REVIEW ARTICLE

Exploring *Moringa oleifera* Bark as a Natural Antidepressant: Phytochemistry, Neuropharmacology, and Future Clinical Perspectives

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ABSTRACT

Moringa oleifera (MO) has gained more scientific attention because of its wide range of phytochemicals composition and wide pharmacological activities, especially in neuropsychiatric diseases. Based on preclinical evidence, there is some indication that multiple bioactive compounds in MO have antioxidant, anti-inflammatory, and neurotransmitter-modulating properties, all of which are very relevant to the pathophysiology of depression. While the leaves and seeds of MO plants have been studied in great detail, the bark is relatively under-researched, despite its unique phytochemical composition. The bark has been found to contain flavonoids, lactones, sterols, tannins and phenolic compounds, many of which have been found to have activity on the central nervous system (CNS). The results indicate that MO bark has a scientific basis for further research as a source of novel plant-based antidepressant drugs. Mechanistic evidence, consisting primarily of studies on MO leaves, indicates that constituents in the bark can exert a neuro-modulating effect by promoting monoaminergic neurotransmission, modulate the γ-aminobutyric acid (GABAergic) signaling pathway, reduce oxidative stress, inhibit pro-inflammatory cytokines, and activate neuro-modulatory pathways such as brain-derived neurotrophic factor (BDNF). These mechanisms are similar to those that are affected by traditional antidepressants, and could account for the mood-stabilizing and neuroprotective effects of these drugs. But there is a significant lack of knowledge about bark behavior, biochemistry and molecules studies. In addition, there is a lack of standardized bark preparations, geographical and extraction-related variation of phytochemical composition, and limited pharmacokinetic and blood–brain barrier (BBB) penetration data which still hampers the translation of these products. Hence, a detailed preclinical study using proven animal models, standardized extracts, and mechanistic molecular pathways is crucial to demonstrate the antidepressant effects and clinical significance of Moringa oleifera bark.

Keyword: Moringa oleifera, Neuropharmacology, Bark extract, Neuroprotective effects, Pharmacological activities

1. Introduction

Moringa oleifera L. (MO) is a Moringaceae member that has attracted significant scientific interest due to its multiple chemical constituents and great range of pharmacological effects. Evidence is mounting in preclinical studies that multiple bioactive compounds found in MO have antioxidant, anti-inflammatory, and neurotransmitter-modulating effects, which are linked mechanistically to the pathophysiology of depression and other mood disorders[1] . Most studies have been carried out using the leaves and seeds, but the bark is relatively underutilized and has been found to possess a number of unique phytoconstituents with CNS activity. Phytochemical studies on the bark of MO have revealed the presence of flavonoids, tannins, sterols, phenolic acids, glycosides, lactones and alkaloids [2]. Several of these compounds exhibit neuroprotective, antioxidant and anti-inflammatory activity, which could be responsible for their antidepressant activity. These phytoconstituents make a plausible scientific basis for investigating the natural antidepressant potential of bark extracts. Existing neuropharmacological studies, mostly based on extracts from the leaves, indicate that MO could affect various pathways associated with depression, such as by increasing the levels of monoaminergic neurotransmission, modulating γ-aminobutyric acid (GABA) signaling, reducing oxidative stress, inhibiting pro-inflammatory cytokines, and enhancing the level of neurotrophic mediators—including brain-derived neurotrophic factor (BDNF) [3]. These pathways play a vital role in the action of modern antidepressant drugs. Nevertheless, behavioral and mechanistic work involving bark is extremely scarce, highlighting a lack of data about this work. In order for a full evaluation of the bark extracts to occur in in vivo evaluation, a thorough assessment of the extracts in proven rodent model

systems is necessary including the Forced Swim Test, Tail Suspension Test and chronic stress pals around mice and rats[4]. This includes with the development and study of molecular components, including neurotransmitter levels and oxidative and inflammatory mediators . One of the biggest problems of translating bark is that there is no standard way to prepare it. The contents of phytochemicals are very variable depending on the extraction process, age of the plant and geographical location as well as polarity of the solvent used [4]. Standardization that includes chromatographic fingerprinting and measuring marker substances is required to ensure reproducibility of results in different labs and investigation in clinical settings. Similarly, there is no pharmacokinetic and blood-brain barrier (BBB) penetration data on the compounds from bark as well; if no such data is available, one cannot well set dosing and safety parameters . There, chromatography fingerprinting quantification of marker compounds, and validation extraction protocols are necessary to ensure reproducibility and facilitate clinical translation. Depression is one of the most common causes of global disability that affect over 300 million people worldwide [5]. It has a significant negative effect on the quality of life, productivity, interpersonal functioning, and general health. The World Health Organisation has identified depression as a leading cause of years lived with disability with a growing prevalence in diverse age groups and socioeconomic settings . Aside from emotional suffering, depression has been linked with a greater risk of cardiovascular disease, metabolic disorders and even suicide, putting a huge burden on healthcare systems[5]. Despite the existence of therapies available many parts of the world, especially low and middle-income countries, suffer from a lack of accessibility to mental health-related treatment services in these communities, hence there is a dire need for alternative therapeutic options. Although there are several classes of antidepressants available, such as the SSRIs, SNRIs, MAOIs, and tricyclics, these therapeutic drugs are less than ideal for many patients. About one-third do not enter into remission, and delayed action (happens often, weeks), limit the use in acute episodes [6]. Side effects like sexual dysfunction, weight gain, insomnia, gastric complaints, and withdrawal symptoms further decrease the adherence . Additionally, there is a good number of drugs that are not effective in treatment-resistant or atypical depression. Pharmacologically interactions and safety issues limit the use of them in vulnerable populations. These limitations have made it clear that novel, safer, and faster-acting replacements are necessary that target more general pathways biochemically implicated in the pathology of depression [7] . Furthermore, late treatment onset and side effects like sexual dysfunction, weight gain, gastrointestinal disturbances and sleep disorders, as well as symptoms of withdrawal, can impair treatment adherence.These restrictions have led to an increased focus of scientists on studying plant-derived neuroactive compounds as alternative or adjunctive drugs for depression treatment. Flavonoids, alkaloids, terpenoids, and polyphenols are among the various phytochemicals found in medicinal plants that have antioxidant, anti-inflammatory and neuromodulatory properties related to mood regulation[8]. Plant-based agents are characterized by many mechanism of action that may be more potent in addressing the complex pathophysiology of the depression compared to drugs with single mechanism of action. In addition natural products have greater potential benefits which include tolerability and lesser chances of serious adverse effects. Such a revival is parallel to trends in the rest of the world to integrative and evidence based herbal medicine as a therapy against psychiatric disorders [9]. The nutritional and medicinal value of moringa oleifera is a well-known fact, whereas the majority of the neuropharmacological studies have been performed on the leaves and seeds. The bark remain an underutilized but promising source of neuroactive phytochemicals that warrants systematic pharmacological and mechanistic investigation [10]. [11] .

2. Botanical and Ethnomedicinal Profile of *Moringa oleifera*

Moringa oleifera is a fast-growing deciduous tree which can grow to 10-12 metres tall in the family Moringaceae. Its soft corky bark, tripinnate foliage, fragrant white flowers and elongated triangular seed pods make it a very fragrant plant [12]. MO is widely grown in tropical and subtropical areas because of its ability to grow in dry conditions and dry soil. Native to the Indian sub-continent but widely spread throughout Africa, South East Asia and South America and other tropical parts of the world. The factors mainly cited for the global cultivation include its nutritional, medicinal and ecological values. Various parts of the plants contain bioactive phytochemicals which have nutritional and therapeutic potentials. Traditional medicine in India (Ayurveda, Siddha, and African ethnomedicine) has long relied on MO to treat inflammatory diseases, metabolic disorders, fatigue, stress-related disorders, and neurological diseases. [13] Preparations of bark, leaves, and roots have traditionally been used in preparation for remedies to be used for headaches, epilepsy-like symptoms, nervous disorders, and mood disturbances. MO has been classified as a

"nerve tonic" which indicates that CNS-related effects have been recognised for a long time.

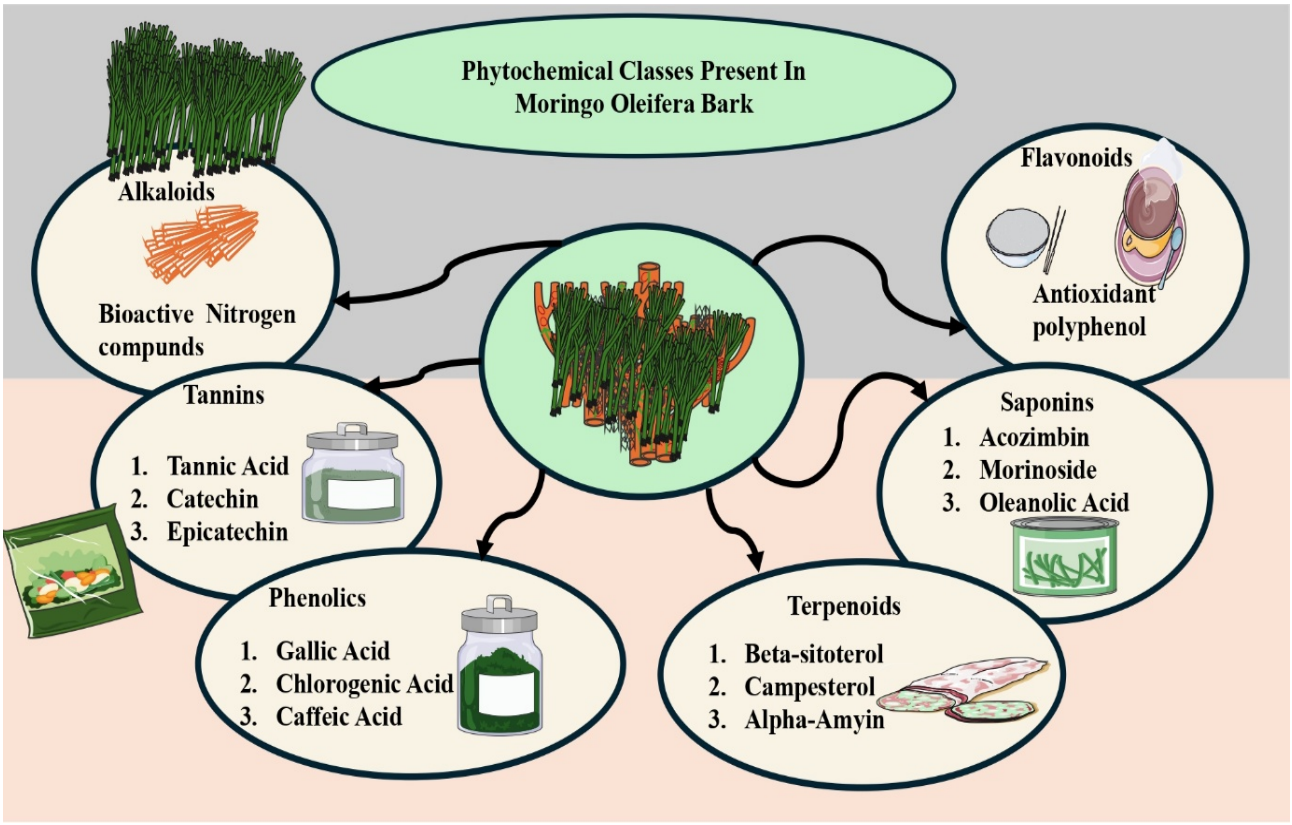

Figure 1: Schematic representation of the major phytochemical classes identified in Moringa oleifera bark that account for the diverse bioactive components within it

The ethnomedicinal uses of MO bark are important to inform scientific studies of its potential as a neuroprotective and antidepressant agent[14].

3. Phytochemistry of *Moringa oleifera* Bark

The bark of Moringa oleifera has various classes of phytochemicals like alkaloids, flavonoids, polyphenol acids, glycosides, saponins, terpenoids, tannins, and sterols. These compounds are responsible for the wide host pharmacological activities of the plant. Phenolics and flavonoids provide anti-oxidant and anti-inflammatory activity and tannins and saponins, antimicrobial and adaptogenic. Sterols & terpenoid might have impact on cell signaling and membrane stability [15]. The wide pharmacological activity of the plant is attributed to these constituents. The phenolic compounds and flavonoids have strong antioxidant and anti-inflammatory properties, while tannins and saponins have antimicrobial and adaptogenic properties. Sterols and terpenoids could affect membranes and intracellular signaling pathways. The constituents that are alkaloid-like could also regulate neurotransmission and neuronal signaling pathways involved in depression. The bioactive compounds found in MO bark are quercetin derivatives, kaempferol, β-sitosterol, ferulic acid, vanillic acid and lactone derivatives[16]. These compounds have antioxidant, anti-inflammatory and neuroprotective effects which are invaluable for mood regulation. Quercetin and kaempferol have effects on monoamine metabolism and neurotrophic signalling. b-sitosterol has membrane-stabilizing and anti-stress effects. Phenolic acids decrease oxidative stress in the neural tissue[17]. The presence of such compounds gives mechanistic plausibility for the antidepressant activity, however, bark specific CNS studies are limited, which also indicates the need for target phytochemical and pharmacological evaluation. Extraction of the MO bark is usually done using solvents such as Methanol, Ethanol, Hydroethanol or Water. Advanced techniques such as Soxhlet, maceration, ultrasonic-assisted extraction and supercritical carbon dioxide extraction increase the yield and selectivity [18]. Standardization will require the definition of chemical markers, development of chromatographic fingerprints (HPLC, UPLC-MS) and quantification of some important chemical constituents such as flavonoids and phenolics.Quality control has to cover the aspects of microbial load, heavy metals, pesticide residues, and batch-to-batch variation. Possibly

without standardization, pharmacological data becomes inconsistent, which is a barrier for clinical translating[19]. **(Figure 1).**

Among the phytochemical groups in Moringa oleifera bark are alkaloids (nitrogen-containing biologically active compounds), flavonoids (antioxidant polyphenols), tannins (tannic acid, catechin, and epicatechin), phenolic compounds (gallic acid, chlorogenic acid, and caffeic acid), saponins (acozimbin, morinoside, and oleanolic acid), and terpenoids (-sitosterol, campesterol, and -amyrin). These phytochemicals together are responsible for the medicinal effects of Moringa oleifera bark by their antioxidant, anti-inflammatory, and neuroprotective activities.

Changing to validated extraction protocols and CC regulatory quality standards is critical for the development of reproducible therapeutic formulations. The phytochemical composition in the MO bark is diverse relative to the nature of soil, climate, altitude, water availability, when harvesting the plant and when the plant is in maturity. Post-harvest factorsAngelica Angels PugachevLatin-styleCompound promoterblood post-harvest acclimatization of the dahlia during drying-temperaturat storage temperaturat extraction method. chemical stability. yield[20]. The flavonoids and phenolic compounds may undergo changes in pharmacological activity during long storage and high drying temperatures. Thus, it is essential to establish strict cultivation, harvesting and processing conditions to guarantee uniformity in therapeutic application[21] **(Table 1).**

Table 1. Phytochemical Constituents Identified in *Moringa oleifera* Bark

Phytochemical class	Representative Compounds	Relevance to CNS / Antidepressant Activity	References
Flavonoids	Quercetin, kaempferol, rutin	Antioxidant, anti-inflammatory, BDNF signalling	[81]
Alkaloids	Moringinine, benzylamine derivatives	Possible MAO inhibition, neuromodulator actions	[37]
Phenolic Compounds	Gallic acid, ferulic acid, chlorogenic acid	Potent antioxidant, reduces MDA, supports mitochondrial integrity	[82]
Tannins	Condensed and hydrolysable tannins	Anti-inflammatory, neuroprotective, modulate oxidative biomarkers	[83]
Glycosides	Flavonoid glycosides, cardiac-like glycosides	CNS modulation, may improve stress resilience	[84]
Terpenoids & Sterols	β-sitosterol, stigmasterol	Anti-inflammatory, membrane-stabilizing, adaptogenic actions	[85]
Lignans & Lactones	Coumarin-like lactones	Potential neuromodulation, antioxidanst roles	[85]
Saponins	Triterpenoid saponins	Neuroprotective, anti-inflammatory effects	[86]

4. Pathophysiology of Depression and Targets for Herbal Interventions

Depression is a multifactorial neuropsychiatric disorder characterized by disturbances in neurotransmission, neuroendocrine function, disturbances of oxidative balance, inflammatory signaling and neuroplasticity. At present, it is unclear whether depression has a simple or complex pathogenesis and whether there is a single mechanism or several biological pathways involved. The monoaminergic theory is still one of the most popular theories of depression. This theory suggests that depressive symptoms are linked to the lack of or abnormality in serotonin (5-HT), norepinephrine (NE) and dopamine (DA) [22]. These neurotransmitters are important in the regulation of mood, motivation, sleep, cognition and emotional behavior. Depression manifestation includes, among other things, a decrease in the supply of neurotransmitters or the receptor's sensitivity. Conventional antidepressants that inhibit the reuptake of monoamines or inhibition of their enzymatic breakdown, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), are the main types used. Likewise, a number of phytochemicals found in herbs, such as flavonoids and alkaloids, have been shown to influence monoaminergic pathways by acting on monoamine oxidase activity, neurotransmitter release and receptor signalling. Another important system that plays a role in depression is the hypothalamic–pituitary–adrenal (HPA) axis. Chronic stress results in chronic activation of HPA axis and sustained high cortisol levels [23]. Chronic stress causes constant activation, and this causes cortisol to become increased, feedback inhibition to become broken, and the hippocampus to become atrophied, and symptoms of depression to resemble. Dysregulated HPA axis function is implicated in sleep disturbances, decreased cognition and emotional instability. Herbal interventions with

adaptogenic action - e.g. extracts with a high content of flavonoids - may be helpful in normalizing the cortisol level and HPA axis balance[24]. Moringa oleifera bark has bioactive compounds with stress modulating properties, thus a promising candidate for neuroendocrine components of depression. Oxidative stress causes neuronal damage, dysfunction of synaptic activities, and depressive symptoms through the overproduction of ROS and reduced antioxidant activity. Antioxidant Enzyme:- SOD, CAT, and GSH play a protective role; they are reduced in depression. Herbal compounds containing high phenolics and flavonoid compounds have anti-oxidative effects due to scavenging of free radicals and the boosting of endogenous antioxidant systems [25]. MO bark, with an extensive history using various body parts to provide benefits patients suffering from a variety of ailments and affected with specific syndromes in a recent review - AMH Maready stated this. AMH Maready stated this in reference to the antioxidant profile of MO bark may help restore mitochondrial functionality and reduce oxidative burden.32 Depression is known to be linked to increased pro-inflammatory cytokines such as IL-1b, IL-6, TNF-a and CRP[26]. These mediators impact the neurotransmission, neuroplasticity, and HPA axis regulation, which form a feedback loop resulting in the worsening of depressive symptoms. Chronic inflammation also affects synaptic signal and lowers neurogenesis. Herbal compounds with anti-inflammatory effects - as are found in the bark of MO - can modulate the release of cytokines, as well as decrease microglial activation[27]. These inflammatory mediators interfere with neurotransmission, reduce neuroplasticity and affect the regulation of the HPA axis, all of which play a role in the worsening of depression symptoms. Chronic neuroinflammation also causes decreased neurogenesis and synaptic connectivity. Anti-inflammatory compounds found in plants could reduce the release of cytokines and stop the activation of microglial cells, thus enhancing neuronal function and behavioral outcomes. The anti-inflammatory phytochemicals found in Moringa oleifera bark thus may be useful therapeutic candidates in depression. Brain-derived neurotrophic factor (BDNF) is an important molecule involved in neuronal growth, synaptic plasticity and stress resistance[28]. Depression is associated with low production of hippocampus and prefrontal cortex and functioning of the BDNF. Restoration of the function of the molecule called Brain-derived Neurotrophic Factor (BDN) improves neurogenesis, synaptic strength, and mood regulation. Many natural compounds - including flavonoids - induce upregulation of BDNF via antioxidant, anti-inflammatory and receptor-mediated mechanisms. Preliminary evidence exists that suggests the effects of MO extracts on neurotrophic pathways that make the bark a possible promoter of neuroplasticity. Increasing the expression of the protein, which is known as the brain derived neurotrophic factor (BDN), is a promising mechanism for herbal antidepressants[29].

5. Neuropharmacological Basis of the Antidepressant Potential of *Moringa oleifera* Bark

Animal studies based on depression-related models like Forced Swim Test (FST), Tail Suspension Test (TST), Chronic Mild Stress (CMS) and Open Field Test (OFT) have shown that extracts from MO have antidepressant-like effects. Although most data comes from leaf extracts, the bark has shown to be potential in reducing immobility and increasing exploratory behaviour suggesting central nervous system activity[30]. While the majority of the investigations have been done with leaf extracts, some preliminary studies have focused on the effect of bark extracts on immobility behavior and exploratory activity, which suggests a CNS effect. Further evidence supporting its mood regulating effects include improved sucrose preference, locomotor activity, and stress-related behavioral markers. The results from these experiments are crucial for further behavioral and mechanistic assessment of MO bark in depression. MO phytochemicals have been shown to have neuro protective effect against oxidative neuronal injury in vitro, to inhibit expression of inflammatory mediators and to enhance mitochondrial function[31]. Further, ex vivo findings offer evidence for modulation of brain tissue homogenates' neurotransmitter levels and antioxidant enzyme activity. The extracts of the bark also exhibited membrane-stabilizing effect, nitric oxide inhibitory effect and possible inhibitory activity of the enzyme monoamine oxidase (MAO) which implies a multi-faceted neuropharmacological mechanism. The phytochemicals present in MO bark, such as quercetin, kaempferol, and phenolic acids, could have a positive effect on monoaminergic neurotransmission by inhibiting monoamine oxidase activity, promoting available neurotransmitter levels, and modulating receptor signaling pathways [32].Preclinical findings suggest elevated levels of serotonin, nor-adrenalin and dopamine in the parts of the brain involved with mood regulation. Bark-derived sterols as well as lactones may further stabilize the synaptic function[33]. These multiple-target interactions are thus a scheduled pharmacological reason for the mood-elevating effects seen in animal modes. 41 Bark phytochemicals possess potent antioxidant activities based on the free radical scavenging, metal chelating and endogenous enzyme (SOD, CAT and GSH) up-

regulation. Anti-inflammatory effects are derived from inhibition of the cytokines such as IL-6, TNF-alpha and IL-1-beta and COX and iNOS pathways[34]**(Figure2.)**

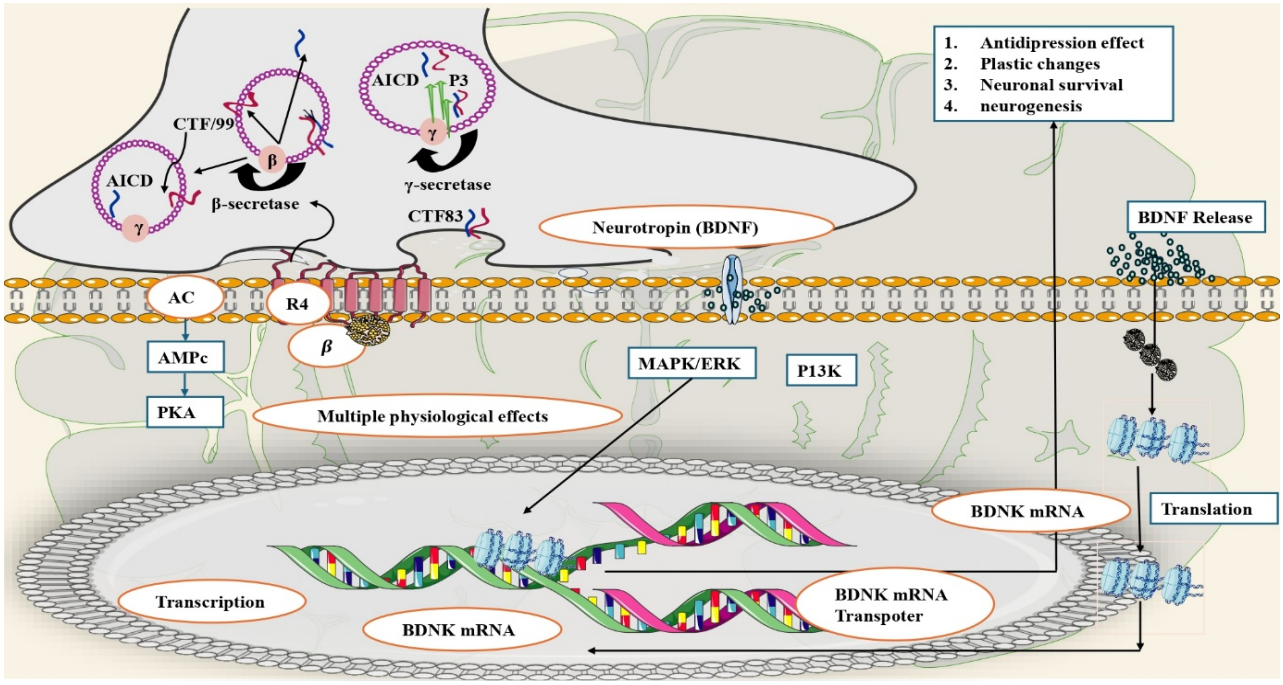

Figure 2: A schematic illustration shows how brain-derived neurotrophic factor (BDNF) signaling and amyloid precursor protein (APP) processing work together in neuronal survival and synaptic plasticity

APP is first cleaved by -secretase and then by -secretase, resulting in the production of amyloidogenic fragments like the A peptide and the APP intracellular domain (AICD). But, activation of BDNF-mediated signaling stimulates several signaling pathways such as adenylate cyclase (AC)/cAMP/PKA, MAPK/ERK, and PI3K, which in turn regulate BDNF gene transcription, mRNA transport, translation, and release. Altogether, these signaling pathways induce antidepressant effects, synaptic plasticity, neuronal survival, and neurogenesis. The diagram also emphasizes the interconnection of amyloidogenic processing and neurotrophic signaling pathways for the maintenance of neuronal homeostasis, as well as their implications in neurodegenerative and neuropsychiatric disorders.

Anti-inflammatory effects include inhibition of pro-inflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], and interleukin-1β [IL-1β]; cyclooxygenase [COX] signaling pathway; and inducible nitric oxide synthase [iNOS] signaling pathway. MO bark could also help to normalize neuronal homeostasis and prevent stress-induced neurodegeneration that is linked to depression by reducing oxidative stress and neuroinflammation. Moreover, MO bark components could help to stimulate the expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which play a vital role in the survival of neurons, their plasticity, and emotional regulation.[35]. These findings suggest that MO bark may counteract neuroplasticity deflicts commonly observed in depressive disorder and contribute to long term neuroprotection and mood stabilization [36] **(Table.2).**

Table 2. Preclinical Studies Evaluating the Antidepressant Activity of *Moringa oleifera* Bark Extract

Study Model / Species	Extract Type & Dose	Key Findings	References
FST & TST (mice/rats)	Ethanolic or methanolic bark extract (100–400 mg/kg)	Reduced immobility time, increased locomotion	[87]
OFT (mice)	Hydroalcoholic extract (200–400 mg/kg)	Increased exploratory behavior	[88]
CMS model (rats)	Ethanolic bark extract (200–300 mg/kg)	Improved sucrose preference, decreased stress behaviors	[89]
In-vitro antioxidant assays	Bark fractions (various)	High free-radical scavenging, strong SOD/CAT support	In-vitro antioxidant [90]

Ex-vivo neurochemical studies	Bark extract-treated brain homogenates	Increased serotonin, noradrenaline levels	[91]
Parameter	MO Bark Extract	Conventional Antidepressants (SSRIs, SNRIs, TCAs)	[2]
Primary Mechanisms	Multi-target: monoamines, antioxidant, anti-inflammatory, BDNF enhancement	Mainly monoamine reuptake inhibition (5-HT, NE, DA)	[92]
Additional Mechanisms	MAO inhibition, cytokine modulation, mitochondrial protection	Limited anti-inflammatory effects; minimal antioxidant action	[93]
Onset of Action	Moderate, linked to neuroprotective and adaptive changes	Typically, 2–4 weeks	[94]
Safety Profile	Generally safe in animals; low acute toxicity	Common side effects: GI upset, sexual dysfunction, insomnia	[95]
Risk of Dependence/ Withdrawal	Very low	Present in SSRIs/ SNRIs (discontinuation syndrome)	[96]
Neurotrophic Support (BDNF)	Significant upregulation in studies	Variable; some increase BDNF indirectly	[97]
Interaction Potential	Possible herb–drug interactions (CYP, MAO) not fully characterized	Well-documented interaction pathways	[98]
Therapeutic Role	Candidate for adjunct or alternative therapy	Established first-line therapy	[99]

6. Molecular Mechanisms Underpinning Antidepressant Activity

MO bark contains compounds that can inhibit the enzymatic activity of the monoamine oxidase (MOA) group of enzymes, specifically MAO-A; an enzyme involved in the metabolism of serotonin and norepinephrine. Partial inhibition increases the reflectant monoamines and helps the antidepressant folds. Flavonoids and phenolic acids exhibited reversible, dose-dependent MAO inhibition and help oppose the breakdown of neurotransmitters and reduce common side effects associated with taking synthetic MAO inhibitors[37]. Further studies are required on the quantification of potency and selectivity. Bark extracts downregulate activation of microglia and downregulate cytokines, such as IL-6, IL-1b and TNF-a. These properties of modulating the immune system help restore neuroimmune equilibrium and avoid damaging inflammation of neurons. By reducing chronic neuro-inflammation, MO bark promotes better synaptic signalling and stress resilience[38]. This pathway is receiving an increasing amount of recognition as a fundamental mechanism of herbal antidepressants. MO bark helps increase the activity of important antioxidant enzymes (superoxide dismutase: SOD, catalase: CAT and glutathione: GSH) as well as reducing malondialdehyde (MDA), an indicator of lipid peroxidation[2]. Through these actions the bark helps to strengthen the defense mechanism of the cells, offers protection against oxidative toxicity, and compares mitochondrial function. Modulation of the oxidative biomarkers is an important aspect in the reversal of the neuronal damage associated with depressive states.Bark phytochemicals trigger signaling cascades like CREB, MAPK and PI3K/Akt which control neuroplasticity [39]. These pathways increase synaptic connections, neurogenesis and improve cognitive emotional processing.Restoration of plasticity brings MO bark effects to the crossroads with modern antidepressant effects but with broader and multi pathway modulation. This increases resilience for neural deficits due to stress [40].

7. Comparative Evaluation with Conventional Antidepressants

MO bark has some mechanistic overlap with conventional antidepressants by their influence on monoamines, anti-inflammatory effects and impact on neurotropic signaling. However, it is different because it's working on multiple levels at the same time in terms of oxidative stress, mitochondrial function, cytokines modulation and synaptic plasticity, this is a holistic approach of a therapeutic[41]. Unlike synthetic drugs which are single-targeted, MO bark may have wider therapeutic effects with less side effects. Preclinical research has always demonstrated antidepressant-like properties of MO extracts with improvements in behavioral tests, stress markers and neurochemical factors[42]. There is still limited data on the specific efficacy of bark but it is promising and similar the standard drug in some models. The multi-target action increases its viability as a good natural antidepressant, and should be subject to further and comprehensive research [43]. MO bark has some mechanistic overlap with conventional antidepressants by their influence on

monoamines, anti-inflammatory effects and impact on neurotropic signaling. However, it is different because it's working on multiple levels at the same time in terms of oxidative stress, mitochondrial function, cytokines modulation and synaptic plasticity, this is a holistic approach of a therapeutic.Unlike synthetic drugs which are single-targeted, MO bark may have wider therapeutic effects with less side effects. Preclinical research has always demonstrated antidepressant-like properties of MO extracts with improvements in behavioral tests, stress markers and neurochemical factors[44]. There is still limited data on the specific efficacy of bark but it is promising and similar the standard drug in some models. The multi-target action increases its viability as a good natural antidepressant, and should be subject to further and comprehensive research. MO is generally considered as safe though extracts of bark requires independent evaluation as it contains unique phytochemistry. Preliminary data evidence low doses toxicity but with higher dose the hepatic or gastrointestinal parameters. Unlike the synthetic antidepressants, herbal extracts are less likely to produce sedation, sexual dysfunction or weight gain[45]. Strict toxicological evaluation is mandatory. MO bark may be able to complement standard antidepressants due to boosting of antioxidant defenses, minimize inflammation and support neuroplasticity. This synergy may lead to dose reduction of synthetic drugs and minimise side effects. However, it is important to consider any possible interactions and see if the patient and condition may indicate combination therapy as potential interactions (most notably with MAO inhibitors or SSRIs) may exist [31].

8. Toxicity, Safety, and Pharmacokinetics

From findings of available preclinical studies, Moringa oleifera (MO) bark has a relatively high margin of safety in experimental animals as evidenced by a high LD50 value and low acute toxicity in rodents [46]. Chronic administration at extremely high doses, however, is sometimes linked to mild changes in liver and kidney function, emphasising the need for standardised dosing guidelines and the assessment of long-term safety. Although there are many documented traditional applications for MO in herbal medicine, comprehensive human safety data specifically for bark extracts are scarce, so there is a need for thorough toxicological studies before clinical use. Currently, there is limited pharmacokinetic data available on the phytochemicals of MO bark. Oral bioavailability of flavonoids, which are present in the bark are relatively high and are quickly metabolized via glucuronidation and sulfation processes, while the bioavailability for the phenolic compounds is generally moderate [47]. Also, numerous phytochemicals found in the bark have a largely unknown ability to cross the blood–brain barrier (BBB). For therapeutic development and dose optimization, comprehensive studies of absorption, distribution, metabolism, elimination, tissue distribution and plasma half-life are therefore necessary. Another important factor to consider is potential herb–drug interactions. MO constituents can affect the activity of cytochrome P450 (CYP450) enzymes that are responsible for the metabolism of drugs or may interact with compounds that regulate monoaminergic signalling pathways[48]. For instance, the pharmacological activity of MO bark, including its MAO-inhibitory and antioxidant effects, could potentiate or modify the effects of antidepressants, antiepileptic drugs or other neuroactive drugs[49]. Therefore, pharmacodynamic and pharmacokinetic studies of combinations should be performed in detail to ensure clinical safety and the reduction of the adverse effects of combination therapy. Metabolic, endocrine, hepatic, renal and reproductive parameters should be assessed as additional safety parameters in long term administration studies. Repeated dose toxicity studies are crucial to determine the no observed adverse effect levels (NOAELs) to establish safe therapeutic ranges. While chronic safety and clinical tolerability of standardized MO bark preparations is not known with certainty, as of this writing, it is believed to be safe based on the long tradition of its use in traditional medicine. [50].

9. Formulation Strategies and Therapeutic Translation

Most phytochemicals have poor solubility rate, rapid metabolism and poor BBB penetration, which degrades the therapeutic potential. MO bark compounds are also plagued by the same limitations. Advantages of nanomaterials in the medical field include improving stability, absorption and targeted delivery, which is necessary for clinical translation[51]. Nanoparticles, liposomes, phytosomes and polymeric carriers enhance solubility, permeable, and aviod release of herbal compounds. These systems increase the delivery of the CNS, and could permit the use of lower doses with improved efficacy. Applying such techniques to MO bark may change its therapeutic potential [52]. Standardized extracts with defined chemical markers may enable consistency, regulatory acceptance and clinical evaluation. Developing capsules, tablets or nano-formulations of MO bark with good quality control can position MO bark in the future as a phytopharmaceutical[53].Development of rational approaches to the formulations of product, the limitations

inherent to physicochemical instability of bioactive compounds, inability to be generally bioavailable, variable PK and unpredictable clinical response in turn are critical in achieving successful therapeutic translation of the potent properties of bioactive compounds of plant origin into neuropsychiatric disease treatment[54]. Even though medicinal vegetation such as Moringa oleifera harbors a potent phytochemical repository with verified potential in antioxidant, anti-inflammatory and neuromodulatory activity, concentrations due to conventional use and preclinical practical use has remained hard to achieve to standardized clinical applications. These are largely due to the complicated and multi-componential structure of botanical extracts and the restricted translational state of the standard dosage forms . Poor oral bioavailability is one of the large formulation issues that are shared with phytochemicals[10]. There are numerous flavonoid, phenolic acid, sterols, and alkaloids with characteristics of low aqueous solubility, high molecular polarity or rapid first-pass metabolism and subsequent low systemic exposure following oral dosage . This is particularly so with the neuroactive phytoconstituents, as not every plasma and central nervous system (CNS) level of concentrations of the neuroactive constituents is needed to generate the effect of antidepressants[55]. In therapeutic regimes that are highly variable (i.e. crude powder formulations, decoction formulations or simple extractions) the reproducible therapeutic levels of active compounds are frequently not attained and this fact is involved in the inconsistent results with clinical regimes and lowered translational validity[56] . In order to overcome these constraints, in modern formulation approach attempt has been focused on enhancing solubility, stability and permeability of bioactive compounds. Incusion going to a solid dispersion techniques with cyclodextrins and lipid based carriers have been found to be encouraging in the upgrading of the dissolution plot and oral assimilation of insoluble phytochemical [57] . Lipid formulations which include self emulsifying drug delivery systems (SEDDS) and nanoemulsions are especially appealing to neuropsychiatric applications due to their ability to increase lymphatic uptake and hence circumvent hepatic first pass metabolism with an increase in bioavailability . These strategies might be particularly relevant for lipophilic constituents that exist Moringa oleifera which is hardly able to reach the oral tract through absorption by mouth. Nanotechnology-based delivery systems are an area of phytopharmaceutical formulation that is advancing at an incredible rate[58]. Polymers and polymer based nanoparticles, Solid lipid nanoparticles (SLS) and nanostructured lipid carriers, and phytosomes, etc. have been explored to improve the pharmacokinetic behaviour and targeted delivery of the plant-derived compounds . Such systems have a number of advantages, including protection of constituents that are prone to degradation by degradation, control of drug release, tissue distribution, and blood-brain barrier (BBB) penetration [59]. In view of the fact that the BBB permeability is a significant challenge in CNS drug development, the nano-enabled delivery of neuroactive phytochemicals can significantly improve their therapeutic potential in depression and syndromes . Another important consideration in the formulation is extract standardization[60]. Unlike single-molecule drug preparations, botanical preparations contain many constituents and may have a synergistic effect. Therefore, strategies for formulation need to maintain the phytochemical integrity but need to guarantee constancy from one batch to the other. The use of marker-based standardization, with the support of complex analysis methods, such as the use of high performance liquid chromatography and mass spectrometry, is fundamental to assure the reproducibility of the pharmacological activity [61]. From a translational approach, standardized formulations allow better interpretation of pharmacokinetic-pharmacodynamic relationships and ease the regulatory evaluation. Also highly promising to facilitate therapeutic outcome are modified-release and controlled-delivery formulations. Delayed release can result in more stable plasma concentrations, the frequency of repeated dosing can also be reduced as well as the possible adverse effects that can directly be associated with peak plasma concentrations that may be particularly pertinent with chronic states of disorders, like depression [62] . In the case of botanical mostly antidepressant precursors, these preparations will be capable of enhancing patient compliance and minimize variance related to varying plasma concentrations of several phytoconstituents. And the added advantage is that systemic delivery and treatment efficacy would be further increased by combination forms that incorporate bioenhancers like piperine or phospholipids [8] . In addition to oral administration, other routes of administration must be investigated which will increase the CNS targeting. Intranasal delivery devices, such as, offer an alternative non-invasive route to pass the BBB using the olfactory and trigeminal routes and offer a route to be able to directly delivery neuroactive agents directly to the brain . While this approach is under-explored for plant-derived antidepressants there is a promising translational avenue by way of compounds that have a limited oral bioavailability or rapid clearance from the body[63]. Therapeutic translation also involves finding

the right integration of formulation science, and pharmacokinetic and pharmacodynamic evaluation. Early phase translational research ought to integrate robust PK profiling that will determine the absorption kinetics, tissue distribution, metabolic pathways and the elimination patterns of the standardized formulations [64]. These data are important to help define how best to give drugs, in terms of dosing, and anything that may be causing a problem with the drug, in terms of its safety in that people. Moreover, the correlation of formulation-dependent PK parameters with pharmacodynamic (biomarkers of inflammation, oxidative stress, neurotrophic factors) is of potential to provide mechanistic validation for the formulation dependence of PK parameters; these can serve as a tool for rational clinical development. From a regulatory point of view, the formulation approaches therefore play a major role in determining the classification and approval pathway of botanical products [65]. Well-characterized, standardized formulations that are manufactured under Good Manufacturing Practice conditions are more likely to meet the expectations of the regulatory authorities for quality, safety and efficacy . On this note, under some regulatory authorities, phytopharmaceutical development models permit a methodical process of the potential of developing botanicals into evidence-based therapeutic agents provided that the consistency of formulation and clinical data considerations is met [66]. With these advances, there are several gaps in translation that are yet to be filled. Numerous formulations studies are more attentive to the enhancement of physicochemical ones and not guarantees the long-term stability, scalability or clinical relevance. There is also minimal focus on patient-centric formulation design including palatability and dosing convenience and acceptability as they are significant factors predicting real-life efficacy[67]. Close interaction between the formulation scientists, pharmacologists, clinicians and regulatory experts will be required in attracting attention to these gaps. The combination of systems pharmacology and formulation science can possibly be of significant importance in future with respect to improving the therapeutic translation[68]. The computational modeling and network pharmacology techniques can have the potential to assist in exploring the most favorable phytochemicals formulation and predict formulation-dependent-interactions on molecular targets, which are implicated in depression [69]. The data-informed approaches can be used to create new-generation botanical preparations that have better efficacy and safety profiles. Moreover, the adaptive clinical trial designs with the possibility of formulation optimisation and dose adjustment on the biomarkers can revolutionize the clinical trials pipeline and reduce the attrition rate [70]. Finally, the strategies used in the medicinal translation of the plant-derived antidepressant candidates are at the centre of interest. The promise of neuropharmacological speaking phytochemicals can significantly improve the clinical viability of phytochemicals with the application of advanced delivery systems, strategy of standardization, pharmacokinetic optimization. Nevertheless, effective translation will rely on a sufficient formulation characterization, incorporation of translational pharmacology and acceptable regulatory standards. As far as these requirements are addressed botanical formulations can become scientifically validated adjuncts or alternative in the treatment of depressive disorders[71].

10. Challenges, Knowledge Gaps, and Future Clinical Perspectives

Although there is increasing scientific attention on the potential of Moringa oleifera (MO) bark in the treatment of neuropsychiatric disorders, several challenges yet remain to be addressed for clinical translation. One of the major limitations is the lack of standardized botanical preparations. Due to differences in plant part used, geographical origin, cultivation conditions, season of harvest, and extraction methods, a significant heterogeneity in phytochemical composition exists from one study to another, which leads to non-reproducibility and non-comparability [71]. This irregularity makes it hard to build solid dose–response relationships and hampers the acceptance of herbal products as evidence-based treatments by regulatory authorities. Another important issue is the inadequate availability of well-designed human clinical trials in comparison with currently available evidence, which largely comes from preclinical studies. While monoaminergic modulation, antioxidant activity, anti-inflammatory effects, and antioxidant neurotrophic signaling all have been shown to have antidepressant-like effects in animal models and in vitro systems, none of these systems capture the complexity and heterogeneity of human depression [72] The forced swim test (FST) and the tail suspension test (TST) are behavioral tests that can be used for preliminary screening, but have limited translational validity, and may overestimate therapeutic efficacy[73] . MO bark phytochemicals are also hindered by pharmacokinetic and bioavailability challenges in their therapeutic development. A large number of flavonoids, alkaloids and phenolic compounds have Further, there can be considerable variability between individuals in their gut microbiota-mediated metabolism, which could have a large effect on treatment efficacy. Therefore, in-

depth absorption, distribution, metabolism, elimination and blood–brain barrier permeation studies are crucial for rational dose optimization and safety assessment. Safety evaluation and herb–drug interaction profiling also remain insufficiently explored. Although *Moringa oleifera* is generally considered safe in traditional medicine, systematic toxicological studies focusing on chronic administration, reproductive toxicity, neurobehavioral safety, and interactions with conventional antidepressants are lacking [75]. Since many patients with depression receive polypharmacy, the possibility of pharmacodynamic and pharmacokinetic interactions involving serotonergic agents, monoamine oxidase inhibitors, or cytochrome P450 enzymes requires careful investigation before clinical application [76]. Other factors such as regulatory and translation barriers make the development of botanical antidepressants challenging. Multi-component herbal drugs are more complicated in terms of quality control, IP protection, standardization, and Good Manufacturing Practice (GMP) requirements as compared to single-molecule drugs [77]. Furthermore, methodological weaknesses like small sample sizes, lack of blinding, lack of statistical power and selective reporting remain a concern in many studies on phytopharmacology. The next challenge is for future research to go beyond pharmacology, toxicology, formulation science, and clinical investigation and take a multidisciplinary translational approach. Mechanistic understanding and reproducibility may be enhanced by the use of validated chemical markers, by the implementation of strict reporting guidelines, and by the use of systems pharmacology strategies for standardisation of extracts. Biomarker-driven clinical trials that target inflammatory mediators, oxidative stress biomarkers, neurotrophic factors and HPA-axis regulation could yield more convincing evidence for the antidepressant activity of MO bark and help to translate it into evidence-based neuropsychiatric therapies [80].of MO bark and facilitate its translation into evidence-based neuropsychiatric therapeutics [78]. [79]. [80] .

Conclusion

Depression is a serious disabling neuropsychiatric condition in the world and the challenges of available antidepressants have spurred interest in phytochemical interventions that can act on multiple neurobiological processes. Overall, Moringa oleifera (MO) bark is considered to be a promising, but under-explored botanical source for new antidepressant drugs. While many studies have been conducted on the leaves and seeds, the bark is also known to have unique phytochemical profile with flavonoids, alkaloids, tannins, phenolics, glycosides, sterols, and lactone derivatives which could have neuroprotective and mood regulating properties.

Furthermore, the traditional ethnomedicinal applications of MO in the treatment of stress, inflammatory, and neurological conditions underscore the therapeutic significance of MO. Preclinical evidence suggests MO bark extracts have antidepressant-like activity in validated preclinical models including the Forced Swim Test (FST), Tail Suspension Test (TST), Open Field Test (OFT) and Chronic Mild Stress (CMS). These behavioral modulations have been confirmed by mechanistic studies that show that the monoaminergic neurotransmissions are modulated, particularly those mediated by serotonin and norepinephrine pathways; there is also evidence of possible inhibition of the monoamine oxidase enzymes.

Furthermore, MO bark phytochemicals have the potential to help dampen various pathophysiological mechanisms associated with depression, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, and cytokine imbalance. In addition to this, many endogenous antioxidants like superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) are restored, while lipid peroxidation markers like malondialdehyde (MDA) are reduced, which further strengthens its neuroprotective potential. Importantly, several phytochemicals contained in the bark have been shown to have an impact on the upregulation of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and related synaptic signaling pathways, which are strongly associated with the mechanisms of modern antidepressant therapy. The available toxicological studies indicate a relatively good safety profile including high LD50s and relatively little acute or sub-chronic toxicity in experimental models. But, in-depth pharmacokinetic studies, metabolite identification, drug–herb interaction studies and long-term safety studies have yet to be conducted. These restrictions prevent the precise human equivalent dosing, bioavailability, blood–brain barrier penetration, and chronic therapeutic safety.

The MO bark shows overlapping and complementary mechanisms of action with classical antidepressants, especially in the domains of modulation of monoamines and antioxidant, anti-inflammatory and neurotrophic signalling. This polypharmacological profile indicates a possible application as a complementary or alternative therapy, particularly in treatment-refractory depression and/or those who prefer to avoid drugs in their treatment. Standardised extraction procedures, validated phytochemical markers, and well-designed clinical trials to demonstrate efficacy and safety in humans will be key to future progress. There are advanced formulation

methods like nanocarriers, phytosomes and liposomal delivery methods which can enhance the bioavailability, stability and CNS targeting of active phytoconstituents. Additionally, botanical antidepressants must undergo stringent quality control, reproducible phytochemical profiling, and clinical validation through pharmacology and clinical trials similar to other pharmacologic depression treatments if they are to be approved for use by the regulatory bodies. At last, The phytochemical profile of MOB and its wide range of neuropharmacological activities indicate that it has significant potential as a multi-target natural antidepressant, with a favourable preclinical safety profile. However, coordinated multi-disciplinary efforts, encompassing pharmacology, toxicology, formulation science and regulatory research, will be required for successful translation into clinical practice. In the future, MO bark could play a crucial role in the development of antidepressant treatments with systematic scientific research, offering a more comprehensive and safer treatment alternative for mental health care worldwide.

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