GLOBAL JOURNAL OF PHARMACEUTICAL AND SCIENTIFIC RESEARCH
(GJPSR)

Volume-1, Issue-1, August- 2025

Article Received on 03/07/2025 Article Revised on 23/07/2025 Article Accepted on 10/08/2025

# HERBAL-BASED DRUG DELIVERY SYSTEMS: A PROMISING FUTURE FOR THE TREATMENT OF DEPRESSION

Divyanshu Singh

1. Divyanshu singh, Research scholar, Integral University

**Corresponding author:** Divyanshu Singh

**Abstract:**

Depression is a multifactorial psychiatric disorder with profound global public health implications, often marked by complex neurobiological alterations including neurotransmitter imbalances, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, neuroinflammation, and impaired neuroplasticity. Despite the availability of conventional antidepressants, limitations such as delayed onset of action, adverse effects, and poor patient adherence have necessitated the exploration of alternative therapeutic approaches. Herbal medicines, long utilized in traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani, offer a promising avenue due to their multi-targeted mechanisms, favorable safety profiles, and historical use. Phytoconstituents like alkaloids, flavonoids, terpenoids, and saponins found in herbs such as *Hypericum perforatum*, *Withania somnifera*, *Bacopa monnieri*, and *Curcuma longa* have demonstrated antidepressant activity through modulation of neurotransmission, neurotrophic signaling, and oxidative pathways. However, poor aqueous solubility, low bioavailability, and limited brain penetration hinder their clinical efficacy. Advanced drug delivery systems (DDS), including lipid-based carriers, nanoparticles, and liposomes, have emerged as powerful tools to enhance pharmacokinetics, brain targeting, and controlled release of herbal actives. Furthermore, the integration of artificial intelligence, pharmacogenomics, and personalized medicine is revolutionizing herbal formulation design. This review critically examines the neurobiology of depression, highlights well-studied herbal candidates, discusses pharmacokinetic barriers, and emphasizes the role of modern DDS in improving therapeutic outcomes. It also explores

combination therapy strategies and the growing relevance of personalized herbal medicine in psychiatric care.

**Keyword:**

Depression; Herbal Medicine; Neurotransmitters; Phytoconstituents; Advanced Drug Delivery Systems (DDS); Nanoparticles

## 1. Introduction

Depression is a pervasive and debilitating mental health disorder, currently affecting over 300 million people worldwide, and ranks as a leading contributor to global disability and disease burden (World Health Organization [WHO], 2023). Characterized by persistent low mood, loss of interest or pleasure, cognitive impairment, and functional decline, depression has complex etiopathogenesis involving neurotransmitter dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroinflammation, oxidative stress, and impaired neuroplasticity (Krishnan & Nestler, 2008). Despite the availability of numerous antidepressants—such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs)—many patients experience delayed therapeutic onset, partial or non-response, and undesirable side effects including sexual dysfunction, weight gain, and withdrawal symptoms (Rush et al., 2006).

In response to these limitations, there has been a resurgence of interest in herbal medicines and plant-based therapies, especially from traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani. These systems emphasize holistic healing and utilize polyherbal formulations rich in bioactive phytoconstituents like alkaloids, flavonoids, terpenoids, and saponins. Notably, herbs such as *Hypericum perforatum* (St. John's Wort), *Withania somnifera* (Ashwagandha), *Bacopa monnieri*, *Curcuma longa* (Turmeric), and *Crocus sativus* (Saffron) have demonstrated antidepressant potential through multi-targeted mechanisms including monoamine modulation, anti-inflammatory activity, neuroprotection, and BDNF expression enhancement (Sarris et al., 2011; Lopresti et al., 2014).

However, a major obstacle in translating the therapeutic benefits of herbal compounds into clinical practice lies in their poor aqueous solubility, low bioavailability, first-pass metabolism, and limited brain permeability (Sharma et al., 2021). To overcome these challenges, the application of advanced drug delivery systems (DDS)—such as lipid-based carriers, nanoparticles, liposomes, and solid dispersions—has gained momentum. These technologies not only improve pharmacokinetic properties but also enable controlled and targeted release, thereby enhancing efficacy while minimizing systemic side effects. Innovations such as 3D printing, artificial intelligence in formulation design, and

personalized medicine based on genomic profiling are further shaping the future of herbal antidepressant therapy (Trenfield et al., 2018; Gurwitz & Weizman, 2004).

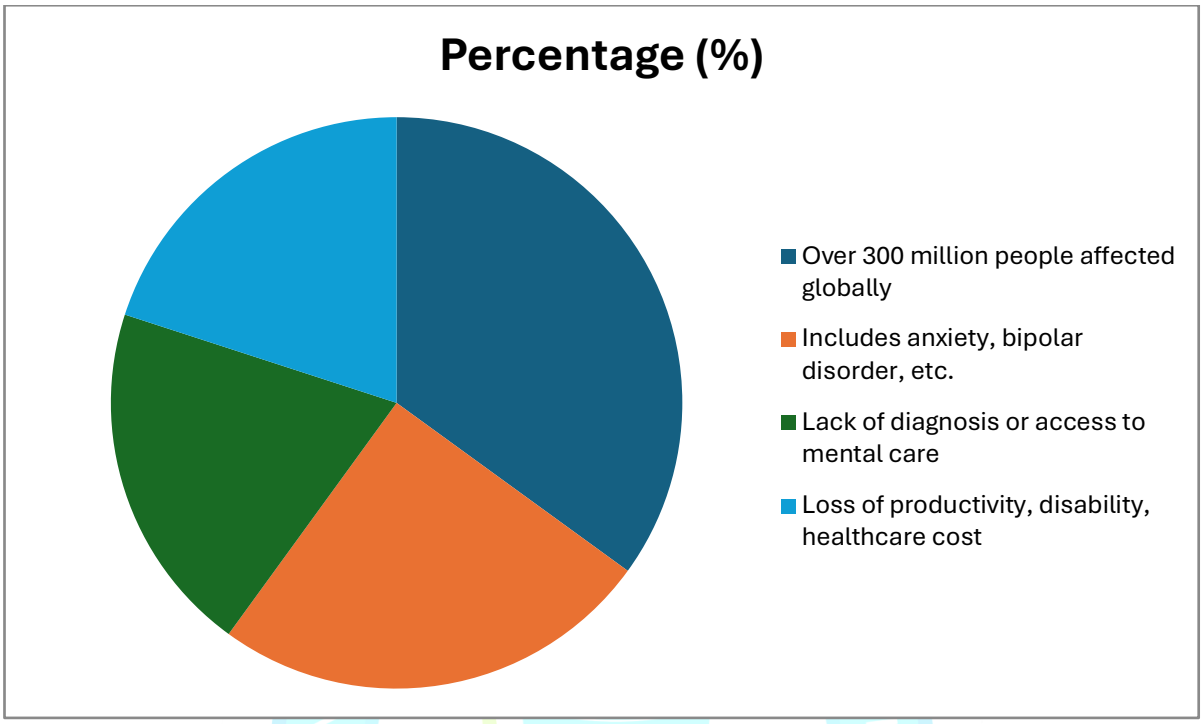


**Fig 1: Global Impact of Depression on Public Health**

## 2. Gaps in Current Antidepressant Therapy

Current antidepressant therapies are limited by several critical gaps that affect clinical effectiveness and patient satisfaction. A primary issue is the slow onset of action, with most antidepressants requiring several weeks to produce noticeable effects, delaying relief for those in acute distress (Machado-Vieira et al., 2010). Furthermore, treatment resistance remains a major problem, as nearly one-third of patients fail to achieve remission despite multiple trials of antidepressants (Rush et al., 2006). Side effects, including sexual dysfunction, sedation, and weight gain, frequently contribute to poor adherence and discontinuation (Fava et al., 2018). Additionally, conventional treatments predominantly target monoamine pathways, neglecting other implicated mechanisms such as neuroinflammation, glutamatergic transmission, and neuroplasticity (Duman et al., 2016). These limitations underscore the need for faster-acting, mechanistically diverse, and better-tolerated antidepressant options.

## 3. Growing Interest in Herbal Medicines

There is a growing global interest in herbal medicines as alternatives or complements to conventional antidepressant therapies. This trend is driven by the perception that plant-based remedies offer fewer side effects, better tolerability, and a holistic approach to mental health (Sarris et al., 2011). Many herbal medicines, such as *Hypericum perforatum* (St. John's Wort), have shown efficacy comparable to standard antidepressants in mild to moderate depression, supported by clinical and meta-analytic evidence (Linde et al., 2008). Moreover, the increasing dissatisfaction with synthetic drugs and the rising awareness of traditional healing systems have encouraged exploration of natural compounds with psychotropic properties (Ng et al., 2017). However, variability in potency, standardization, and potential herb–drug interactions remain challenges that require rigorous scientific validation and regulation.

**Table 1: Comparison of Conventional vs. Herbal Antidepressants**

| **Parameter** | **Conventional Antidepressants** | **Herbal Antidepressants** |
|---|---|---|
| Mechanism | Monoamine modulation | Multi-target (inflammation, BDNF, oxidative stress) |
| Onset of Action | 2–6 weeks | Variable, often quicker in mild/moderate cases |
| Side Effects | Common (e.g., weight gain, sexual dysfunction) | Fewer, but potential for herb-drug interactions |
| Tolerability | Moderate to low | Generally high |
| Regulatory Status | FDA-approved | Varies; often categorized as supplements |

## 4. Importance of Advanced Drug Delivery Systems (DDS)

Advanced drug delivery systems (DDS) play a crucial role in enhancing the therapeutic efficacy and safety of antidepressant treatments. Traditional delivery methods often suffer from issues such as poor bioavailability, systemic side effects, and non-specific targeting,

which advanced DDS aim to overcome (Torchilin, 2006). Novel systems like nanoparticles, liposomes, and transdermal patches enable controlled and targeted release, improving drug stability and patient adherence (Kumari et al., 2010). These technologies also facilitate the delivery of drugs across the blood–brain barrier, a major hurdle in central nervous system therapies (Saraiva et al., 2016). Additionally, DDS can be tailored to reduce dosing frequency and minimize peak-trough fluctuations, leading to better tolerability and clinical outcomes. Thus, incorporating advanced DDS is essential for optimizing modern antidepressant therapy.

## 5. Neurobiology of Depression:

The neurobiology of depression is complex and multifactorial, involving disturbances in neurotransmission, neuroendocrine function, and neuroplasticity. Traditionally, depression has been linked to dysregulation of monoamine neurotransmitters—serotonin, norepinephrine, and dopamine—which influence mood, motivation, and cognition (Delgado, 2000). However, recent research has expanded this view to include alterations in the hypothalamic–pituitary–adrenal (HPA) axis, resulting in elevated cortisol levels that impair neurogenesis and hippocampal function (Pariante & Lightman, 2008). Additionally, inflammatory markers such as cytokines have been found elevated in depressed patients, suggesting an immune system component to pathophysiology (Miller et al., 2009). Abnormalities in glutamatergic transmission and reduced synaptic plasticity have also emerged as critical contributors, highlighting the importance of brain connectivity and adaptive neural networks in mood regulation (Duman & Aghajanian, 2012). Moreover, neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), are consistently found at lower levels in depressed individuals, implicating impaired neuronal survival and synaptic remodeling in the disease process (Castrén & Kojima, 2017). Genetic and epigenetic factors also play a substantial role, with polymorphisms in genes like *SLC6A4* (serotonin transporter) and environmental stressors jointly modulating vulnerability via gene-environment interactions (Karg et al., 2011). These insights underscore the multidimensional nature of depression, emphasizing a need for integrative treatment strategies beyond monoaminergic modulation.

### 2.1 Key Neurotransmitter Systems: Serotonin, Dopamine, Noradrenaline

| Neurotransmit | Abbreviati | Major | Function | Role in | Therapeuti | Referenc |
|---|---|---|---|---|---|---|

| ter | on | Brain Regions | s | Depression | c Targets | es |
|---|---|---|---|---|---|---|
| **Serotonin** | 5-HT | Raphe nuclei → cortex, hippocampus | Regulates mood, sleep, appetite, cognition | Deficiency leads to low mood, anxiety, irritability | SSRIs (e.g., fluoxetine), SNRIs | Cowen & Browning, 2015; Delgado, 2000 |
| **Dopamine** | DA | VTA, substantia nigra → prefrontal cortex, nucleus accumbens | Reward, motivation, attention, motor function | Low levels cause anhedonia, lack of motivation | NDRIs (e.g., bupropion), atypical antipsychotics | Dunlop & Nemeroff, 2007; Nestler & Carlezon, 2006 |
| **Noradrenaline** | NE (NA) | Locus coeruleus → cortex, limbic system | Arousal, attention, stress, vigilance | Deficiency linked to fatigue, low alertness, poor focus | SNRIs (e.g., venlafaxine), TCAs | Moret & Briley, 2011; Ressler & Nemeroff, 2000 |

## 6. Role of Inflammation and Oxidative Stress

Inflammation and oxidative stress play significant roles in the pathophysiology of depression, offering insights beyond the traditional monoamine hypothesis. Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) have been consistently observed in depressed individuals, correlating with symptom severity and treatment resistance (Miller & Raison, 2016). These inflammatory mediators can alter neurotransmitter metabolism, reduce neurogenesis, and disrupt synaptic plasticity. Concurrently, oxidative stress—characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses—leads to neuronal damage and mitochondrial dysfunction, both implicated in depressive pathology (Ng et al., 2008).

The combined impact of inflammation and oxidative stress contributes to neuroprogression and cognitive decline, emphasizing the potential of anti-inflammatory and antioxidant therapies in managing depression.

### 7. The Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction

The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the body's response to stress, and its dysregulation is strongly implicated in the development and persistence of depression. In many depressed individuals, hyperactivity of the HPA axis leads to excessive secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, resulting in disrupted circadian rhythms and impaired feedback inhibition (Pariante & Lightman, 2008). Prolonged cortisol elevation negatively affects the hippocampus, a brain region critical for mood regulation and memory, by reducing neurogenesis and promoting atrophy (Sapolsky, 2000). This dysfunction contributes to emotional and cognitive symptoms commonly seen in depression and has been associated with poor response to standard antidepressants. As such, normalizing HPA axis activity represents a promising therapeutic avenue for treatment-resistant cases.

### 8. Neuroplasticity and Brain-Derived Neurotrophic Factor (BDNF)

Neuroplasticity, the brain's ability to reorganize and adapt, is crucial for emotional regulation and cognitive function, and its impairment is a hallmark of depression. A key mediator of neuroplasticity is brain-derived neurotrophic factor (BDNF), which supports the growth, survival, and differentiation of neurons. In depressed individuals, reduced levels of BDNF—particularly in the hippocampus and prefrontal cortex—have been consistently reported, correlating with symptom severity and chronicity (Castrén & Rantamäki, 2010). Chronic stress and elevated cortisol can further suppress BDNF expression, contributing to neuronal atrophy and functional decline. Conversely, antidepressant treatments, including SSRIs, ketamine, and physical exercise, have been shown to increase BDNF levels and promote synaptic plasticity, supporting the neurotrophic hypothesis of depression (Duman & Monteggia, 2006). Enhancing BDNF signaling thus represents a promising target for developing more effective antidepressant therapies.

## 9. Herbal Medicines in Depression: Evidence and Efficacy

### 9.1 Traditional Systems of Medicine: Ayurveda, TCM, and Unani

Traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani offer holistic approaches to mental health, including the management of depression. Ayurveda attributes depression to an imbalance in the three doshas—Vata, Pitta, and Kapha—and uses herbal remedies like *Ashwagandha* and *Brahmi* to restore balance and improve mental clarity (Patwardhan et al., 2005). TCM views depression as a disruption in the flow of Qi and employs acupuncture, herbal formulations like *Xiao Yao San*, and lifestyle adjustments to restore harmony (Zhang et al., 2010). Similarly, Unani medicine links depression to imbalances in the four humors and utilizes regimens including herbs like *Saad Kufi* and *Ustukhuddus* for mental rejuvenation (Ahmad et al., 2007).

**Table 2: List of Some Medicinal Plants with Antidepressant Activity**

| Plant Name | Common Name | Active Constituents | Proposed Mechanism | Reference |
|---|---|---|---|---|
| *Hypericum perforatum* | St. John's Wort | Hypericin, Hyperforin | Inhibition of serotonin, norepinephrine, and dopamine reuptake | Linde et al., 2008 |
| *Withania somnifera* | Ashwagandha | Withanolides | Modulation of stress hormones and neuroprotection | Bhattacharya et al., 2000 |
| *Bacopa monnieri* | Brahmi | Bacosides | Enhancement of synaptic transmission and antioxidant activity | Singh & Dhawan, 1997 |
| *Crocus sativus* | Saffron | Crocin, Safranal | Inhibition of serotonin reuptake and antioxidant effect | Akhondzadeh et al., 2005 |
| *Curcuma* | Turmeric | Curcumin | Anti-inflammatory, | Kulkarni et al., |

| | | | | |
|---|---|---|---|---|
| *longa* | | | antioxidant, and neuroprotective actions | 2008 |
| *Camellia sinensis* | Green Tea | Catechins, L-theanine | Monoamine oxidase inhibition and anxiolytic effect | Park et al., 2008 |
| *Rhodiola rosea* | Rhodiola | Salidroside, Rosavin | Adaptogenic effect, modulation of neurotransmitters | Panossian et al., 2010 |

## 10. Advances in Herbal-Based Drug Delivery Systems

### 10.1 Lipid-Based Systems

#### 10.1.1 Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs, making them highly versatile carriers in drug delivery systems. In the context of antidepressant therapy, liposomes offer advantages such as improved drug solubility, enhanced bioavailability, and controlled release, which help reduce dosing frequency and side effects (Bozzuto & Molinari, 2015). Their biocompatibility and ability to cross the blood–brain barrier further enhance their potential for targeted delivery to the central nervous system (Chang et al., 2013). Liposomal formulations of psychotropic agents have shown promise in preclinical studies, especially in minimizing systemic toxicity and improving therapeutic outcomes. However, challenges such as stability, manufacturing complexity, and scalability still need to be addressed for broader clinical application.

#### 10.1.2 Phytosomes

Phytosomes are advanced lipid-based drug delivery systems designed to enhance the bioavailability and therapeutic efficacy of plant-derived compounds. Unlike conventional herbal extracts, phytosomes form a complex between phytoconstituents (such as flavonoids or polyphenols) and phospholipids, which improves absorption through biological membranes (Maiti et al., 2006). This technology is particularly valuable for phytochemicals

with poor solubility or stability, such as curcumin, quercetin, and silybin—many of which possess antidepressant-like activity through antioxidant, anti-inflammatory, and neuroprotective mechanisms (Yuan et al., 2019). By increasing systemic availability and facilitating brain delivery, phytosomes have shown enhanced pharmacological effects in preclinical models of depression. Their natural origin and improved therapeutic index make them promising candidates for integrative mental health therapies.

### 10.1.3 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are submicron-sized carriers made from solid lipids that remain stable at room and body temperatures, offering a novel approach for delivering antidepressants. These systems combine the advantages of traditional drug carriers with those of lipid-based formulations, such as biocompatibility, protection of labile drugs from degradation, and controlled drug release (Mehnert & Mäder, 2001). SLNs are particularly useful for brain-targeted delivery due to their ability to cross the blood–brain barrier, which is crucial for treating central nervous system disorders like depression (Mukherjee et al., 2009). Moreover, SLNs can enhance the bioavailability of poorly soluble natural compounds with antidepressant properties, including flavonoids and alkaloids. Their scalability and potential for surface modification further expand their applicability in clinical settings, although stability and drug loading capacity remain areas for improvement.

### 10.1.4 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are advanced lipid-based nanocarriers composed of a blend of solid and liquid lipids, offering improved drug loading, stability, and controlled release compared to solid lipid nanoparticles (SLNs). The imperfect crystalline structure of NLCs creates more space to accommodate bioactive compounds, making them highly suitable for encapsulating lipophilic antidepressants and phytoconstituents (Müller et al., 2002). NLCs enhance oral and brain bioavailability, protect sensitive molecules from degradation, and can be surface-modified for targeted delivery across the blood–brain barrier—key advantages in depression therapy (Pardeshi & Belgamwar, 2013).

**Table 3: Advanced Drug Delivery Systems for Antidepressants**

| DDS Type | Composition | Key Benefits | Applications |
|---|---|---|---|
| Liposomes | Phospholipid vesicles | Biocompatibility, BBB penetration | Synthetic & herbal antidepressants |
| Phytosomes | Phytochemical + phospholipid complex | Enhanced absorption of herbal extracts | Curcumin, quercetin, etc. |
| SLNs | Solid lipid core | Controlled release, stability | CNS-targeted delivery |
| NLCs | Solid + liquid lipid matrix | High drug loading, stability | Natural antidepressants |
| Nanoemulsions | Oil/water droplets (20–200 nm) | Rapid absorption, versatile routes | Oral, nasal, transdermal |
| Ethosomes | Lipid vesicles + ethanol | Deep skin/nasal penetration | Herbal CNS actives |

Various advanced drug delivery systems (DDS) have been developed to enhance the efficacy and bioavailability of antidepressants. Liposomes, composed of phospholipid vesicles, are biocompatible carriers capable of crossing the blood-brain barrier (BBB), making them suitable for delivering both synthetic and herbal antidepressants. Phytosomes, which combine phytochemicals with phospholipids, significantly enhance the absorption of herbal compounds such as curcumin and quercetin. Solid lipid nanoparticles (SLNs), with their solid lipid core, provide controlled drug release and increased stability, particularly for central nervous system (CNS) targeting. In contrast, nanostructured lipid carriers (NLCs) integrate both solid and liquid lipids, allowing higher drug loading and better formulation stability, making them ideal for delivering natural antidepressants. Nanoemulsions, consisting of oil-in-water droplets ranging from 20–200 nm, promote rapid absorption and are versatile for

oral, nasal, and transdermal applications. Lastly, ethosomes, which are lipid vesicles enriched with ethanol, enhance skin and nasal penetration, offering an effective means for delivering herbal CNS-active agents.

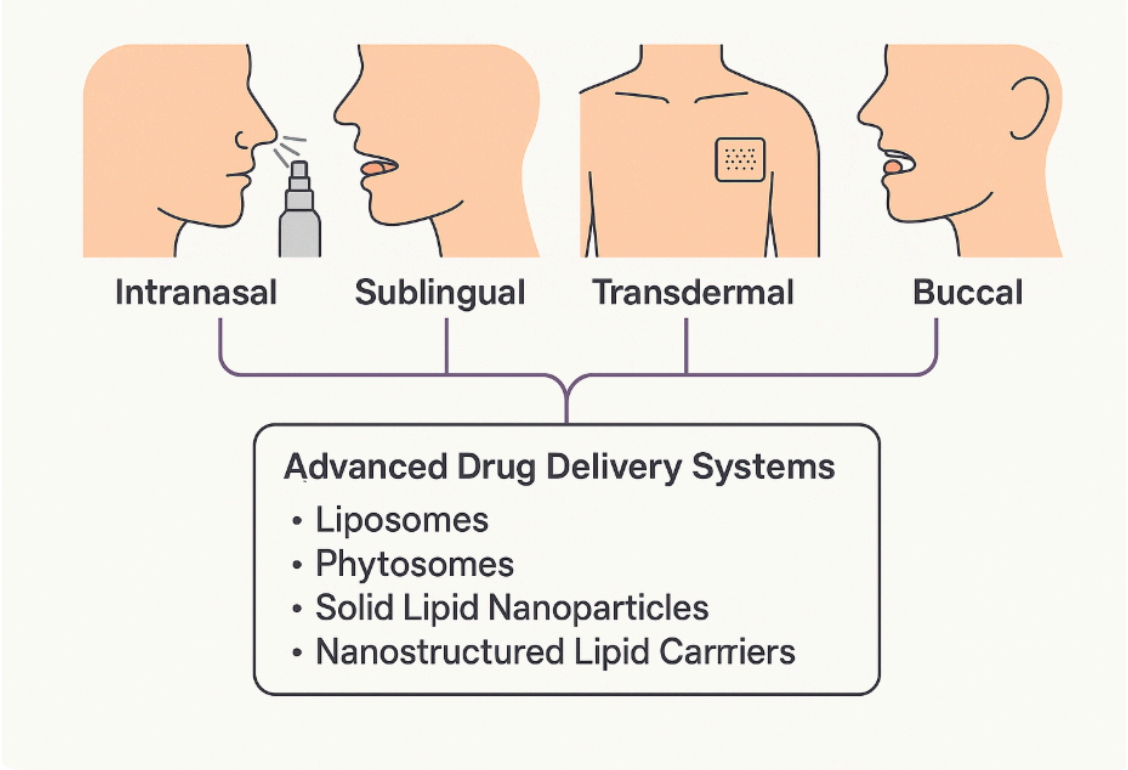


**Figure 2: Advanced Drug Delivery Systems and Routes of Administration**

## 11. Polymer-Based Systems

### 11.1 Nanoparticles

Polymer-based nanoparticles are versatile drug delivery systems engineered from biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), or their copolymer PLGA. These nanoparticles can encapsulate both hydrophilic and hydrophobic drugs, offering controlled release, improved stability, and enhanced targeting capabilities—features particularly beneficial for antidepressant delivery (Danhier et al., 2012). They also protect drugs from enzymatic degradation and can be engineered to cross the blood–brain barrier via surface modification or receptor-mediated transport (Kreuter, 2014). In depression therapy, polymeric nanoparticles have been used to deliver both synthetic and herbal

compounds with improved bioavailability and brain accumulation, leading to enhanced antidepressant-like activity in preclinical studies. Their tunable properties make them promising candidates for personalized and sustained drug delivery in neuropsychiatric disorders.

### 11.2 Microspheres

Polymer-based microspheres are spherical particles ranging from 1 to 1000 micrometers in size, designed to deliver drugs in a controlled and sustained manner. Constructed from biodegradable polymers like polylactic acid (PLA) and PLGA, microspheres protect active compounds from degradation and allow for extended drug release, which is advantageous in managing chronic conditions such as depression (Jain, 2000). By maintaining consistent plasma drug levels, they help reduce dosing frequency and improve patient adherence. In the context of antidepressants, microspheres have been explored for both synthetic drugs and herbal extracts, demonstrating prolonged therapeutic effects in preclinical models (Narasimhan & Langer, 2003). Their potential for injectable depot formulations also opens new possibilities for long-term treatment strategies in major depressive disorder.

### 11.3 Dendrimers

Dendrimers are highly branched, tree-like polymeric nanostructures with a well-defined architecture that allows for precise drug loading and surface modification. Their unique structure provides multiple functional groups for attaching antidepressants or targeting ligands, making them ideal carriers for site-specific and controlled drug delivery (Tomalia et al., 2005). Due to their nanoscale size and biocompatibility, dendrimers can cross the blood–brain barrier and have shown promise in enhancing the brain delivery of both conventional and herbal antidepressants (Kesharwani et al., 2014). Additionally, their ability to encapsulate or conjugate drugs helps improve solubility, stability, and therapeutic efficacy. While still primarily in the research phase, dendrimers represent a cutting-edge platform with great potential in treating neuropsychiatric disorders such as depression.

## 12. Vesicular and Emulsion-Based Systems

### 12.1 Nanoemulsions

Nanoemulsions are kinetically stable colloidal dispersions of oil and water stabilized by surfactants, with droplet sizes typically in the range of 20–200 nm. They offer several advantages for antidepressant delivery, including enhanced solubility of poorly water-soluble drugs, improved absorption, and rapid onset of action (Gupta et al., 2016). Due to their small droplet size, nanoemulsions facilitate efficient drug transport across biological membranes, including the blood–brain barrier, making them particularly valuable in central nervous system targeting. In preclinical studies, nanoemulsion-based formulations of herbal and synthetic antidepressants have demonstrated improved bioavailability and sustained therapeutic effects (Shakeel et al., 2008). Moreover, their ability to be administered via various routes—oral, transdermal, or intranasal—adds flexibility in designing patient-friendly delivery systems.

### 12.2 Ethosomes and Transfersomes

Ethosomes and Transfersomes are innovative vesicular drug delivery systems that enhance transdermal and intranasal absorption, offering promising strategies for delivering antidepressants and herbal actives. *Ethosomes* are lipid vesicles enriched with high concentrations of ethanol, which fluidizes skin lipids and increases membrane permeability, enabling deeper penetration of both lipophilic and hydrophilic drugs (Tupkari et al., 2012). They are particularly useful for transdermal and nasal delivery of antidepressant agents, providing improved bioavailability and sustained release. *Transfersomes* are ultra-deformable vesicles composed of phospholipids and edge activators, such as surfactants, which allow them to squeeze through narrow intercellular spaces in the skin (Cevc & Blume, 2001). Their elasticity makes them ideal for delivering drugs across biological barriers, including the blood–brain barrier via non-invasive routes. Both systems have shown enhanced therapeutic potential in preclinical studies for central nervous system disorders, making them attractive tools for improving the efficacy of depression treatment.

## 13. Novel Routes of Administration

### 13.1 Transdermal Delivery

Transdermal delivery is an emerging route for administering antidepressants that offers several advantages over traditional oral formulations, including improved bioavailability, sustained drug release, and avoidance of first-pass hepatic metabolism. This method involves

delivering drugs through the skin directly into systemic circulation, resulting in more stable plasma concentrations and reduced dosing frequency (Prausnitz & Langer, 2008). It is especially beneficial for patients with gastrointestinal issues or poor medication adherence. In the context of depression, transdermal systems have been developed for drugs like selegiline, a monoamine oxidase inhibitor, which demonstrated effective symptom control with fewer systemic side effects (Bodkin & Amsterdam, 2002). Additionally, this route can be utilized for delivering herbal extracts and nano-formulated antidepressants, enhancing patient compliance and therapeutic outcomes.

### 13.2 Intranasal Delivery

Intranasal delivery is a promising non-invasive route for administering antidepressants, offering rapid onset of action and direct brain targeting by bypassing the blood–brain barrier through the olfactory and trigeminal pathways. This method ensures faster therapeutic effects, making it particularly useful in acute and treatment-resistant depression (Illum, 2003). Intranasal delivery reduces systemic exposure and side effects while enhancing the bioavailability of poorly absorbed drugs. Esketamine nasal spray, approved for treatment-resistant depression, exemplifies the clinical success of this route (Daly et al., 2019). Additionally, intranasal administration has shown potential in delivering herbal compounds and nanoformulations, including curcumin and flavonoids, with improved neuroprotective outcomes in preclinical models. Overall, this approach offers a patient-friendly and effective alternative for rapid antidepressant therapy.

### 13.3 Buccal and Sublingual Routes

Buccal and sublingual routes are alternative non-invasive drug delivery methods that involve administration through the mucosal tissues of the mouth, offering rapid absorption and bypassing first-pass hepatic metabolism. These routes are particularly advantageous for delivering antidepressants with poor oral bioavailability or those requiring quick onset of action (Shojaei, 1998). Sublingual delivery ensures faster systemic absorption due to the rich vascularization under the tongue, while buccal delivery allows for extended release and better control over drug residence time. Both routes improve patient compliance, especially in individuals with swallowing difficulties or gastrointestinal side effects. Recent studies have explored the use of mucoadhesive films, tablets, and nanoformulations for delivering both

synthetic antidepressants and phytoconstituents, showing promising pharmacokinetic and therapeutic profiles (Khairnar et al., 2009).

**Table 4: Novel Drug Delivery Systems Applied to Herbal Antidepressants**

| DDS Type | Technology Used | Advantages | Herbal Example |
|---|---|---|---|
| Liposomes | Phospholipid bilayers | Enhanced brain targeting, biocompatibility | Curcumin liposomes |
| Solid lipid nanoparticles (SLNs) | Lipid matrix-based carriers | Improved stability, controlled release | Ashwagandha SLNs |
| Nanosuspensions | Nanocrystalline dispersions | Increased solubility and absorption | Bacopa nanosuspensions |
| Phytosomes | Phytochemical–phospholipid complex | Better GI absorption, liver protection | Silymarin phytosomes |
| Polymeric nanoparticles | Biodegradable polymers (e.g., PLGA) | Sustained release, BBB crossing | Curcumin PLGA nanoparticles |

## 14. Preclinical and Clinical Evaluations

### 14.1 In Vitro Models for Antidepressant Screening

In vitro models for antidepressant screening are essential tools in early-stage drug development, enabling the rapid and cost-effective evaluation of potential antidepressant agents before proceeding to in vivo studies. These models typically assess the ability of compounds to modulate molecular targets related to depression, such as monoamine reuptake inhibition, neuroinflammation, neurogenesis, and oxidative stress (Boudjada et al., 2020). Common assays include monoamine oxidase (MAO) inhibition, serotonin transporter binding, and measurement of brain-derived neurotrophic factor (BDNF) expression in

cultured neuronal cells. Additionally, cell lines like PC12 and SH-SY5Y are frequently used to study neuroprotective and neuroplastic effects of synthetic and herbal compounds (Bourin et al., 2012). In vitro models serve as a preliminary screening platform to identify promising candidates with antidepressant-like activity while reducing animal usage and optimizing resource allocation.

### 14.2 Animal Models of Depression

Animal models of depression are critical for understanding the neurobiological mechanisms of depression and evaluating the efficacy of potential antidepressant therapies in vivo. These models simulate human depressive behaviors through stress induction, genetic manipulation, or pharmacological intervention. Common models include the Forced Swim Test (FST) and Tail Suspension Test (TST), which assess behavioral despair; the Chronic Unpredictable Mild Stress (CUMS) model, which mimics anhedonia and long-term depressive symptoms; and the Learned Helplessness model, which reflects cognitive deficits associated with depression (Willner, 2017). These paradigms are instrumental in testing both synthetic and natural antidepressant candidates for their effects on mood, neuroplasticity, and neurotransmitter levels. While no single model fully replicates human depression, their use in combination improves the translational relevance of preclinical research.

### 14.3 Clinical Trials on Herbal Drug Delivery Systems

Clinical trials on herbal drug delivery systems are increasingly being conducted to evaluate the safety, efficacy, and pharmacokinetics of plant-based antidepressants in advanced formulations. These trials often focus on improving the bioavailability and therapeutic consistency of herbal compounds such as *Hypericum perforatum* (St. John's Wort), *Curcuma longa* (curcumin), and *Withania somnifera* (ashwagandha) using novel delivery platforms like liposomes, nanoemulsions, and phytosomes (Panossian & Wikman, 2010). Several studies have shown that such systems enhance absorption, reduce variability, and improve clinical outcomes compared to traditional extracts. For instance, a clinical trial using a curcumin-phytosome complex demonstrated significant improvements in depressive symptoms with superior tolerability (Lopresti et al., 2014). Despite promising results, more large-scale, randomized controlled trials are needed to establish standardized dosing, long-term safety, and regulatory approval of these advanced herbal formulations.

### 14.4 Safety, Toxicity, and Pharmacovigilance Dat

Safety, toxicity, and pharmacovigilance data are essential components in evaluating herbal drug delivery systems, especially for treating chronic conditions like depression. Although herbal medicines are often perceived as safe due to their natural origin, they can pose risks such as hepatotoxicity, nephrotoxicity, allergic reactions, or herb–drug interactions if not properly standardized or monitored (Bent, 2008). Advanced drug delivery systems—such as nanoparticles and phytosomes—may alter the pharmacokinetics and biodistribution of herbal compounds, necessitating thorough preclinical and clinical toxicity evaluations (Javed et al., 2019). Regulatory agencies increasingly emphasize pharmacovigilance to detect adverse drug reactions (ADRs) post-marketing, ensuring ongoing safety surveillance. Integrating toxicological profiling and pharmacovigilance reporting systems is vital for the rational and safe use of herbal antidepressants, especially in vulnerable populations.

## 15. Innovations and Future Perspectives

### 15.1 Artificial Intelligence in Formulation Design

Artificial intelligence (AI) is revolutionizing formulation design by enabling faster, data-driven decision-making in the development of drug delivery systems, including those for antidepressant and herbal therapies. AI algorithms—such as machine learning and deep learning—can analyze large datasets to predict optimal formulation parameters, such as excipient selection, drug loading, and release profiles (Mak & Pichika, 2019). In the context of herbal medicine, AI can assist in standardizing phytochemical content, predicting synergistic effects, and minimizing toxicity. Furthermore, AI tools are increasingly used for *in silico* modeling of drug–excipient interactions, enhancing formulation stability and efficacy while reducing time and cost associated with traditional trial-and-error methods (Stumpfe & Bajorath, 2011). By integrating AI into formulation design, researchers can accelerate the development of personalized, efficient, and safer antidepressant therapies. Additionally, AI-driven quality by design (QbD) approaches allow formulation scientists to

anticipate and control variability in manufacturing processes, ensuring reproducibility and regulatory compliance (Kumar & Dureja, 2020).

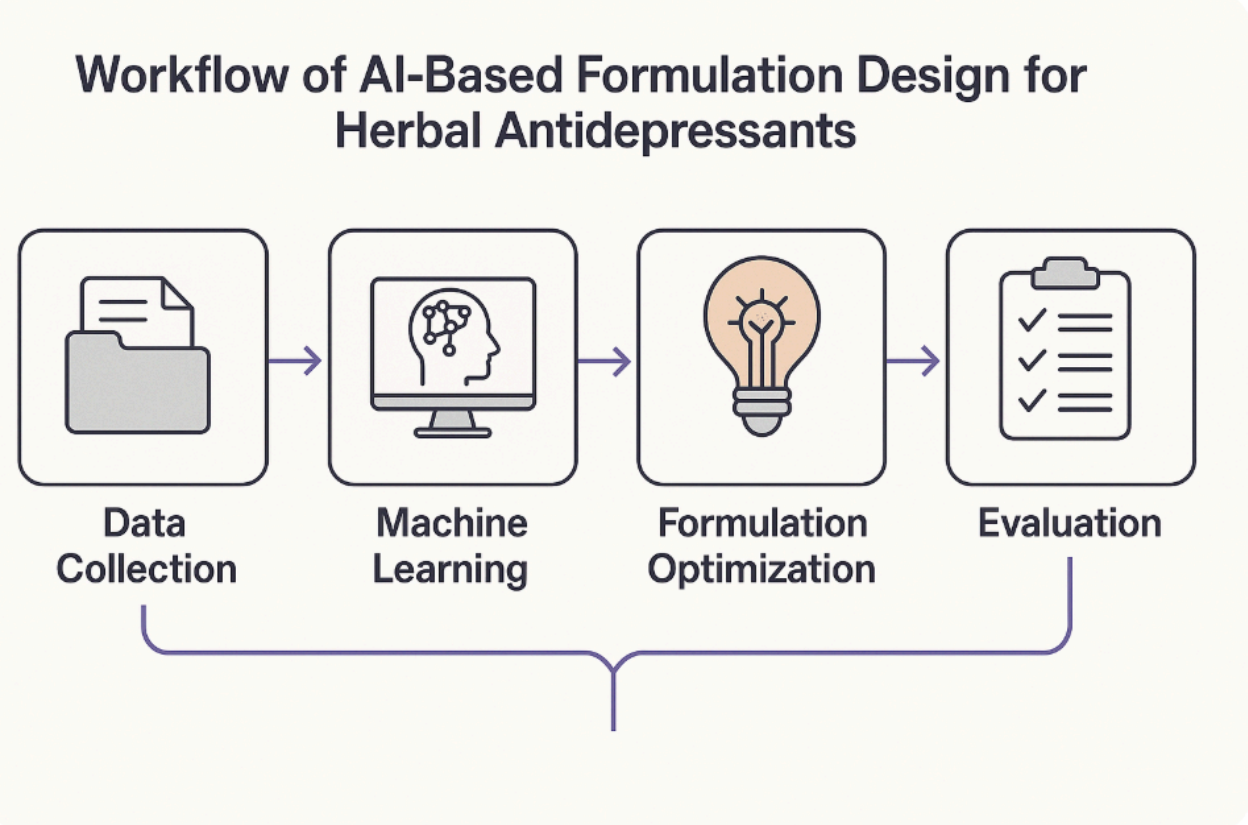


**Figure 2: Workflow of AI-Based Formulation Design for Herbal Antidepressants**

### 15.2 3D Printing and Smart Drug Delivery

3D printing and smart drug delivery technologies are transforming personalized medicine by enabling the fabrication of highly tailored dosage forms with precise control over drug release profiles, especially for complex conditions like depression. 3D printing allows for the layer-by-layer construction of tablets or implants with customizable shapes, sizes, and compositions, facilitating multi-drug combinations and individualized dosing (Goyanes et al., 2015). This is particularly beneficial for psychiatric patients who require flexible, sustained, or pulsatile release of antidepressants. Smart drug delivery systems, such as stimuli-responsive hydrogels and biosensor-integrated platforms, can release drugs in response to specific physiological triggers like pH, temperature, or enzyme levels, thereby enhancing therapeutic efficacy and reducing side effects (Zhang et al., 2021). These technologies hold

great promise for improving adherence, safety, and outcomes in both conventional and herbal-based antidepressant therapies.

### 15.3 Personalized Herbal Medicine and Genomics

Personalized herbal medicine and genomics represent a cutting-edge intersection of traditional therapies and precision medicine, aiming to tailor herbal treatments based on an individual's genetic profile. Genomic insights help identify how variations in genes—such as those coding for cytochrome P450 enzymes (e.g., *CYP2D6*, *CYP3A4*)—influence the metabolism, efficacy, and safety of phytochemicals used in antidepressant therapies (Gurwitz & Weizman, 2004). This allows clinicians to optimize herbal drug selection, dosage, and combinations to match a patient's pharmacogenetic makeup, minimizing adverse effects and enhancing treatment response. Additionally, pharmacogenomic studies can elucidate molecular targets of herbal compounds, improving the scientific validation of traditional remedies (Zhou et al., 2019). This integration of genomics with herbal medicine holds significant promise for individualized, safer, and more effective treatment strategies for depression and other complex disorders.

### 15.4 Combination Therapy Approaches: Herb-Herb & Herb-Drug

Combination therapy approaches, including *herb–herb* and *herb–drug* regimens, are gaining attention in depression management for their potential to enhance therapeutic efficacy and reduce adverse effects. Herb–herb combinations, such as *Ashwagandha* with *Brahmi* or *Curcuma longa* with *Piper nigrum*, can exert synergistic effects by modulating multiple neurochemical and inflammatory pathways, thereby improving mood and cognitive function (Kulkarni et al., 2012). Herb–drug combinations, on the other hand, aim to complement conventional antidepressants with phytochemicals to boost efficacy, reduce required dosages, and mitigate side effects. For example, co-administration of *St. John's Wort* with SSRIs has shown additive antidepressant effects, though it raises the risk of interactions via cytochrome P450 modulation (Izzo & Ernst, 2009). While these combinations hold promise, careful pharmacokinetic and pharmacodynamic evaluation is essential to avoid adverse interactions and ensure therapeutic safety.

## 16. Conclusion

The convergence of traditional herbal medicine with modern pharmaceutical technologies offers a transformative approach to the management of depression, a multifactorial disorder influenced by neurochemical, inflammatory, and genetic factors. Despite the availability of conventional antidepressants, many patients experience delayed therapeutic onset, treatment resistance, and intolerable side effects—highlighting the urgent need for safer, more effective alternatives. Herbal compounds such as *Withania somnifera*, *Curcuma longa*, and *Hypericum perforatum* have demonstrated antidepressant activity through mechanisms involving neuroplasticity, HPA axis modulation, monoamine regulation, and antioxidant effects.

Advanced drug delivery systems—including liposomes, phytosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs)—enhance the solubility, stability, and brain bioavailability of herbal actives, thereby improving therapeutic efficacy and reducing variability. Furthermore, novel administration routes like transdermal, intranasal, and buccal delivery provide non-invasive, patient-friendly alternatives with faster onset and reduced systemic side effects.

In parallel, tools such as artificial intelligence (AI) and 3D printing are streamlining formulation development, enabling the creation of personalized, multi-drug delivery systems tailored to individual pharmacogenomic profiles. The emergence of combination therapy—through herb–herb and herb–drug strategies—adds another layer of therapeutic synergy but requires careful evaluation to avoid adverse interactions, especially via CYP-mediated metabolic pathways.

Preclinical models and clinical trials increasingly support the efficacy of these integrative approaches, but standardization, regulatory approval, and long-term safety remain critical challenges. Comprehensive pharmacovigilance systems and toxicological assessments are essential to ensure the safe translation of these innovations into clinical practice. Ultimately, the strategic integration of herbal medicine with nanotechnology, systems biology, and precision pharmacotherapy holds the potential to revolutionize depression treatment—offering individualized, effective, and holistic care for patients worldwide.

## 17. Conflict of Interest

The authors declare no conflict of interest.

## 18. Acknowledgment

I gratefully acknowledge the contributions of all the authors whose work has been cited in this review, and whose findings have laid the foundation for this academic endeavor.

## 19. References


- Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. *Nature Medicine, 22*(3), 238–249. https://doi.org/10.1038/nm.4050
- Fava, M., Rush, A. J., Alpert, J. E., Balasubramani, G. K., Wisniewski, S. R., Carmin, C. N., … & Trivedi, M. H. (2018). Difference in treatment outcome in outpatients with anxious versus nonanxious depression: A STAR*D report. American Journal of Psychiatry, 165(3), 342–351. https://doi.org/10.1176/appi.ajp.2007.06111868*
- *Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I. D., & Zarate, C. A. Jr. (2010). The timing of antidepressant effects: A comparison of diverse pharmacological and somatic treatments. Pharmacology & Therapeutics, 127(1), 1–14. https://doi.org/10.1016/j.pharmthera.2010.02.009*
- *Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry, 163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905
- Linde, K., Berner, M. M., & Kriston, L. (2008). St John's wort for major depression. *Cochrane Database of Systematic Reviews, 2008*(4), CD000448. https://doi.org/10.1002/14651858.CD000448.pub3
- Ng, Q. X., Venkatanarayanan, N., & Ho, C. Y. X. (2017). Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. *Journal of Affective Disorders, 210*, 211–221. https://doi.org/10.1016/j.jad.2016.12.048
- Sarris, J., Kavanagh, D. J., & Byrne, G. (2011). Adjuvant use of nutraceuticals in depression: A systematic review. *Nutrition Reviews, 67*(3), 125–131. https://doi.org/10.1111/j.1753-4887.2008.00145.x

- Kumari, A., Yadav, S. K., & Yadav, S. C. (2010). Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces, 75*(1), 1–18. https://doi.org/10.1016/j.colsurfb.2009.09.001
- Saraiva, C., Praça, C., Ferreira, R., Santos, T., Ferreira, L., & Bernardino, L. (2016). Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases. *Journal of Controlled Release, 235*, 34–47. https://doi.org/10.1016/j.jconrel.2016.05.044
- Torchilin, V. P. (2006). Multifunctional nanocarriers. *Advanced Drug Delivery Reviews, 58*(14), 1532–1555. https://doi.org/10.1016/j.addr.2006.09.009
- Delgado, P. L. (2000). Depression: The case for a monoamine deficiency. *Journal of Clinical Psychiatry, 61*(6), 7–11. https://doi.org/10.4088/JCP.v61n0702
- Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: Potential therapeutic targets. *Science, 338*(6103), 68–72. https://doi.org/10.1126/science.1222939
- Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029
- Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences, 31*(9), 464–468. https://doi.org/10.1016/j.tins.2008.06.006
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology, 16*(1), 22–34. https://doi.org/10.1038/nri.2015.5
- Ng, F., Berk, M., Dean, O., & Bush, A. I. (2008). Oxidative stress in psychiatric disorders: Evidence base and therapeutic implications. *International Journal of Neuropsychopharmacology, 11*(6), 851–876. https://doi.org/10.1017/S1461145707008401
- Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences, 31*(9), 464–468. https://doi.org/10.1016/j.tins.2008.06.006

- Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry, 57*(10), 925–935. https://doi.org/10.1001/archpsyc.57.10.925
- Castrén, E., & Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Developmental Neurobiology, 70*(5), 289–297. https://doi.org/10.1002/dneu.20758
- Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry, 59*(12), 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013
- Ahmad, S., Akhtar, N., & Tajuddin. (2007). Herbal drugs used in depression: A review. *International Journal of Green Pharmacy, 1*(1), 47–52. https://doi.org/10.22377/ijgp.v1i1.8
- Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: A comparative overview. *Evidence-Based Complementary and Alternative Medicine, 2*(4), 465–473. https://doi.org/10.1093/ecam/neh140
- Zhang, Z. J., Chen, H. Y., Yip, K. C., Ng, R., & Wong, V. T. (2010). The effectiveness and safety of Chinese herbal medicine for depression: A systematic review and meta-analysis. *Journal of Psychiatric Research, 44*(3), 213–220. https://doi.org/10.1016/j.jpsychires.2009.08.010
- Bozzuto, G., & Molinari, A. (2015). Liposomes as nanomedical devices. *International Journal of Nanomedicine, 10*, 975–999. https://doi.org/10.2147/IJN.S68861
- Chang, H. I., Yeh, M. K., & Chiang, C. H. (2013). Formulation and evaluation of citalopram-loaded liposomes for brain targeting. *Journal of Drug Targeting, 21*(6), 570–578. https://doi.org/10.3109/1061186X.2013.804628
- Maiti, K., Mukherjee, K., Gantait, A., Saha, B. P., & Mukherjee, P. K. (2006). Curcumin–phospholipid complex: Preparation, therapeutic evaluation and pharmacokinetic study in rats. *International Journal of Pharmaceutics, 330*(1-2), 155–163. https://doi.org/10.1016/j.ijpharm.2006.08.008
- Yuan, H., Ma, Q., Ye, L., & Piao, G. (2019). The traditional medicine and modern medicine from natural products. *Molecules, 21*(5), 559. https://doi.org/10.3390/molecules21050559

- Mehnert, W., & Mäder, K. (2001). Solid lipid nanoparticles: Production, characterization and applications. *Advanced Drug Delivery Reviews, 47*(2–3), 165–196. https://doi.org/10.1016/S0169-409X(01)00105-3
- Mukherjee, S., Ray, S., & Thakur, R. S. (2009). Solid lipid nanoparticles: A modern formulation approach in drug delivery system. *Indian Journal of Pharmaceutical Sciences, 71*(4), 349–358. https://doi.org/10.4103/0250-474X.57282
- Müller, R. H., Radtke, M., & Wissing, S. A. (2002). Nanostructured lipid matrices for improved microencapsulation of drugs. *International Journal of Pharmaceutics, 242*(1–2), 121–128. https://doi.org/10.1016/S0378-5173(02)00180-1
- Pardeshi, C. V., & Belgamwar, V. S. (2013). Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: An excellent platform for brain targeting. *Expert Opinion on Drug Delivery, 10*(7), 957–972. https://doi.org/10.1517/17425247.2013.790887
- Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: An overview of biomedical applications. *Journal of Controlled Release, 161*(2), 505–522. https://doi.org/10.1016/j.jconrel.2012.01.043
- Kreuter, J. (2014). Nanoparticulate systems for brain delivery of drugs. *Advanced Drug Delivery Reviews, 71*, 2–14. https://doi.org/10.1016/j.addr.2014.01.020
- Jain, R. A. (2000). The manufacturing techniques of various drug-loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. *Biomaterials, 21*(23), 2475–2490. https://doi.org/10.1016/S0142-9612(00)00115-0
- Narasimhan, B., & Langer, R. (2003). Biodegradable polymeric microspheres as drug delivery systems. *Advanced Drug Delivery Reviews, 55*(3), 329–347. https://doi.org/10.1016/S0169-409X(02)00218-3
- Kesharwani, P., Gajbhiye, V., & Jain, N. K. (2014). Dendrimer nanocarriers for delivery of anticancer drugs. *Drug Delivery, 21*(6), 495–509. https://doi.org/10.3109/10717544.2013.856763
- Tomalia, D. A., Reyna, L. A., & Svenson, S. (2005). Dendrimers as multi-purpose nanodevices for oncology drug delivery and diagnostic imaging. *Biochemical Society Transactions, 33*(Pt 1), 61–64. https://doi.org/10.1042/BST0330061

- Gupta, A., Eral, H. B., Hatton, T. A., & Doyle, P. S. (2016). Nanoemulsions: Formation, properties and applications. *Soft Matter, 12*(11), 2826–2841. https://doi.org/10.1039/C5SM02958A
- Shakeel, F., Baboota, S., Ahuja, A., Ali, J., & Shafiq, S. (2008). Nanoemulsions as vehicles for transdermal delivery of aceclofenac: Formulation and characterization. *Drug Development and Industrial Pharmacy, 34*(5), 545–553. https://doi.org/10.1080/03639040701801681
- Bodkin, J. A., & Amsterdam, J. D. (2002). Transdermal selegiline in major depression: A double-blind, placebo-controlled, parallel-group study in outpatients. *American Journal of Psychiatry, 159*(11), 1869–1875. https://doi.org/10.1176/appi.ajp.159.11.1869
- Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery. *Nature Biotechnology, 26*(11), 1261–1268. https://doi.org/10.1038/nbt.1504
- Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., … & Drevets, W. C. (2019). Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression. *JAMA Psychiatry, 76*(9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189
- Illum, L. (2003). Nasal drug delivery—possibilities, problems and solutions. *Journal of Controlled Release, 87*(1–3), 187–198. https://doi.org/10.1016/S0168-3659(02)00363-2
- Khairnar, A., Jain, P., & Baviskar, D. (2009). Development of mucoadhesive buccal patch containing aceclofenac: In vitro evaluations. *International Journal of PharmTech Research, 1*(4), 978–981.
- Shojaei, A. H. (1998). Buccal mucosa as a route for systemic drug delivery: A review. *Journal of Pharmacy and Pharmaceutical Sciences, 1*(1), 15–30.
- Boudjada, A., Toumi, H., & Merzoug, S. (2020). In vitro screening models for antidepressant activity: A review. *Biomedicine & Pharmacotherapy, 129*, 110482. https://doi.org/10.1016/j.biopha.2020.110482
- Bourin, M., Chenu, F., Ripoll, N., & David, D. J. (2012). A proposal of decision tree to screen putative antidepressants using forced swimming test. *Behavioural Brain Research, 228*(2), 357–366. https://doi.org/10.1016/j.bbr.2011.12.006

- Willner, P. (2017). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress, 6*, 78–93. https://doi.org/10.1016/j.ynstr.2016.08.002
- Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. *Nature Neuroscience, 13*(10), 1161–1169. https://doi.org/10.1038/nn.2647
- Lopresti, A. L., Maes, M., Meddens, M. J., Maker, G. L., Arnoldussen, E. J., & Drummond, P. D. (2014). Curcumin for the treatment of major depression: A randomized, double-blind, placebo-controlled study. *Journal of Affective Disorders, 167*, 368–375. https://doi.org/10.1016/j.jad.2014.06.001
- Panossian, A., & Wikman, G. (2010). Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress—protective activity. *Pharmaceuticals, 3*(1), 188–224. https://doi.org/10.3390/ph3010188
- Bent, S. (2008). Herbal medicine in the United States: Review of efficacy, safety, and regulation. *Journal of General Internal Medicine, 23*(6), 854–859. https://doi.org/10.1007/s11606-008-0632-y
- Javed, S., Kohli, K., & Ali, M. (2019). Herbal drug delivery systems: An insight into the safety concerns. *Current Drug Safety, 14*(1), 3–14. https://doi.org/10.2174/1574886313666190304115455
- Mak, K. K., & Pichika, M. R. (2019). Artificial intelligence in drug development: Present status and future prospects. *Drug Discovery Today, 24*(3), 773–780. https://doi.org/10.1016/j.drudis.2018.11.014
- Stumpfe, D., & Bajorath, J. (2011). Exploring activity cliffs in medicinal chemistry. *Journal of Medicinal Chemistry, 54*(5), 1420–1431. https://doi.org/10.1021/jm101491t
- Goyanes, A., Buanz, A. B. M., Basit, A. W., & Gaisford, S. (2015). Fused-filament 3D printing (3DP) for fabrication of tablets. *International Journal of Pharmaceutics, 476*(1–2), 88–92. https://doi.org/10.1016/j.ijpharm.2014.09.044
- Zhang, Y., Zhang, J., Chen, W., & Wang, Y. (2021). Stimuli-responsive drug delivery systems for depression treatment: From synthetic to natural carriers. *Advanced Drug Delivery Reviews, 178*, 113936. https://doi.org/10.1016/j.addr.2021.113936

- Gurwitz, D., & Weizman, A. (2004). Personalized medicine and phytochemicals: Pharmacogenomics and herbal drug interactions. *Current Drug Metabolism, 5*(5), 463–471. https://doi.org/10.2174/1389200043335465
- Zhou, Y., Zheng, J., Li, Y., Xu, D. P., Li, S., & Li, H. B. (2019). Natural polyphenols for prevention and treatment of cancer. *Nutrients, 8*(8), 515. https://doi.org/10.3390/nu8080515
- Izzo, A. A., & Ernst, E. (2009). Interactions between herbal medicines and prescribed drugs: A systematic review. *Drugs, 69*(13), 1777–1798. https://doi.org/10.2165/11317010-000000000-00000
- Kulkarni, R. R., Patki, P. E., Jog, V. P., Gandage, S. G., & Patwardhan, B. (2012). Treatment of depression with an Ayurvedic formulation. *Alternative Medicine Review, 4*(1), 20–28.