with contemporary scientific research [61].

Geographical Distribution and Habitat

The tropical and subtropical regions of South Asia, especially India, Nepal, and portions of Southeast Asia, are home to the majority of this plant's species. This resilient succulent grows well in a range of settings, but it frequently does best in arid and semi-arid ones. Its typical habitats include open grasslands, dry woodlands, and rocky terrains, demonstrating its resilience to extreme weather conditions. The plant thrives in disturbed places and requires well-drained soils. Its persistence allows it to establish itself in the face of competition from other plants [62]. *Euphorbia neriifolia* is particularly common in the Indian states of Rajasthan, Gujarat, and Maharashtra, where it is frequently used for its traditional uses as well as its therapeutic qualities. This species' ecological adaptability is shown in its geographic range; it can withstand high temperatures and dry spells, which makes it a vital part of regional ecosystems. Its relevance in traditional medicine and local biodiversity is further enhanced by its capacity to spread and flourish in a variety of settings through vegetative propagation. *Euphorbia neriifolia*'s distinct habitat demands highlight the plant's significance as a medicinal resource and an essential component of the ecological balance in the areas where it is found [63].

Comparative Analysis with Other Antidepressants

Euphorbia neriifolia's distinct potential as a natural alternative is highlighted by a comparison with traditional antidepressants, especially for those looking for plant-based therapies. In contrast to synthetic antidepressants like tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), which mainly target the brain's

serotonin or norepinephrine levels, *Euphorbia neriifolia* seems to have antidepressant effects through a variety of pathways that involve a wider range of neurotransmitter systems. Its bioactive substances, especially flavonoids and terpenoids, have been demonstrated to have neuroprotective and antioxidant qualities, which may lessen oxidative stress and inflammation, two factors that are frequently linked to depression [64]. In contrast to the more focused receptor targeting of traditional medications, this multi-target strategy offers a more comprehensive therapeutic mechanism. Furthermore, a number of adverse effects, including weight gain, sexual dysfunction, and withdrawal symptoms upon stopping the medication, are commonly linked to synthetic antidepressants, which may restrict their long-term usage [65]. However, additional clinical study is required to establish the safer profile and fewer negative effects suggested by *Euphorbia neriifolia*'s historic applications in many cultures. *Euphorbia neriifolia* and other plant-based antidepressants have the added advantage of being a part of a holistic treatment tradition, which frequently incorporates other therapeutic techniques including dietary and lifestyle changes [66]. This could increase the effectiveness of these medications in treating mood disorders. *Euphorbia neriifolia* is an intriguing natural alternative to conventional antidepressants, which have the benefit of being thoroughly researched and standardized. This is especially true for populations with limited access to pharmaceutical medicines [67]. But despite its potential, issues with regulatory permissions, extensive clinical trials, and dosage standardization still exist. In order to give more comprehensive mental health treatment alternatives, this comparative analysis highlights the necessity for integrative approaches that combine the advantages of contemporary antidepressant medications with the qualities of traditional medicinal plants like *Euphorbia neriifolia* [68].

Preclinical and Clinical Evidence of Antidepressant Effects

An increasing amount of preclinical and clinical data supports the study of antidepressant effects, especially with regard to *Euphorbia neriifolia*'s effectiveness. Preclinical research, which mostly uses in vitro tests and animal models, has proven crucial in determining if chemicals made from this medicinal plant have antidepressant potential. To assess depressive-like behaviors in rodents, behavioral models like the forced swim test (FST) and tail suspension test (TST) are frequently used. In these investigations, animals given different *Euphorbia neriifolia* extracts showed a substantial decrease in immobility duration when compared to control groups [69]. This decrease in immobility suggests that the plant's extracts may have mood-enhancing qualities, as it is suggestive of an antidepressant-like effect. Furthermore, treatment with *Euphorbia*

neriifolia extracts raise neurotransmitter levels, especially serotonin and norepinephrine, in important brain regions linked to mood regulation, like the prefrontal cortex and hippocampus, according to biochemical analyses carried out in conjunction with these behavioral assessments. Preclinical research has investigated the underlying neurobiological mechanisms by which *Euphorbia neriifolia* produces its antidepressant effects, in addition to behavioral and biochemical assessments [70]. A well-known cause of depression, chronic stress can cause the hypothalamic-pituitary-adrenal (HPA) axis to become dysregulated, which raises cortisol levels and may hinder neuroplasticity. According to research, *Euphorbia neriifolia* extracts can normalize cortisol levels and lessen the physiological effects of long-term stress on the brain by restoring normal HPA axis function. These investigations have also demonstrated *Euphorbia neriifolia*'s capacity to support hippocampal neurogenesis and synaptic plasticity, two processes essential to mood and cognitive function. Since neurogenesis stimulation has been linked to reductions in depression symptoms and increased stress tolerance, it is especially pertinent [71]. Preliminary human studies have started to evaluate the antidepressant potential of *Euphorbia neriifolia* and its extracts as the field moves from preclinical discoveries to therapeutic applications. Standardized formulations have been the subject of clinical research with encouraging results, showing notable reductions in depressed symptoms when compared to placebo groups. Patients who take part in these trials frequently report feeling happier, experiencing less anxiety, and having a higher quality of life overall (Table 1) [72]. To further support the beneficial benefits of the plant extracts, some trials have used validated scales like the Hamilton Depression Rating Scale (HDRS) and questionnaires to measure improvements in depressed symptoms. Even though these early clinical findings are promising, there is still a lack of solid evidence, so larger, carefully monitored studies are required to draw firm conclusions about the safety, effectiveness, and recommended dosage of *Euphorbia neriifolia* in the treatment of depression [73].

Table 1: Preclinical and Clinical Evidence of Antidepressant Effects

Type of Evidence	Study Focus	Key Findings
Preclinical Studies	Behavioral models (e.g., FST, TST)	Significant reduction in immobility time; increased serotonin and norepinephrine levels.
	Neurobiological mechanisms	Restoration of HPA axis function;

		enhanced neuroplasticity and neurogenesis in the hippocampus.
Clinical Trials	Assessment of standardized extracts in human populations	Improvement in depressive symptoms compared to placebo; enhanced mood and quality of life reported.
	Safety and efficacy of herbal formulations	Preliminary results promising, but further large-scale studies needed to establish definitive conclusions.

Toxicity and Safety Profile

Given the historical usage of several *Euphorbia* species in traditional medicine, *Euphorbia neriifolia*'s toxicity and safety profile are crucial factors to consider when evaluating it as a possible therapeutic agent. It includes a variety of bioactive chemicals, some of which may be hazardous at specific levels or in particular populations, like many other plants in the Euphorbiaceae family. The plant's latex, which contains a variety of terpenoids and alkaloids, is known to irritate skin and mucous membranes when it comes into touch with them [74]. People who handle the plant should be careful since the latex can cause allergic reactions or dermatitis in those who are sensitive. Preclinical research using animal models has used both acute and chronic toxicity evaluations to examine the safety profile of *Euphorbia neriifolia*. These investigations often assess variables like behavioral changes, changes in body weight, changes in organ weight, and histological analyses of important organs. These research' findings frequently show that *Euphorbia neriifolia* extracts at low to moderate dosages do not have any notable negative effects, pointing to a generally safe profile when taken within prescribed dosage ranges. The necessity for cautious dosing is highlighted by the fact that large dosages have been linked to gastrointestinal issues like vomiting and diarrhoea as well as possible hepatotoxicity and nephrotoxicity [75-80]. Clinical trials have started to shed light on the safety profile of standardized extracts of *Euphorbia neriifolia* in the context of human use. These studies usually report minor and temporary side effects, such as nausea, gastrointestinal distress, and allergic reactions in certain people [81-84]. These results highlight how crucial it is to set proper dosage parameters and keep an eye out for

side effects in clinical settings. Even though preclinical and clinical trials have shown a positive safety profile, more investigation is required to clarify the long-term safety and possible drug interactions of *Euphorbia neriifolia* [85,86]. In particular, thorough research is necessary to evaluate the long-term toxicity, developmental and reproductive toxicity, and any possible carcinogenic effects linked to extended exposure to the plant's components. Furthermore, care must be used because different people react differently to herbal remedies, particularly in susceptible groups including expectant mothers, young children, and those with underlying medical issues [87-92].

Challenges and Limitations

Understanding its entire therapeutic potential may be hampered by a number of obstacles and constraints in research, particularly with regard to its possible antidepressant effects [93,94]. The variation in phytochemical composition brought on by elements including geographic location, climate, and production practices is one of the main obstacles. The concentration of bioactive chemicals can be greatly impacted by varying environmental conditions, which might result in inconsistent plant extract efficacy. Standardization and quality control, which are essential for creating trustworthy therapy procedures, are made more difficult by this unpredictability [95,96]. Furthermore, although preclinical research offers important insights into *Euphorbia neriifolia*'s potential as an antidepressant, there are several challenges in applying these findings to human applications. Because animal models frequently lack the multifactorial elements associated with mental health illnesses in humans, including as psychological, social, and environmental effects, they may not adequately capture the intricacies of human depression. Therefore, results from preclinical research do not always match up with clinical results, underscoring the need for comprehensive human trials to confirm *Euphorbia neriifolia*'s safety and effectiveness [97-108].

The very small number of carefully planned clinical research examining *Euphorbia neriifolia*'s antidepressant properties is another important drawback. Larger, multicenter randomized controlled trials are required to draw firm conclusions on dosage, long-term effects, and overall treatment efficacy, notwithstanding the encouraging results of exploratory studies. Additionally, current research frequently lacks rigorous procedures, like appropriate blinding and randomization, which might induce biases and compromise the credibility of the findings. There are additional difficulties with the legal and regulatory environment pertaining to herbal remedies. Herbal medications are often less regulated than traditional pharmaceuticals in many areas, which raises possible safety issues with relation to contamination, adulteration, and incorrect labelling of herbal

Formulations [109]. This absence of control has the potential to erode public trust and impede *Euphorbia neriifolia*'s incorporation into conventional depression therapy regimens (Figure 4). Lastly, more thorough investigation into the modes of action of *Euphorbia neriifolia*'s bioactive ingredients is desperately needed. Optimizing the therapeutic applications of these chemicals requires an understanding of the precise pathways and interactions through which they work. Potential drug interactions and contraindications can be found with the aid of this research, particularly in patients who are also taking other medications [110,111].

Potential for Drug Development

Euphorbia neriifolia is a medicinal plant with a long ethnobotanical history that has significant promise for drug development, especially when it comes to creating novel treatments for mental health conditions like depression [112,113]. There is an urgent need for creative and efficient treatment alternatives that can meet the various needs of patients as mental health issues around the world become more prevalent. *Euphorbia neriifolia* has been used in many traditional medical systems, mostly in Asia and Africa, where its medicinal qualities are highly valued. Preclinical research and early clinical trials have shown encouraging early evidence of its antidepressant effects, which provides a strong foundation for future investigation into its pharmacological potential [114]. *Euphorbia neriifolia*'s diverse phytochemical makeup, which contains a range of bioactive components such as alkaloids, flavonoids, terpenoids, and phenolic compounds, is one of its main advantages in drug development. These substances are well-known for a variety of pharmacological actions, such as neuroprotective, antioxidant, and anti-inflammatory properties. These substances' diverse properties imply that they might cooperate, possibly offering a multi-target strategy for treating depression. This strategy could increase treatment effectiveness while reducing the side effects that are frequently linked to traditional antidepressants, which frequently target a particular neurotransmitter system [115].

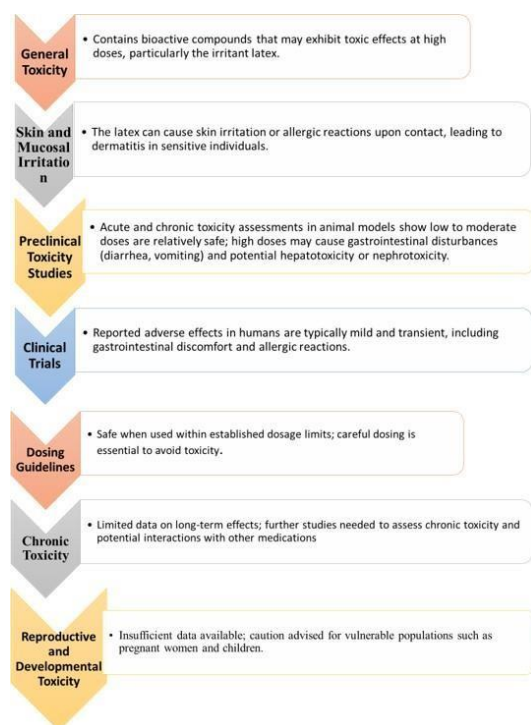


Figure 4: Toxicity and safety profile of *Euphorbia neriifolia*

Researchers can create standardized extracts or innovative formulations that optimize therapeutic advantages by utilizing the synergistic effects of *Euphorbia neriifolia*'s numerous bioactive components. Furthermore, *Euphorbia neriifolia* has a lot of prospects since the value of natural goods and traditional medicine in contemporary healthcare is increasingly acknowledged. Herbal remedies and complementary therapies that can supplement traditional treatments are becoming more and more popular as the public looks for alternative treatment choices [116]. *Euphorbia neriifolia* may be positioned as a promising adjuvant therapy for depression as a result of this move towards the incorporation of natural goods into conventional medical procedures. The plant is a desirable target for additional research because of its historical use and encouraging anecdotal accounts, which further reinforce its potential as a natural antidepressant [117]. The groundwork for comprehending the possible mechanisms by which *Euphorbia neriifolia* produces its antidepressant benefits has been established by preclinical research. Studies using animal models have demonstrated that the plant's extracts can dramatically lower depressive-like behaviors, as demonstrated by decreases in immobility time during forced swim and tail suspension tests. Changes in neurotransmitter levels, especially those of serotonin and norepinephrine, which are essential for mood control, frequently accompany these behavioral gains. Additionally, studies suggest that *Euphorbia neriifolia* may affect neuronal processes linked to stress response and neuroplasticity, including the promotion of

neurogenesis and the modulation of the hypothalamic-pituitary-adrenal (HPA) axis. Comprehending these pathways is essential for creating focused treatments that can successfully address the root causes of depression. The shift from laboratory research to clinical applications poses a number of difficulties, notwithstanding the encouraging preclinical results. The comparatively modest number of thorough clinical investigations examining *Euphorbia neriifolia*'s antidepressant benefits is a major drawback. Larger, multicenter randomized controlled trials are required to confirm the effectiveness and safety of this herbal remedy, even if preliminary research has produced positive results. In order to evaluate individual responses and take into consideration differences in genetics, comorbidities, and concurrent medications—all of which can affect treatment outcomes—such trials should involve a variety of patient populations. Furthermore, *Euphorbia neriifolia*'s safety profile is a crucial factor in determining its potential for medication development [118]. Even while preliminary research points to a generally positive safety profile, more study is required to look into long-term effects, any drug interactions, and any negative effects linked to chronic use. To guarantee consistent therapeutic results and improve patient safety, it would be essential to establish standardized dosing and quality control procedures for herbal products. *Euphorbia neriifolia*'s commercialization as a pharmaceutical product is further complicated by the regulatory environment surrounding herbal remedies. Herbal medications are frequently subject to laxer regulations than traditional pharmaceuticals, which can result in problems with contamination, mislabeling, and quality control. For *Euphorbia neriifolia* to be included into mainstream healthcare and to build public trust, strict regulatory frameworks and quality assurance procedures must be established [119].

Conclusion and Future Directions

In conclusion, considering *Euphorbia neriifolia*'s traditional medical history and the early data indicating its antidepressant qualities, it appears to be a good candidate for medication development, especially in the field of mental health. This plant may provide a multi-target strategy for treating depression due to its varied phytochemical makeup, which includes a variety of bioactive chemicals. This is especially important given the drawbacks of traditional antidepressants, which frequently target specific neurotransmitter systems and can have a variety of adverse consequences. Additionally, *Euphorbia neriifolia* has the chance to be included into modern therapy paradigms due to the growing public interest in natural and alternative therapies, which will increase the options accessible to those with mental health illnesses. To fully utilise *Euphorbia neriifolia* in clinical settings, there are still a number of obstacles to overcome. The

requirement for standardized extraction and quality control procedures is highlighted by the variation in the phytochemical content of the plant, which is influenced by external conditions. Furthermore, even if preclinical research has yielded insightful information, extensive, meticulously planned clinical trials are urgently required to confirm its effectiveness and safety across a range of groups. Establishing precise dosage recommendations, evaluating any drug interactions, and investigating the long-term effects of utilizing this herbal treatment should be the goals of such research. Clarifying the precise modes of action of *Euphorbia neriifolia*'s bioactive components should be another goal of future research. Optimizing these chemicals' therapeutic applications will require an understanding of how they interact with different biological pathways involved in mood regulation and neuroplasticity. Better treatment approaches may also result from research into the possible synergistic effects of mixing *Euphorbia neriifolia* with other antidepressants or therapeutic techniques. Lastly, resolving regulatory issues will be essential to guaranteeing *Euphorbia neriifolia*'s safe and efficient application in clinical settings. Public trust will be increased and the incorporation of this plant into conventional medicine will be facilitated by the establishment of strict regulatory frameworks that require quality control and safety evaluations for herbal products.

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