

Natural Products as Potential Antidepressant Agents: Experimental Evidence, Molecular Mechanisms and Therapeutic Perspectives – A Review

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Abstract

Depression is a heterogeneous neuropsychiatric disorder associated with disturbances in monoaminergic signaling, hypothalamic–pituitary–adrenal axis regulation, neuroinflammation, oxidative stress, impaired neuroplasticity, mitochondrial dysfunction and alterations in the microbiota–gut–brain axis. Although conventional antidepressants are clinically effective, delayed response, adverse effects and inadequate remission in some patients highlight the need for complementary therapeutic approaches. Natural products provide diverse bioactive compounds capable of modulating multiple pathways involved in depression. This review summarizes experimental and clinical evidence for plant-derived natural products and phytochemicals, including curcumin, saffron, St. John's wort, *Rhodiola rosea*, resveratrol, naringenin, quercetin, baicalin, berberine and *Withania somnifera*. Evidence from animal models, neurochemical studies and clinical trials is discussed in relation to monoaminergic signaling, BDNF–TrkB/CREB, PI3K/Akt, MAPK/ERK, NF-κB, NLRP3, Nrf2, mitochondrial function, autophagy and the microbiota–gut–brain axis. The review also highlights pharmacokinetic limitations, standardization, safety, herb–drug interactions and the translational gap between preclinical and clinical evidence. Natural products represent promising sources of antidepressant candidates and adjunctive therapies, although further standardized, mechanistically guided and adequately powered clinical studies are required.

Keywords

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1. INTRODUCTION

Depression is a major neuropsychiatric disorder characterized by persistent low mood, loss of interest or pleasure, cognitive and motivational disturbances, sleep and appetite changes, psychomotor abnormalities and, in severe cases, suicidal thinking. Its biological basis is not adequately explained by a single neurotransmitter deficiency. Instead, depression is increasingly viewed as a systems-level disorder involving interactions among monoaminergic signaling, stress neuroendocrinology, immune and inflammatory processes, oxidative balance, synaptic plasticity, mitochondrial function and peripheral metabolic and microbial signals. This complexity is important for antidepressant discovery because a compound capable of influencing several converging pathways may theoretically address a broader set of disease-associated processes than a highly selective molecular intervention.^{1,2,3}

Current antidepressant pharmacotherapy includes selective serotonin reuptake inhibitors, serotonin–noradrenaline reuptake inhibitors, atypical antidepressants, tricyclic agents and monoamine oxidase inhibitors. These treatments have substantial clinical

value, yet limitations remain. Therapeutic improvement often requires several weeks, not every patient achieves remission, and adverse effects can reduce adherence. These limitations do not mean that conventional antidepressants are ineffective; rather, they highlight the need for additional treatment options and mechanistically distinct adjuncts. Natural products have therefore attracted sustained interest because medicinal plants, foods, fungi and other biological sources contain structurally diverse molecules capable of modulating neurotransmitter systems, intracellular signaling and inflammatory or redox pathways.

Recent literature has moved beyond the simple description of plants as “natural antidepressants” and increasingly examines the biological networks affected by their constituents. Recent reviews identify neurotransmitter systems, the HPA axis, inflammatory signaling, oxidative stress, neuroplasticity, mitochondrial quality control, autophagy and the microbiota–gut–brain axis as recurring mechanisms. Phytochemical reviews also identify PI3K/Akt, MAPK/ERK and NF-κB as important signaling nodes. These observations suggest that natural products may

exert multi-target actions that converge on neuronal resilience and synaptic function.

The term natural antidepressant should nevertheless be used carefully. Much of the literature is preclinical, botanical preparations are frequently incompletely standardized, experimental doses may not correspond to achievable human exposure, and pharmacokinetic information is often limited. Even when randomized clinical trials exist, sample size, treatment duration, comparator selection, diagnostic criteria and outcome measures vary. For this reason, the present review distinguishes antidepressant-like activity in experimental models from established clinical efficacy and considers safety and translational limitations alongside biological promise.

The objective of this review is to integrate experimental evidence, molecular mechanisms and therapeutic perspectives for natural products with potential antidepressant activity. Emphasis is placed on representative agents for which biological mechanisms or clinical evidence have been investigated, while avoiding the assumption that all botanicals possess equivalent evidence. The review also identifies research strategies that may improve reproducibility and the progression of natural-product discoveries from experimental observations to clinically useful interventions.

A narrative literature approach was used to identify relevant experimental, mechanistic and clinical evidence. Search concepts included combinations of depression, major depressive disorder, antidepressant, natural product, phytochemical, medicinal plant, chronic unpredictable stress, chronic mild stress, forced swim test, tail suspension test, sucrose preference, BDNF, neuroinflammation, oxidative stress, mitochondrial dysfunction, microbiota–gut–brain axis and the names of representative natural products. Priority was given to primary experimental studies, randomized controlled trials, systematic reviews and meta-analyses. Recent literature available through 2026 was considered where relevant. The evidence was organized into biological mechanisms, representative natural products, experimental models, clinical evidence, safety, translational barriers and future directions.

This article is a narrative review and is not presented as a formal PRISMA systematic review or quantitative meta-analysis. Clinical findings are discussed according to the population studied, and evidence from diagnosed major depressive disorder is distinguished from studies of general or subclinical depressive symptoms. Likewise, behavioral effects in experimental animals are described as antidepressant-like effects rather than as direct proof of treatment of human depression.

1.1 Monoaminergic signaling

Serotonin, noradrenaline and dopamine participate in mood, reward, motivation, cognition and stress adaptation. Conventional antidepressants demonstrate that modulation of monoaminergic signaling can

improve depressive symptoms, but the downstream biological effects of chronic treatment extend beyond acute transporter inhibition. Natural products may influence monoamine synthesis, release, degradation, receptor signaling or transporter activity. Hypericum preparations, for example, contain several constituents and have been investigated for effects involving monoamine-related systems. Experimental phytochemicals can also modify brain serotonin, dopamine and noradrenaline concentrations in stress-exposed animals.^{4,7}

Monoaminergic effects should not be inferred from behavioral testing alone. The forced-swim and tail-suspension tests are sensitive to several centrally acting drugs, but they are not diagnostic models of depression. Open-field activity is important because reduced immobility may otherwise be confused with nonspecific motor activation. Strong preclinical studies therefore combine behavioral measures with neurochemical, endocrine and molecular endpoints and, where possible, use chronic stress paradigms that reproduce anhedonia, altered motivation and stress-related neuroendocrine changes.

1.2 HPA-axis dysregulation and chronic stress

Chronic stress activates the hypothalamic–pituitary–adrenal axis and can disturb glucocorticoid feedback. Prolonged glucocorticoid exposure affects hippocampal structure, neurogenesis, synaptic function and inflammatory signaling. Natural products with adaptogenic, neuroendocrine or anti-inflammatory properties are consequently evaluated in chronic unpredictable stress, chronic mild stress and social-defeat models. Curcumin, Rhodiola constituents and several flavonoids have been investigated for effects on stress-related endocrine pathways. The therapeutic relevance is less about suppressing cortisol as an isolated target and more about restoring appropriate stress-response regulation.^{8,9}

1.3 Neuroinflammation

Microglia and astrocytes are central to neuroimmune signaling. Persistent inflammatory activation can alter synaptic transmission, glutamate homeostasis, neurotrophic signaling and neuronal survival. Increased activity of NF- κ B, NLRP3 inflammasome components and inflammatory mediators such as TNF- α , IL-1 β and IL-6 has been reported in experimental depression and in subsets of patients. Natural products are attractive because many polyphenols and terpenoids influence redox-sensitive inflammatory pathways. Recent literature on natural products and neuroinflammation emphasizes modulation of microglial activation and polarization, while newer antidepressant reviews connect these effects to neuroplasticity and mitochondrial homeostasis.^{10,13}

1.4 Oxidative and nitrosative stress

Oxidative stress occurs when reactive oxygen and nitrogen species exceed cellular antioxidant capacity. Brain tissue is particularly vulnerable because of high

oxygen consumption, abundant polyunsaturated lipids and relatively limited antioxidant reserve. Increased lipid peroxidation, altered glutathione status and changes in antioxidant enzymes have been associated with stress-related neuronal dysfunction. Phytochemicals such as curcumin, quercetin, resveratrol and naringenin can influence Nrf2/HO-1 signaling and endogenous antioxidant defenses. However, radical-scavenging activity in a chemical assay does not demonstrate antidepressant efficacy because biological activity depends on absorption, metabolism, tissue distribution and relevant cellular exposure.¹⁴

1.5 Neuroplasticity and BDNF–TrkB signaling

Brain-derived neurotrophic factor supports neuronal survival, dendritic remodeling, synaptic plasticity and learning. Reduced neurotrophic signaling has been implicated in stress-related changes in the hippocampus and other limbic regions. The BDNF–TrkB–CREB axis is consequently an important downstream pathway in antidepressant research. Several natural products increase BDNF expression or signaling in animal models, sometimes together with restoration of synaptic proteins and neurogenesis. The strongest studies examine BDNF together with behavioral recovery and upstream signaling rather than treating BDNF elevation alone as evidence of clinical efficacy.^{16,18,19}

1.6 Mitochondrial dysfunction and programmed cell death

Mitochondria integrate energy production, calcium regulation, redox balance and apoptotic signaling. Depression-associated stress can alter mitochondrial membrane potential, ATP production, mitochondrial dynamics and mitophagy. Recent natural-product research has therefore expanded toward mitochondrial quality control. Natural compounds have been reported to affect ATP homeostasis, mitophagy, calcium balance, mitochondrial dynamics and biogenesis. Autophagy and programmed cell death are additional emerging mechanisms; recent reviews discuss links between natural products and apoptosis, pyroptosis, ferroptosis and necroptosis. These mechanisms may be especially relevant when oxidative stress and inflammation converge on neuronal survival.^{20,21}

1.7 Microbiota–gut–brain axis

The microbiota–gut–brain axis provides a framework for understanding how peripheral biological processes can influence brain function. Microbial metabolites, intestinal barrier integrity, immune signaling, vagal pathways and tryptophan metabolism may contribute to mood regulation. Natural products may alter microbial composition or microbial metabolites while simultaneously affecting inflammatory and neurotrophic pathways. Recent reviews report that flavonoids, alkaloids, polysaccharides, saponins and terpenoids can influence gut microbiota and downstream mediators such as short-chain fatty acids, serotonin and BDNF. Causality remains difficult to establish because microbial associations can be secondary to diet, stress or

drug exposure; mechanistic studies using fecal transfer, microbiota depletion and metabolomics are therefore needed.²²

Table 1. Major classes of natural products and representative antidepressant mechanisms.

Class	Representative agents	Main proposed pathways	Evidence level	Major limitation
Polyphenols	Curcumin, resveratrol	NF-κB, Nrf2, SIRT1/Akt, BDNF, HPA axis	Preclinical + selected clinical	Bioavailability; dose heterogeneity
Flavonoids	Naringenin, quercetin, baicalin, apigenin	BDNF/TrkB, PI3K/Akt, ERK, NF-κB	Mostly preclinical	Exposure and metabolism
Botanical preparations	Hypericum	Monoaminergic and multi-target signaling	Substantial clinical literature	Drug interactions; standardization
Saffron	Crocins, crocetin, safranal	Serotonergic, antioxidant, inflammatory and stress pathways	Multiple RCTs/meta-analyses	Small heterogeneous trials
Adaptogenic botanicals	Rhodiola, Withania	Stress response, HPA axis, monoamines	Preclinical + selected clinical	Preparation-specific evidence
Alkaloids	Berberine and others	Monoamines, inflammation, metabolism, mitochondria	Mainly preclinical	Toxicology and exposure

Evidence quality is not uniform across natural products. A standardized botanical preparation supported by randomized clinical trials should not be placed in the same evidentiary category as an isolated phytochemical tested only in a rodent model. The strongest development programs connect chemical identity,

exposure, mechanism and clinically relevant outcomes across sequential experimental stages.

2. Curcumin

Curcumin is a principal curcuminoid of *Curcuma longa* and has been extensively investigated for anti-inflammatory, antioxidant and neuroprotective effects. Antidepressant-like activity has been reported in several stress and inflammatory models. Proposed mechanisms include modulation of monoaminergic signaling, NF- κ B-associated inflammation, oxidative and nitrosative stress, HPA-axis activity and BDNF-associated plasticity. Curcumin therefore illustrates how a single phytochemical can influence several processes that converge on neuronal resilience.^{14,23}

Clinical evidence is more developed than for many isolated phytochemicals but remains incomplete. A randomized double-blind placebo-controlled study enrolled 56 individuals with major depressive disorder and evaluated curcumin at 500 mg twice daily for eight weeks. Earlier meta-analytic evidence involving six trials and 377 participants reported improvement in depressive symptoms. A 2026 GRADE-assessed meta-analysis included 19 randomized trials and found statistically significant pooled effects but substantial heterogeneity; the authors emphasized that the findings were fragile and that additional high-quality trials were required. Curcumin is therefore best considered a promising candidate or adjunct rather than an established replacement for conventional antidepressant treatment.^{24,25,26}

2.1 Saffron and crocin-related constituents

Crocus sativus, commonly known as saffron, contains crocins, crocetin, picrocrocin and safranal. Saffron is among the natural products with comparatively substantial clinical investigation. Proposed mechanisms include serotonergic modulation, antioxidant activity, reduction of inflammatory signaling, neuroendocrine regulation and neuroprotection. These mechanisms are biologically plausible because saffron constituents can influence several pathways involved in mood regulation.^{27,32}

Early systematic reviews identified randomized trials suggesting benefit in mild-to-moderate depressive symptoms, although studies were generally small. A 2019 meta-analysis reported a positive effect on depressive symptoms compared with placebo but noted publication-bias concerns and regional limitations. A 2026 GRADE-assessed meta-analysis included 34 randomized controlled trials comprising 1,769 participants and found reductions in self-reported depressive and anxiety symptoms; clinician-rated measures were less consistent and heterogeneity was high. These findings support continued research while emphasizing the need for standardized extracts, defined chemical markers and adequately powered trials.^{28,30}

2.2 *Hypericum perforatum* (St. John's wort)

Hypericum perforatum is one of the most extensively investigated herbal preparations for depression.

Constituents include hyperforin, hypericin, flavonoids and other secondary metabolites. Rather than acting through a single receptor, *Hypericum* preparations have been associated with modulation of monoamine-related signaling and intracellular pathways. Older meta-analyses reported superiority to placebo and broadly comparable efficacy with standard antidepressants in selected populations, especially mild-to-moderate depression. Interpretation requires attention to extract composition, standardization and clinical population.^{4,5,6}

The major translational concern is herb–drug interaction. *Hypericum* can induce drug-metabolizing enzymes and transport systems, potentially reducing exposure to concomitant medicines. Therefore, natural origin should not be interpreted as evidence of pharmacological neutrality. Any clinical application requires standardized preparations, interaction testing and appropriate patient selection.⁴

2.3 *Rhodiola rosea*

Rhodiola rosea contains salidroside, rosavin-related phenylpropanoids and other constituents and has traditionally been described as an adaptogenic botanical. Experimental work suggests effects on stress-response systems, neurotransmitter signaling and cellular resilience. A randomized placebo-controlled phase II study compared standardized *R. rosea* extract with sertraline and placebo in 57 participants with mild-to-moderate major depressive disorder over 12 weeks. Symptom reductions occurred in all groups, but the main depression measures did not demonstrate a statistically significant between-group difference. Another randomized study evaluated *Rhodiola* combined with sertraline and reported improvement, illustrating that botanical effects can differ according to dose and adjunctive context.^{33,35,9}

These studies also show why clinical replication is important. Evidence from one formulation should not automatically be generalized to all *Rhodiola* products. Botanical identity, extraction method, marker-compound content and dose can materially affect pharmacology.

2.4 Resveratrol

Resveratrol is a stilbene polyphenol found in several plant sources and has been investigated in models of stress-related behavioral dysfunction. Preclinical work has associated resveratrol with BDNF modulation, anti-inflammatory effects, antioxidant responses and SIRT1/AMPK-related signaling. Animal studies have reported reduced immobility and changes in sucrose preference. However, recent translational analysis indicates that many experiments use preventive or concurrent dosing, male animals, high doses or non-oral routes, while human depression-specific evidence remains limited. Resveratrol should therefore be viewed as a mechanistic and hypothesis-generating candidate rather than an established antidepressant.^{15,36}

2.5 Naringenin

Naringenin is a flavanone abundant in citrus fruits and has antioxidant, anti-inflammatory and neuroprotective properties. Experimental depression studies have investigated its influence on oxidative stress, inflammatory mediators, neurotrophic pathways and monoaminergic function. A 2026 systematic review and meta-analysis specifically assessed preclinical evidence for naringenin in animal models of depression, reflecting the increasing effort to move beyond isolated positive experiments. Nevertheless, the evidence remains preclinical and requires careful interpretation with respect to bioavailability, dose translation and methodological quality.³⁷

Naringenin also illustrates a general flavonoid problem: glycosylation, metabolism and intestinal transformation can change the compounds that reach systemic circulation and the brain. Future studies should characterize pharmacokinetic exposure and active metabolites alongside behavioral and molecular endpoints.

2.6 Quercetin, baicalin and apigenin

Quercetin, baicalin and apigenin are representative flavonoids repeatedly investigated for neuroprotective and antidepressant-like activity. Reported pathways include BDNF/TrkB signaling, ERK and PI3K/Akt cascades, NF- κ B suppression, antioxidant responses and regulation of inflammatory mediators. Recent reviews of plant-derived flavonoids identify antidepressant-like effects across flavonols, flavones, isoflavones, flavanones and anthocyanins and repeatedly highlight BDNF/TrkB and NF- κ B as mechanistic nodes. These observations provide a coherent biological rationale but do not remove the need for human validation.^{14,23}

Differences in absorption, metabolism, brain penetration and formulation mean that an effective rodent dose cannot be directly extrapolated to human supplementation. Standardized pharmacokinetic–pharmacodynamic studies and early-phase clinical trials are needed before strong therapeutic claims can be made.

2.7 Berberine and other alkaloids

Berberine is an isoquinoline alkaloid with extensive pharmacological activity. Experimental studies link its actions to monoamine metabolism, inflammatory signaling, oxidative stress, mitochondrial function and metabolic pathways. This pleiotropy is scientifically attractive but creates challenges in identifying which targets are necessary for antidepressant-like activity. Other alkaloids from medicinal plants also show activity in animal models, but some have narrow therapeutic windows. Early toxicology and exposure assessment are therefore essential and should accompany behavioral screening.¹⁴

3. *Withania somnifera* and stress-related botanicals

Withania somnifera contains withanolides and related constituents and has been investigated primarily for stress, anxiety and neurocognitive outcomes, with

growing interest in depressive symptoms. Proposed mechanisms include modulation of stress responses, inflammation, oxidative balance and neuroplasticity. Recent randomized research on standardized extracts continues to evaluate mood and stress-related endpoints. Evidence in diagnosed major depressive disorder is less developed than evidence for stress or anxiety, and different formulations should not be treated as chemically identical.^{23,4}

3.1 Serotonergic and monoaminergic regulation 4

Natural products may influence monoaminergic function through transporter modulation, receptor signaling, monoamine synthesis, degradation or indirect restoration of neuronal function. A complex botanical preparation may contain constituents with modest effects on several targets, potentially producing a network response. Mechanistic claims should, however, be supported by receptor, transporter or enzyme assays rather than inferred from behavioral changes alone.⁴

3.2 BDNF–TrkB–CREB signaling

BDNF signaling links molecular pharmacology with structural plasticity. TrkB activation can engage ERK/MAPK, PI3K/Akt and PLC γ pathways and influence CREB-dependent transcription. Natural products that restore BDNF in chronic-stress models may therefore act downstream of diverse upstream processes. The mechanistic sequence can be conceptualized as stress or inflammation $\rightarrow$ impaired intracellular signaling $\rightarrow$ reduced neurotrophic support $\rightarrow$ synaptic dysfunction $\rightarrow$ behavioral abnormalities; natural-product intervention may interrupt several steps. Future work should measure BDNF protein, TrkB activation and synaptic markers together to improve causal inference.^{18,19}

3.3 PI3K/Akt and MAPK/ERK pathways 14

PI3K/Akt and MAPK/ERK are central pathways connecting growth factors, metabolism, neuronal survival and synaptic plasticity. Natural-product antidepressant research repeatedly reports regulation of these pathways. Because they are highly interconnected, pathway activation must be interpreted in cellular context. Akt may support survival, while ERK contributes to plasticity and transcription. Natural products may affect these pathways indirectly through changes in oxidative and inflammatory signaling.¹⁴

3.4 NF- κ B and NLRP3 inflammasome 13

NF- κ B regulates inflammatory gene transcription, whereas NLRP3 is a major inflammasome involved in maturation of IL-1 β and IL-18. Chronic stress can increase inflammatory signaling in brain and peripheral tissues. Polyphenols and flavonoids can reduce NF- κ B activation and inflammasome-related signaling in experimental systems. The potential benefit is preservation of neuronal function and neurotrophic signaling. However, immune pathways are context-dependent; the therapeutic objective should be restoration of inflammatory homeostasis rather than indiscriminate immune suppression.¹³

3.5 Nrf2/HO-1 antioxidant signaling 14

Nrf2 coordinates endogenous antioxidant and cytoprotective responses. Natural products may activate Nrf2 or reduce oxidative pathways upstream of cellular injury. Curcumin and several flavonoids are frequently investigated through Nrf2/HO-1 signaling. This mechanism is more informative than a simple chemical radical-scavenging assay because it addresses cellular defense. Nevertheless, *in vitro* antioxidant potency should not be equated with antidepressant efficacy without pharmacokinetic and *in vivo* confirmation.¹⁴

3.6 Mitochondrial quality control 20

Mitochondrial quality control includes biogenesis, dynamics, mitophagy, membrane potential and calcium homeostasis. Recent reviews identify these processes as emerging targets of natural antidepressants. Compounds may improve ATP availability, reduce mitochondrial oxidative damage, promote removal of damaged mitochondria and restore fission–fusion balance. These actions may converge on synaptic plasticity because neuronal remodeling is energetically demanding. Future studies should measure mitochondrial endpoints only when linked to a clearly stated mechanism.²⁰

3.7 Autophagy and programmed cell death

Autophagy is required for cellular quality control, whereas excessive apoptosis, pyroptosis, ferroptosis or necroptosis may contribute to neuronal injury. Recent reviews have expanded natural-product research into these pathways, including PI3K/Akt, caspases, gasdermin-mediated pyroptosis and iron-dependent lipid peroxidation. A major challenge is determining whether altered cell-death signaling is a cause, consequence or compensatory response. Temporal studies and cell-specific analyses are necessary to establish causality.²¹

3.8 Microbiota-derived mechanisms 22

Natural products can influence the gut microbiome directly or through dietary and host metabolic changes. Potential antidepressant mechanisms include increased short-chain fatty acids, improved intestinal barrier integrity, altered tryptophan metabolism and reduced peripheral inflammatory signaling. Many polyphenols undergo extensive microbial transformation, meaning that metabolites may contribute substantially to pharmacological effects. Germ-free, antibiotic-depletion, fecal-transfer and metabolomic approaches can help determine whether microbiota changes are mechanistically necessary.²²

Common behavioral paradigms include the forced-swim test, tail-suspension test, sucrose-preference test, open-field test and chronic stress models. The forced-swim and tail-suspension tests are useful screening tools, whereas sucrose preference is relevant to anhedonia. Open-field testing helps identify locomotor confounding. Chronic unpredictable mild stress models provide broader phenotypic coverage by combining repeated stressors and can be paired with endocrine, oxidative, inflammatory and histological endpoints.

Animal models have important limitations. No rodent paradigm reproduces the full phenomenology of human major depressive disorder. Behavioral endpoints can be affected by locomotion, anxiety, sedation, appetite and sensory function. Strong studies should therefore use multiple complementary tests, randomization and blinding where feasible, report sex and age, characterize dosing, and examine molecular endpoints linked to a stated mechanism. Reproducibility across laboratories is especially important before a compound progresses toward clinical development.^{40,41,42}

Clinical evidence is strongest for a limited number of botanical preparations and phytochemicals. Saffron has been examined in numerous randomized trials and recent meta-analyses, while curcumin has a growing clinical literature. Hypericum has a much longer clinical history but is constrained by interaction potential and preparation variability. Rhodiola has smaller and more mixed evidence. For many isolated flavonoids, alkaloids and terpenoids, human evidence remains insufficient to establish efficacy in major depressive disorder.^{28,24,5,33}

A recurring issue is mismatch between experimental dose and clinically achievable exposure. A compound may show activity at concentrations difficult to attain in plasma or brain after oral administration. Metabolism can further modify activity. Pharmacokinetic studies should therefore accompany efficacy studies, including measurement of parent compounds and relevant metabolites. Nanotechnology-based delivery systems may improve exposure for poorly soluble compounds, but improved delivery does not itself establish efficacy or safety.

Standardization is equally important. Turmeric, saffron and Rhodiola extracts can differ substantially in chemical profile. Botanical authentication, extraction method, chromatographic fingerprint, marker-compound content, contaminant testing and batch-to-batch reproducibility should be treated as essential scientific variables. Without standardization, positive or negative results can be difficult to reproduce or compare.^{4,23}

Natural origin does not guarantee safety. Some natural products have clinically important pharmacokinetic interactions, while others can produce organ toxicity at high exposure. Hypericum is a prominent example because induction of metabolic enzymes and transport systems can reduce concentrations of concomitant medicines. Concentrated botanical preparations can also differ markedly from traditional dietary use. Toxicological assessment should therefore include acute and repeated-dose studies, organ-function biomarkers, reproductive or developmental assessment where relevant, genotoxicity when indicated and interaction studies for candidates intended as adjuncts.^{4,5}

Interaction studies are particularly important because patients with depression may already receive serotonergic, cardiovascular, anticonvulsant, anticoagulant or metabolic medicines. Combination

with a conventional antidepressant should not be assumed safe merely because each component has an acceptable standalone profile. Standardized exposure data and pharmacodynamic monitoring are required before widespread adjunctive use.

The future of natural-product antidepressant development is likely to move from empirical screening toward mechanism-guided discovery. Systems pharmacology, metabolomics, transcriptomics and network analysis can identify convergent pathways affected by complex extracts. Computational target prediction can generate hypotheses, but molecular docking does not establish pharmacological activity, target engagement or clinical efficacy. Experimental validation remains essential.^{39,14}

A second direction is precision-oriented use of natural products. Depression is biologically heterogeneous, and an agent that primarily influences inflammation may be more relevant to a subgroup characterized by inflammatory activation than to all patients. Similarly, compounds affecting metabolic or microbiota pathways may be informative in specific biological phenotypes. Biomarker-guided clinical trials could improve signal detection compared with treating depression as biologically uniform.

Combination strategies also warrant investigation. A standardized natural product could serve as an adjunct to an established antidepressant and potentially address pathways incompletely influenced by monoamine reuptake inhibition. Combination trials require appropriate controls, adequate sample sizes and interaction monitoring. The objective should be evidence-based augmentation rather than substitution of established therapy without clinical justification.

- Preclinical predominance: Most natural products have stronger animal evidence than human evidence.
- Standardization: Extract composition, marker compounds and preparation methods vary among studies.
- Dose translation: Experimental doses may exceed clinically achievable exposure.
- Bioavailability: Poor absorption, rapid metabolism and limited brain penetration can reduce activity of parent compounds.
- Mechanistic overinterpretation: A biomarker change does not establish that a pathway is necessary for antidepressant activity.
- Model limitations: Behavioral assays cannot reproduce the full heterogeneity of major depressive disorder.
- Sex and population diversity: Many animal studies use only male animals, while clinical studies may have limited demographic diversity.
- Publication and reporting bias: Positive results may be more likely to be published, particularly in early preclinical research.

- Interaction risk: Natural products can alter metabolism or pharmacodynamics of conventional medicines.
- Regulatory complexity: Botanical products may be regulated differently across jurisdictions, complicating quality control and clinical translation.

A practical development pathway should proceed through linked stages rather than isolated efficacy claims. First, the botanical source should be authenticated and chemically characterized. Second, in vitro screening can identify antioxidant, anti-inflammatory, receptor, enzyme or neuroprotective activity, but only as hypothesis generation. Third, pharmacokinetic studies should establish exposure and metabolites. Fourth, multiple validated animal models should be used, including a chronic stress paradigm and tests for locomotor confounding. Fifth, molecular studies should verify a predefined mechanism. Sixth, repeated-dose toxicology and interaction studies should be conducted. Finally, randomized clinical trials should use standardized preparations, clinically meaningful outcomes and adequate follow-up.

Table 2. Representative natural products, experimental models, molecular targets and principal findings.

Stage	Key question	Recommended evidence	Decision point
Authentication & chemistry	What exactly is being tested?	Botanical identity, chromatographic fingerprint, marker compounds	Batch consistency
In vitro pharmacology	What biological pathways are affected?	Target/enzyme assays; inflammatory and redox models	Mechanistic plausibility
Pharmacokinetics	Is active exposure achievable?	Plasma/brain levels; metabolites; bioavailability	Dose selection
Preclinical efficacy	Does it work across models?	Chronic stress + anhedonia + locomotor controls	Reproducibility
Mechanism validation	Is the proposed	Inhibitors, knockdown/knockout,	Causal mechanism

	pathway necessary?	target engagement	
Safety	Is exposure tolerable?	Repeated-dose toxicology and interaction studies	Clinical readiness
Clinical trials	Does it improve patient outcomes?	Randomized, adequately powered standardized trials	Therapeutic evidence

Natural products constitute a broad and chemically diverse source of potential antidepressant agents. Experimental evidence indicates that their activity can involve interacting mechanisms including monoaminergic regulation, HPA-axis normalization, attenuation of neuroinflammation and oxidative stress, restoration of BDNF-dependent neuroplasticity, mitochondrial quality control, programmed cell-death pathways and microbiota–gut–brain signaling. This multi-pathway behavior is scientifically attractive because depression itself is biologically heterogeneous and cannot be adequately represented by a single molecular abnormality.

At the same time, evidence should be interpreted cautiously. Strong preclinical findings do not establish clinical efficacy, and positive clinical trials for selected natural products do not justify generalization to all botanicals or phytochemicals. Saffron, curcumin and Hypericum have comparatively developed clinical evidence, whereas many flavonoids, alkaloids and terpenoids remain experimental. Standardization, pharmacokinetics, toxicity, drug interactions and rigorous clinical validation remain central requirements. The most productive future strategy is not to replace conventional antidepressants with natural alternatives by assumption, but to develop natural products using the same standards expected for other pharmacological candidates: reproducible chemistry, defined exposure, validated mechanisms, rigorous safety assessment and controlled clinical evaluation. With this approach, natural-product research may generate novel antidepressant leads, rational adjunctive therapies and mechanistically informative tools for understanding the biological heterogeneity of depression.

Conclusion

Natural products represent a chemically diverse source of compounds with potential relevance to antidepressant drug discovery. The evidence reviewed indicates that their effects may involve multiple interconnected processes, including monoaminergic regulation, modulation of the HPA axis, attenuation of neuroinflammatory and oxidative pathways, restoration of BDNF-dependent neuroplasticity, regulation of mitochondrial function and programmed cell-death pathways, and interactions with the microbiota–gut–brain axis. These multi-target effects provide a biological rationale for continued investigation of phytochemicals and standardized botanical preparations in depression research.

However, the strength of evidence varies substantially among natural products. Clinical evidence is relatively more developed for selected preparations such as saffron, curcumin and Hypericum, whereas many flavonoids, alkaloids and other isolated phytochemicals remain supported mainly by preclinical findings. Differences in botanical composition, dose, bioavailability, metabolism, brain exposure and experimental models can limit comparison and translation of results. Antidepressant-like behavioral effects in animal models should therefore not be considered equivalent to established clinical efficacy.

Future research should emphasize authenticated and chemically standardized preparations, pharmacokinetic and metabolite profiling, validated molecular and behavioral endpoints, appropriate toxicological and drug-interaction assessment, and adequately powered randomized clinical trials. Mechanism-guided studies combining molecular, cellular and systems-level approaches may help identify reproducible therapeutic candidates. Overall, natural-product research provides promising experimental leads and may contribute to the development of novel antidepressant agents or evidence-based adjunctive approaches, provided that preclinical findings are supported by rigorous clinical validation

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