Open Access

Review

Precis. Nanomed. 2022, 6(2):1023-1047

The Application of Nanotechnology and Nanomaterials in Depression: An Updated Review

Khushbu Yadav[1], Anjna Rani[1*], Pankaj Tyagi[2], Malakapogu Ravindra Babu[3]

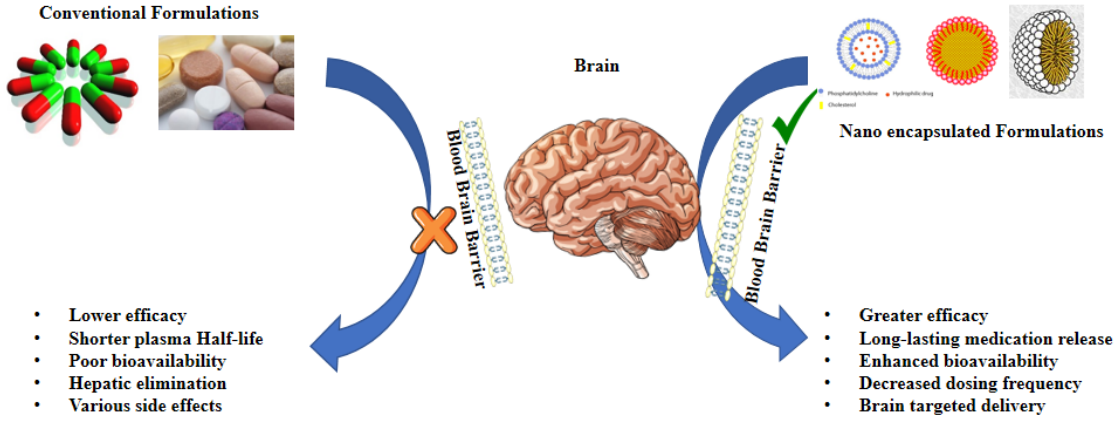
[1]*Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, UP – 201306*

[2]*Noida Institute of Engineering and Technology, Greater Noida, UP – 201306*

[3]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab*

Submitted: May 5, 2023 Accepted: June 23, 2023 Published: June 28, 2023

Graphical Abstract:



Abstract:

Depression is the most common stress-related mental illness. It has an impact on millions of individuals globally. Genetic, biochemical, environmental, and psychological elements can all play a role in its development. Medications, psychotherapy, and lifestyle changes are frequently used to treat depression. Antidepressant medications work by altering the levels of certain chemicals in the brain. At the same time, psychotherapy aims to help individuals better understand and manage their emotions and thoughts, which otherwise may lead to depression. The current treatment strategy for the illness has several drawbacks, such as adverse effects, ineffectiveness, long-term use, stigma, and cost-related issues of the medication used. These negative effects underscore the need for more successful and novel methods of treating depression, such as the investigation of medication delivery techniques based on nanotechnology. Increased medication effectiveness, fewer side effects, long-lasting medication effects, a good understanding of the neural underpinnings of depression, and the potential for the creation of personalized medicines are some of the potential benefits of using nanotechnology in depressive disorder treatment. In several scientific domains, nanotechnology has many benefits. Nanoparticles are the fundamental building blocks of nanotechnology in this regard. Nanoparticles hold great promise for use in medical applications, as recently developed nanotechnology has shown. This review focuses on the most popular nanomaterials that are used to treat depression, in addition to how well these nanomaterials are at managing depression based on their physical, chemical, and biological properties. We have also talked about the difficulties that the various nanomaterials face, which limit their uses and prevent the development of effective clinical therapies.

Keywords: antidepressant, depression, nanomaterial, nanotechnology, therapy for depression

* Corresponding author. Email: anjna.sharma89@gmail.com

Purpose, Rationale, and Limitations

This review aims to summarize the state-of-the-art progress in using nanomaterials as drug delivery systems for depression management, focusing on their physical, chemical, and biological properties and the difficulties faced by nanomaterials limiting their use, and the development of new clinical approaches.

Introduction: Depression is a psychiatric or mental disorder characterized by signs such as sadness, hopelessness, or guilt, a lack of interest or energy, changes in eating or sleep patterns, or other irregularities in behavior. [1] All over the world, depression impacts more than 264 million individuals, and 850,000 people die every year as a result, based on the World Health Organization (WHO) 2020. [2]

Several clinically recognized conditions have been named after depression due to their close association with depressive symptoms. One such condition is "Dysthymia," which is characterized by a persistent depressive disorder lasting for at least two years. People with dysthymia often experience low mood, lack of energy, sleep disturbances, and hopelessness. Another condition is "Seasonal Affective Disorder (SAD)," which typically occurs in winter with less natural sunlight. SAD is characterized by recurring depressive episodes, increased sleep, weight gain, and a carbohydrate craving. "Postpartum Depression" is another well-known condition that affects women after giving birth. It is characterized by sadness, extreme fatigue, and difficulty bonding with the newborn. These conditions named after depression highlight the diverse ways in which depression can manifest and emphasize the importance of accurate diagnosis and appropriate treatment.[3]

Predisposing factors like genetics and biological and environmental factors cause depression. [4] Neurotransmitters are brain chemicals typically out of balance and contribute to depression. Serotonin, Norepinephrine, and Dopamine are the three primary neurotransmitters at play.[5] A loss in energy metabolism, and a change in body hormones, are some of the pathological causes of depression. [6] There are various classes of antidepressant medication available today, including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin, and noradrenaline reuptake inhibitors, which are included in pharmacological therapy for depression. [7] Recognizing the heterogeneity of depression is crucial for providing personalized and effective treatment approaches.

Tailoring interventions to address the specific symptoms, subtypes, and underlying causes of depression can significantly improve outcomes and help individuals on their path to recovery. [8] The disadvantages of conventional formulations used to treat depression include limited penetration, frequent dosing, toxicity, patient compliance issues, and brain barriers that make it difficult for antidepressant medications to penetrate the brain using standard formulations. By lowering the amount and frequency of dosing, enhancing the efficacy, and demonstrating that it is a secure and efficient technique for treating depression, nano-based formulations are becoming increasingly popular to get around the limits of conventional formulations.

Nano formulations offer a system with high penetration capability, targeted transmissions, and better safety and efficiency, which holds great promise for managing depression. These medications' nano-forms have special properties, including a high surface-to-mass ratio and quantum-size effects like electron confinement with absorption and the capacity to transport drugs. These characteristics are essential for solving the problem of limited therapeutic absorption related to using phytochemicals as medicines and newer chemical entities.[9] Several nanoformulations, including ethosomes, nanocapsules, dendrimers, silver and gold nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and liposomes. [10] Nano therapy use systems with dimensions between 10 to 100 nm and special chemical and physiological characteristics. Nano preparations stand out due to their flexibility, plasticity, and changeable surface qualities. Nanotherapeutics offer focused central nervous system (CNS) active drug delivery to the brain, crucial for medications intended to treat mental disease. [11,12]

In this review, we address various drug carriers, ligands, and biopolymers that can enhance the therapeutic efficiency and bioavailability of antidepressants by lowering unfavorable side effects and dose frequency to reach safe, desirable clinical benefits. The literature survey was done using an electronic database such as Google Scholar, Science Direct, and PubMed

based on the keywords of depression, nanomaterials, and therapy for depression, novel drug delivery systems, and clinical studies related to depression. Studies reported until 2023 focusing on depression were included to obtain factual findings, highlighting the role of various drug delivery systems for managing depression, and clinical studies related to the same were included in the study.

Routes of administration of antidepressants:

Oral route

Because of its benefits, including painlessness, ease of self-administration, good patient compliance, and viability for outpatients, oral delivery is the most often used drug administration route among the several delivery paths. The enzymatic and chemical barrier nevertheless hinders the efficiency of oral medication administration in the gastrointestinal (GI) tract. [13] Researchers are focusing on improving medication delivery to improve the effectiveness of antidepressants. Antidepressant sustained-release formulations are an example of advances in oral drug administration because they have softened the plasma drug concentrations maxima and minima, reduced adverse effects, and boosted tolerance. [14]

The blood-brain barrier is a complicated physiological barrier that prevents harmful chemicals from entering the brain. Biopolymers can be used to increase medication permeability via the blood-brain barrier and increase neural availability. The desirable properties of biopolymers, such as sustained drug release patterns, size, durability, biodegradability, biocompatibility, and reduced toxicity, make them promising techniques for the oral delivery of antidepressants. [15] The study's primary goal was to increase venlafaxine's oral bioavailability because it is soluble easily in water, travels through first-pass metabolism, has a small window for absorption, and has a brief half-life. Unique mucoadhesive multiarticulate drug delivery systems loaded with venlafaxine increase oral bioavailability and enhance pharmacodynamic efficacy. [16] Serotonin and norepinephrine reuptake are both potently inhibited by duloxetine, while dopamine reuptake is inhibited less potently.

For the management of depressive disorders, Sindhu et al. attempted to incorporate duloxetine into an o/w microemulsion for oral administration. The findings demonstrated that the produced oral microemulsion was likewise more efficient than the oral drug suspension or vehicle, which may be inferred as directly correlated with a more efficient brain drug transport, resulting in greater serotonin levels and, as a result, antidepressant effect. [17] One well-known antidepressant, paroxetine, has the drawback of limited oral bioavailability due to significant hepatic first-pass metabolism. This study developed a paroxetine-loaded self-Nano emulsifying drug delivery system to improve oral bioavailability. By reducing serotonin and norepinephrine depletion and improving behavioral activities, paroxetine SNEDDS administered orally for depression was better than drug suspension. [18]

Intranasal Route

Antidepressants administered by the intranasal route are an appealing and ensuring method for treating mental illnesses because it is non-invasive, provides a quick onset of action and enhanced medicine bioavailability, enable drug dosage reduction, and provide a way to bypass the blood-brain barrier to some extent and minimize systemic adverse reactions.[19] These benefits are related to the special anatomy of the nasal cavity, which directly connects to the CNS and enables the medicine to be delivered to the brain. [20] A study was conducted in which intranasal administration of desvenlafaxine-loaded PLGA-chitosan nanoparticles (172 nm/+35 mV) significantly decreased depressive symptoms and increased the concentration of monoamines in the brain compared to desvenlafaxine taken orally. Desvenlafaxine PLGA-chitosan nanoparticles delivered via the nose to the brain had improved brain/blood ratios and pharmacokinetics profiles at various points in time.[21]

Another study was to create paroxetine nanoemulsions for intranasal administration of paroxetine to the brain to treat depression. Intranasal administration of paroxetine nanoemulsion dramatically enhanced the behavioral activities of depressed rats as compared to paroxetine suspension (orally administered). [22] A non-invasive, secure, and effective treatment method is drug delivery by intranasal. Another study examined the improvement in

duloxetine-containing nanostructured lipid carrier (NLC) absorption in the brain following intranasal delivery. Drug targeting potential, drug targeting efficiency, and biodistribution studies of duloxetine-loaded nanostructured lipid carriers (DLX-NLC) were assessed pharmaco-scintigraphically in various organs, including the brain. When compared to intravenous injection of the duloxetine solution, the intranasal treatment showed an approximately 8 times greater concentration of duloxetine in the brain. Using intranasal NLC containing DLX as a depressive disorder therapy strategy is beneficial. [23]

Parenteral Route

The parenteral route of drug delivery has desirable properties such as avoiding hepatic first-pass metabolism, increased bioavailability, and consistent dosages, which increase the effectiveness of antidepressants. [24]

For instance, chitosan nanoparticles containing sertraline have been developed and explored as a potential treatment for depression. Sertraline nanoparticles were injected intravenously into a rabbit through the vein on the border of the ear. Sertraline nanoparticles had better half-lives and entrapment rates. Due to the chitosan's mucoadhesive qualities, the loaded nanoparticles' plasma bioavailability increased when compared to pure medication. The result indicated that sertraline's circulation time was enhanced by chitosan-loaded nanoparticles, which also improved sertraline's plasma bioavailability. [25] To manage depression, L-tyrosine-loaded nanoparticles have also been produced, described, and given to rat models. The loaded nanoparticles' size was determined to be ±141.8 nm, and their entrapment efficiency was 87.45%. L tyrosine-loaded nanoparticles had a sustained release profile of ±86.65% over 48 hours in vitro tests. The study demonstrated the nanoparticles' safety and increased therapeutic efficacy by ±86.65%. The results showed that the effectiveness of L-tyrosine-loaded nanoparticles administered parenterally is improved. [26]

Implantation

Some recent developments in implant technology focus on mood regulation. One of these is implantable neurostimulation technology, which can alter electrical nerve activity and be applied to treat severe depression.

Another technique uses input-output interactions or brain-computer interfaces (BCI), which, in conjunction with neurofeedback, may enable user/computer interface using electrical impulses. In the future, these techniques might be applied to treating depression. These kinds of advances look likely in the short to medium term, albeit being in their early stages. Using "a closed-loop brain-machine interface," for instance, neurobiologists led by Miguel Nocolesis announced success in teaching rhesus monkeys to consciously manipulate a robot arm in October 2003. [27]

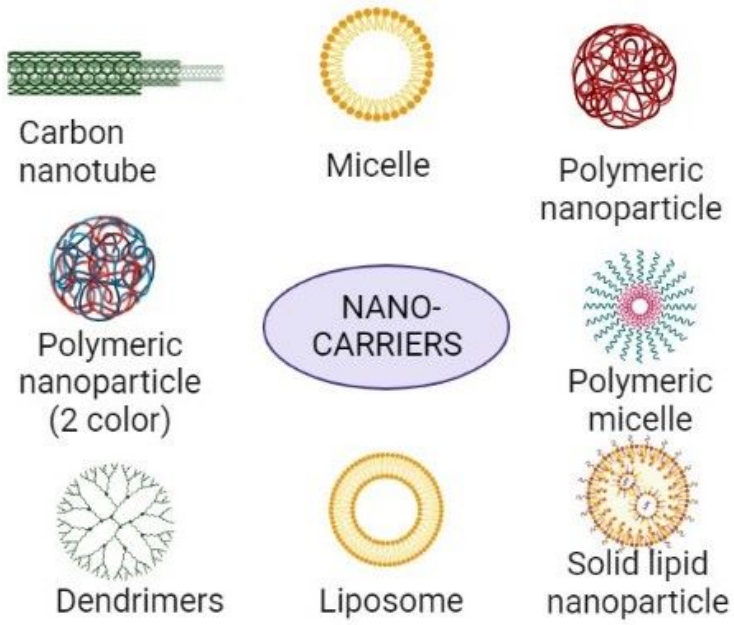


Fig. 1 Various types of nanoparticles

Nanomaterials used as delivery platforms for antidepressants

There has been a rising demand for the creation of nanocarriers with a variety of features that target various diseases. Nanocarriers have superior efficacy, reduced adverse effects, and better stability than conventional drug dosage forms because of their microscopic size, enormous surface area, and practicable target ability. [28] Recently created nanomaterials called nanozymes have enzyme-like functions. Comparing nanozymes to natural enzymes reveals they are more structurally stable, less expensive, more functionally diverse, more catalytically efficient, recyclable, and practical for large-scale manufacture. [29] The many kinds of nanomaterials employed to treat neurodegenerative illnesses are depicted in Figure 1.

Polymeric nanoparticles

Polymeric nanoparticles can take the form of nanospheres or nanocapsules and are made up of a mixture of biocompatible, non-toxic, and biodegradable polymers that can be synthetic, natural-based, and hybrid polymeric nanoparticle systems are the most often used polymeric nanoparticle platforms that have been used for brain targeting. The most commonly used polymers for manufacturing nanoparticles that are polymeric include chitosan, albumin, gelatin, and alginate, which are all-natural polymers. Synthetic polymers like polylactide and poly (lactic-co-glycolic acid) (PLGA) are also frequently employed.[30,31] The U.S. Food and Drug Administration (FDA) has recognized PLGA/PLA nanoparticles for use in human medications, biodegradable scaffolds, and implantation. [32]

There are two main forms of polymeric nanoparticles: Nanocapsules and nanospheres. The vesicular form of Nanocapsules makes them useful as drug reservoirs. In an aqueous or nonaqueous liquid core that is placed in the vacuole cavity and covered by the hardened polymeric shell, the retained active pharmaceutical ingredients are kept. Nanospheres are solids or masses of matrix polymers. In other words, any nanosphere can be represented as a total polymeric spherical mass in which drug molecules may be entrapped at the mass's surface or adsorbed at the sphere's center. [33] Polymeric nanoparticles pass through the blood-brain barrier (BBB) via endocytosis. They can also prevent the reticular endothelial system from being phagocytized, increasing the amount of drug concentration in the brain. [34] In one investigation into the antidepressant effects of L-tyrosine-loaded polymeric nanoparticles, improved treatment effectiveness and drug safety were noted. [26] Gallic acid has been claimed to have antidepressant-like properties. This effect may be linked to the CNS effects of enhanced catalase activity, decreased glutathione levels, and reduced malonaldehyde levels in the brain. [35] A study with chitosan:tripolyphosphate=1:1.5 ratio showed that the optimized escitalopram-loaded nanoparticles displayed a particle size range of 60 - 115 nm with a polydispersity index of 0.117, which TEM further validated. The zeta potential was determined to be −1.89 mV. The same's virtually smooth shape was visible in the SEM EDX scans. According to the FT-IR data, there is no contact between the medication molecules and the polymers. The sustained drug release pattern of ETP nanoparticles was demonstrated in an in vitro drug release research utilizing a dialysis membrane. [36]

Dendrimers

Monodisperse, dendrimers are symmetric macromolecules with an inner core surrounded by a succession of equally branching units. The number of arms (and surface groups) exponentially grows with each generation, i.e., proportionally to the reactive groups on the surface.[37] Dendrimers have piqued the interest of many researchers as potential drug carriers for several neurological disorders because of their desirable properties, including an extended half-life, rapid cellular entry, a large amount of drugs capability, better delivery effectiveness, biocompatibility, aimed capability, strength, and decreased adverse reactions.[38] treating disorders of the CNS continues to be challenging for researchers. The BBB inhibits the brain's movement and interferes with the efficacy of certain pharmacological therapies. Promising solutions to this problem have been provided by rapid advances in nanotechnology. As a result, numerous nanocarriers have been developed during the past few decades to deliver medications to the brain. Highly branching, three-dimensional macromolecules known as dendrimers are an intriguing drug delivery system because of their interior voids and custom-designed surface activity. [39] A fresh approach to medication deliv-

ery by adding venlafaxine-based dendrimer carriers to hydrogels. The drug release rate is often influenced by the amount of drug trapped in a hydrogel. More drug loading increases burst, which causes a quicker release rate.[40]

Solid-lipid nanoparticles

The early 1990s saw the development of solid lipid nanoparticles (SLNs). Due to their many benefits, this delivery system was created to replace earlier carrier systems like liposomes, emulsions, and polymeric nanoparticles.

Having a size range of 1–1000 nm, SLNs are solid, submicron colloid nanocarriers. The majority of the particles are between 150 and 300 nm. The matrix for controlled release provided by these drug delivery methods is similar to that of polymeric nanoparticles.[41] Furthermore, SLNs have controlled release features and are non-toxic, simple to make, and biodegradable. SLNs can potentially enhance the efficacy of antidepressant medication administration because of their appealing qualities. Improved stability, increased bioavailability, increased epithelial permeability, extended half-life, increased permeability through the BBB, and decreased toxicity are all characteristics of SLNs.[42-43] SLN innovation (e.g., drug incorporation), potential drug-lipid interactions, and targeting approaches for managing various illnesses treated with hesperidin.[44] Antidepressant administration with SLNs has received a lot of research.

The bioavailability of medications used to treat CNS diseases can be improved with the help of SLNs. The antidepressant activity of Hibiscus rosa sinensis Linn. Plants are exhibited by normalizing neurotransmitters serotonin, dopamine, and norepinephrine in the brain. The current study demonstrated that loading hibiscus extract into SLNs successfully enhanced the pharmacological effects.[45] By administering a single, much smaller dose (10 times) of curcumin-loaded SLNs, which have greater bioavailability and permeability, an antidepressant's potential is greatly increased.[46]

Sertraline is one example of an antidepressant medicine whose poor oral bioavailability relates to weakly water-soluble medicines that may be successfully delivered using SLNs. The improved SLN formulation showed the greatest zeta potential value (−36.5 mV), providing nanodispersion stability. Compared to pure medication, sertraline-loaded SLN showed a 10-fold greater maximum plasma concentration and a 6-fold higher area under the curve. [47]

Nanogels

Cross-linked polymeric nanoparticles with a 100 to 200 nm diameter make up the promising drug delivery technology known as nano-gels (NGs). With quick advancements occurring every day, NGs represent an innovative area of research. Due to their tiny size, simplicity in formulation, enhanced retention period, and swelling qualities, NGs that are thought to be more appropriate for optimal delivery at the target site were created.[48] After swelling up in the water, nano gels can transport oligonucleotides, DNA, proteins, low-molecular-weight medicines, and other tiny molecules. In vivo crossing of the BBB by cross-linked nano gels containing oligonucleotides was investigated by Vinogradove et al. [49] When given orally, the formulation hinders the liver's first-pass metabolism, which causes venlafaxine to act more slowly. This issue is resolved when the formulation is loaded onto nano gels, which allows the medicine to act more quickly.

Alginate nano gels filled with venlafaxine were created by Hague et al. for intranasal delivery. The electrostatic interactions between the positive charge formulation and the negatively charged cell membranes provide the nano gel's adhesion and transport capabilities, which are facilitated by the positive zeta potential. The nano gel released 86% of the medication in vitro over 24 hours, showing a controlled drug release process. Ex vivo studies on isolated porcine nasal mucosa revealed enhanced drug permeation. The interaction between an amino group on the positively charged alginate and a sialic acid residue on the cell membranes and tight junctions of the mucosal epithelial cells, which are negatively charged, is thought to be responsible for mucosal absorption. [50]

Compared to previous nanocarrier systems, the nano gels have some advantages, including less untimely drug leakage, the ability to encapsulate multiple therapeutic compounds in a single formulation, and simple delivery through parental or mucosal routes. Biosensors, biochemical separation, cell culture, bio-catalysis, administration of drugs, and other uses for nano gels are just a few. Among the most extensively researched uses of nanogels include the administration of medicines such as nucleic acids, vaccinations, cytokines, and nasal vaccines. [51]

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) offer a special set of properties that have shown significant promise in various biomedical engineering applications, including bioseparation, contrast enhancement for magnetic resonance imaging, and intracellular drug delivery.[52] The appealing qualities of MNPs, such as their magnetic properties, biocompatibility, low toxicity, and easily changing surfaces, have sparked interest in drug delivery studies.[53] A family of non-invasive imaging agents called magnetic nanoparticles (MNPs) has been created for magnetic resonance imaging. Historically, these magnetic nanoparticles were employed for passive targeting for disease imaging, but more developments in recent years have made it possible to use these nanoparticles for cellular-specific targeting, delivery of drugs, and multi-modal imaging.[54] While some formulations have already achieved clinical approval for usage in therapeutic and medical imaging applications, several MNPs are currently undergoing preliminary clinical investigations.[55] Excitingly, employing magnetic nanoparticles to increase the therapeutic effect may be a novel approach. According to research by Kong et al., magnetic nanoparticles could cross the BBB in mice. Moreover, Li et al. administered magnetic nanoparticles containing a Fe3O4 core intravenously to rats, which can improve the therapeutic impact of transcranial magnetic stimulation. The depression symptoms of the CUMS mice treated with repetitive transcranial magnetic stimulation at 10 Hz/0.1 T for 5 days were dramatically reduced when our research team created a unique superparamagnetic Fe2O3 nanoparticle and precisely injected it into the left prelimbic cortex.[56]

Carbon nanotubes:

With a diameter of 1 nm and a length of 1–100 nm, carbon-based tubular structures are known as carbon nanotubes. Graphene, a single sheet of graphite, can be formed into a seamless cylinder to create these structures. The three different varieties of carbon nanotubes are C60 fullerenes, single-walled nanotubes, and multi-walled nanotubes.[51] Carbon nanotubes are considered promising quasi-one-dimensional nano reinforces due to their low density, high aspect ratio, and extraordinarily strong mechanical properties.[57]

Liposomes

Since their 1965 discovery, liposomes have developed a solid reputation as a medication delivery mechanism. They are renowned for their advantages in biology and technology, biocompatibility, biodegradability, controlled drug release, reduced toxicity, and their capacity to be created in various chemical compositions and sizes.[58]

Liposomes are amphiphilic nanovesicles or microscopic lamellae drug delivery systems having a spherical form. Small unilamellar vesicles, Large unilamellar vesicles, and Multilayer Vesicles are the three different types of liposomes based on size and the presence of a bilayer (Multi lamellae vesicles). Small unilamellar vesicles are 20 to 25 nm and contain a single lipid. Huge unilamellar vesicles feature a single lipid layer with a bigger size >100 nm. Several lipid layers are separated by an aqueous layer in multilamellar vesicles. Liposomes are frequently used to transport drugs to the brain. Liposomes have improved the pharmacokinetic characteristics of medications for quick metabolism and chemotherapeutic treatments and have decreased side effects. They have also increased drug stability and solubility. [59] The stability of vortioxetine hydrobromide was also improved by the liposomal formulation. Using the tail suspension test on mice, the antidepressant-like effect was present for VXT-Ls at doses ranging from 2.5 mg/kg to 10 mg/kg. [60] Overview of nanocarriers being employed for the various delivery techniques listed in Table 1.

Characterization of Nanocarriers: Difficulties and Limitations

For researchers and regulatory organizations, drug-loaded nanocarriers present a variety of difficulties (Figure 2). Robust characterization techniques, scalable optimization methodologies, safety regulations, and stability upkeep are required to address these issues. [28]

Table 1: Overview of Nanocarrier's Applications Using Various Delivery Methods

Nanocarrier	Drug	Route	Outcomes	Challenges	Refs.
Solid lipid nanoparticle	Agomelatine	Intranasal	Effectively improve the delivery to the brain as well as the total bioavailability	The retention and absorption of medications are influenced by the length, surface areas, volumes, histology, and geometry of the nasal cavity and anatomical differences between human and animal nasal canals, which are species-dependent.	61-62
Thiolated chitosan nanoparticle	Selegiline hydrochloride	Nasal route	For managing depression, strong mucoadhesion, great permeation enhancement, in situ gelling nature, and nasal-to-brain administration are all important factors.	It is extremely challenging to encourage effective drug administration through the nasal valve because of the complicated geometry of the nasal cavity.	63-64
Liposomes	Paroxetine	Transdermal	Good bioavailability, acceptable plasma blood levels, and a controlled pace, ideally without any unwanted side effects, while also enhancing patient compliance	The main drawback of the topical application of liposomes is that liposomes may leak from the application location. The solution to this problem is to incorporate the vesicles into an appropriate vehicle that maintains the vesicle's original shape while modifying its rheological and/or mucoadhesive qualities.	65
Liposomes	Venlafaxine	Transdermal	Increased entrapment efficacy, self-penetration enhancing capacity.	The immune system's involvement with liposome components has made translating research into clinical usage challenging. The clinical translation of several liposomal-based medicines may be hampered by quality control and cost-benefit analyses, even at this early stage.	66-67
Polymeric nanoparticle	Agomelatine	Intranasal	It improves drug bioavailability, increases permeability, and increases retention time	The primary causes of using intranasal formulations have been identified as the wrong extrapolation of the dose from animals to humans and the nasal anatomical changes between animal species.	68-69
Solid lipid nanoparticle	Duloxetine	Oral	Increased BDNF (Brain-derived neurotrophic factor) levels in plasma and brain	The issue in certain created SLNs, the strong initial release and the low encapsulation, and the loading capacity efficiency should be addressed.	70-71

Lipid nanoparticle	Fluoxetine hydrochloride	Nasal	Sustained drug release, longer-lasting, and more potent antidepressant action.	The nasal route has become the predominant method of medication administration, although there are still challenges with nasal aerodynamics, anatomy, and physiology.	72-73
Polymeric nanoparticle	Agomelatine	Transdermal	Improved formulation's particle size, polydispersity index, zeta potential, and percentage of efficiency of entrapment were found to be 104.5 3.98 nm, 0.135 0.02 mV, (-) 13.3 0.48 mV, and 83.6 4.12%, respectively.		74
Chitosan nanoparticle	Venlafaxine	Intranasal	When administered intranasally, mucoadhesive venlafaxine-loaded chitosan nanoparticles improved venlafaxine uptake in the brain.	There are many ways to make chitosan nanoparticles. Still, formulators need to modify the methods to fit the particular drug's physicochemical characteristics, carefully considering chemistry, molecular weight, and the degree of acetylation of the chosen chitosan. Chitosan has so far shown little to no toxicity in studies on animals, and there haven't been any reports of serious adverse effects in healthy human volunteers, but there is no clinical data.	75-76
Solid lipid nanoparticle (SLN)	Thymoquinone	Oral	Suspension demonstrated antidepressant-like activity	Before SLNs are authorized for clinical use, several obstacles must be addressed, including standardizing the synthetic techniques, improving the sterilization procedure, scaling up the production processes, and solving present stability problems.	77-78
Polymeric nanoparticle	Fluoxetine hydrochloride	Oral mucosal (buccal)	Extended-release rate, avoids the first-pass effect, effective and reduced side effect	The creation of the polymeric delivery system might be challenging because of the difficulties of biocompatibility and biodegradable properties. It may also be toxic.	79-80
Liposomes	Sertraline	Transdermal	Increased mouse striving behavior	After decades of investigation, the protective role of the stratum corneum continues to be	81

			and reduced immobility time result in improved antidepressant action.	an issue, resulting in the creation of new transdermal drug delivery systems, a challenging task.	
Eudragit-chitosan	Duloxetine	Oral	After oral administration, the duloxetine-loaded eudragit-chitosan nanosystem can improve duloxetine bio- and neuro-availability.	–	82
Carbon nanotubes (CNTs)	Vortioxetine hydrobromide		The method's sensitivity comes from the controlled interfacial adsorption of Vortioxetine hydrobromide and the positive interaction with carbon nanotube sites.	Particular challenges restrict the use of CNTs. Challenges to using CNTs in nanomedicine include the presence of contaminants, non-uniformity in morphology and structure, large surface area (which promotes protein opsonization), hydrophobicity, insolubility, and CNTs' propensity to bundle.	83-84
Carbon nanotubes	Amitriptyline		Sulfuric acid enhances amitriptyline electrooxidation by producing radical cations and one-electron oxidation of the alkylamine nitrogen atoms.	The toxicity of CNTs is a significant challenge. The structural resemblance between CNTs and asbestos fibers has been substantially implicated in the reported toxicity. Therefore, the toxicological assessment of CNTs has drawn much interest in recent years.	85-84
Nanostructured lipid carrier	Thymoquinone	Nasal route	Using a thymoquinone-enriched naringenin-nanolipid carrier to treat depression improved brain delivery and therapeutic effects of the drug.	Preclinical NLC-based preparations may not work well in the clinical stage for a variety of reasons. First, there are anatomical differences between human and animal nasal canals. Second, the amounts of IN administrations vary depending on the species.	86-62
Chitosan nanoparticle	Tramadol hydrochloride	Intranasal	Antidepressant-like effects in a rat depression model.	Shorter residence period and mucociliary clearance.	87
Nanostructured lipid carrier	Silymarin	Oral	Similar to fluoxetine in mice, but 12.46 times better than silymarin for higher brain concentrations.	Traditional in vitro nanotoxicology is ineffective for the human body. Also, it compromises the normal function of organs caused by increased penetration and mobility.	88-89

Niosomes	Sertraline hydrochloride	Transdermal	The sertraline HCl noisome demonstrated potential for transdermal delivery by producing a slow and prolonged release of sertraline HCl via mouse skin.	One of the biggest problems with transdermal medication delivery is inter-subject variability in response. The fact that mouse skin has a thin layer and different characteristics from human skin makes the fact that animal models are not always attractive more clearly. Therefore, it is imperative to provide evaluation techniques for the same.	90-91

Therapies for depression

Drug delivery therapy

It's crucial for medicine to keep its bioavailability, pharmacodynamics, and pharmacokinetics to have the most therapeutic effect possible. As a result, drug incorporation into or onto polymeric and/or lipid nanoparticles dramatically enhances the medication's pharmacologic action. The use of nanoparticles (NPs) in the drug delivery process is advantageous because it increases a drug's bioavailability by increasing its aqueous solubility and prolonging its half-life, which lowers the rate of drug clearance and delivers the medication to its intended action site.[92-93] There are many antidepressant medications on the market that treat depression, including SSRIs, MAO inhibitors, and TCAs.[94] Some clinical trials for drug delivery therapy are included in Table 2.

Music therapy

The depressive disorders treatment using music therapy is effective. Compared to other psychological approaches, it permits the development of numerous types of interpersonal communication, opening up various emotional expression outlets and promoting therapeutic relationships. There is little research on client-therapist musical interaction, particularly in treating depression, although many studies have examined client and/or therapist musical characteristics.[95] A review of current research on music therapy and substance abuse treatment guided an experimental receptive music therapy study that looked at correlations between music taste and diagnoses among children and teens receiving substance abuse treatment and found that music helped them feel relaxed, escape reality, and lift their mood.

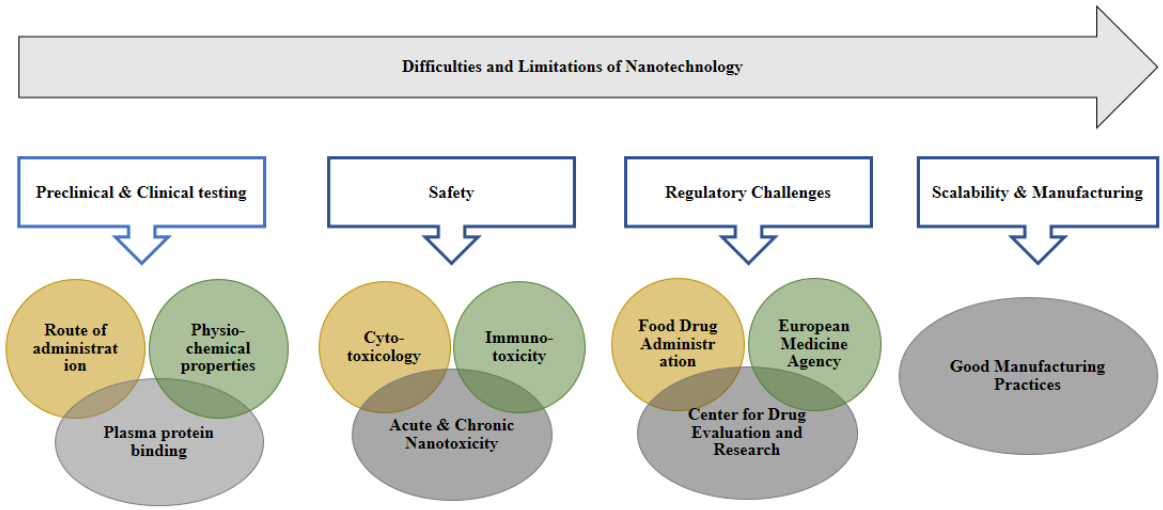


Fig. 2 Limitations of nanotechnology applications.

Table 2: Clinical Trials of Drug Delivery for Depression

Status	Study Title	Actual Enrollment and Treatment	Conditions	References
Completed May 23, 2018	Pharmacogenetics-informed tricyclic antidepressant dosing (PITA)	125 participants randomized controlled clinical trial.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT03548675?term=imipramine&cond=depression&draw=3&rank=13
Completed May 2013	A study of fluoxetine in major depressive disorder (MDD) long-term dosing	200 participants 20 to 40 mg administered orally, once daily, for approximately 52 weeks.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT01808651?term=fluoxetine&cond=depression&draw=2&rank=29
Completed by January 2014	Effects of bupropion on depression	80 participants participants get 150 mg of od for a week. After then, over the next five weeks, the dosage will be raised to 150 mg bd.	Depression	https://clinicaltrials.gov/ct2/show/NCT02104128?term=bupropion&cond=depression&draw=2&rank=1
Completed April 2010	Biomarkers of antidepressant treatment in adolescents with major depression (the adolescents MDD study)	26 participants One-week single-blind PBO-lead-in phase, fluoxetine (FLX) 10 mg/d for 4 days, then 20 mg/d of FLX after that.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT01185977?term=fluoxetine&cond=depression&draw=2&rank=42
Completed May 30, 2018	Assessing symptomatic clinical episodes in depression	97 participants took bupropion twice a day for six weeks.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT03595579?term=bupropion&cond=depression&draw=2&rank=24

According to studies on active music therapy, activities like drumming, improvising, performing to music, and playing musical games might reduce depression symptoms by increasing relaxation, comfort, and healthy physiological changes.[96] Some clinical trials of music therapy mention in Table 3.

Family therapy:

Family-based therapies for adolescent depression are promising. In contrast, family strengths, including cohesiveness, warmth, psychological support, and family monitoring and availability, all work as protective factors in reducing depression.[97] Family environment significantly influences childhood depression, and family therapy can be helpful in treating and preventing depression in young people.[98] Table 4 lists a few clinical trials for family therapy.

Table 3: Clinical Trials of Music Therapy for Depression

Status	Study Title	Actual Enrollment and Treatment	Conditions	References
Completed March 2008	Receptive music therapy for the treatment of depression	203 participants Over a period of 5 to 15 weeks, the music is heard for 30 minutes in the morning and 30 minutes in the evening.	Depressions	https://clinicaltrials.gov/ct2/show/NCT0644527?term=music+therapy&cond=depression&draw=2&rank=3
Completed April 2016	Treating major depressive disorder with music and low-frequency rhythmic sensory stimulation	20 participants The stimulation comprises 30 minutes of daily stimulation using tracks of soothing music that have been particularly created and mixed with gamma frequency noises in the 30-70 Hz range.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT0685982?term=music+therapy&cond=depression&draw=5&rank=3
Completed January 11, 2021	Music as an intervention to improve hemodynamic tolerability of ketamine in depression	32 participants All 6 ketamine treatments will have music delivered through headphones, starting at the beginning of each infusion and lasting 55 minutes.	Depressive disorder, unipolar depression, depression, bipolar	https://clinicaltrials.gov/ct2/show/NCT0701866?term=music+therapy&cond=depression&draw=5&rank=3
Completed April 2014	Music therapy in obsessive-compulsive disorder	30 participants. Receptive music treatment in 12 sessions of 30 minutes each, under the direction of the treating psychiatrist.	Obsessive-compulsive disorder, anxiety, depression	https://clinicaltrials.gov/ct2/show/NCT0314195?term=music+therapy&cond=depression&draw=2&rank=9
Recruiting July18, 2018	Music Interactions for dementia and depression in elderly care	1000 participants The main goal of group music therapy (GMT) is to provide for each individual living with dementia's psychosocial requirements, which has been shown to reduce depressive symptoms.	Depression, dementia	https://clinicaltrials.gov/ct2/show/NCT0496675?term=music+therapy&cond=depression&draw=2&rank=1

Table 4: Clinical trials of family therapy for depression.

Status	Study Title	Actual Enrollment and Treatment	Conditions	References
Completed April 2009	Designing and testing a family therapy for adolescent depression	56 participants The cognitive-behavioral family treatment that will be created throughout this study will include 11 to 15 sessions.	Depression	https://clinicaltrials.gov/ct2/show/NCT00867919?term=family+therapy&cond=depression&draw=2&rank=2
Completed November 18, 2015	Technology-enhanced family treatment	65 participants 12 sessions of family-focused therapy plus using a mobile app that enhances the skill training taught in the sessions.	Mood disorders, bipolar disorder, major depression	https://clinicaltrials.gov/ct2/show/NCT03913013?term=family+therapy&cond=depression&draw=3&rank=19
Recruiting September 30, 2022	Family-centered treatment for depression in Hispanic youth	200 participants At three months and six months, MetroHealth research staff would follow up with all participants (parents) to assess improvements in parent mental health outcomes as well as satisfaction.	depression, family research, teen depression	https://clinicaltrials.gov/ct2/show/NCT05407051?term=family+therapy&cond=depression&draw=4&rank=23
Completed October 1, 2012	Brief multifamily psychoeducation for families of patients with chronic major depression	49 participants Family psychoeducational therapy every two weeks for six weeks in addition to treatment as usual administered by physicians.	Major depressive disorder (MDD)	https://clinicaltrials.gov/ct2/show/NCT01734291?term=family+therapy&cond=depression&draw=11&rank=34

Electroconvulsive therapy:

Electroconvulsive treatment (ECT), which was first created more than 80 years ago, is a crucial, evidence-based medical practice. Using brief general anesthesia, a muscle relaxant, and continuing oxygenation, this brain stimulation technique includes releasing an electrical charge to the brain to cause generalized seizure for about 30 seconds under controlled settings. Two or three times a week, 8–12 treatments are typically given during a course. Treatment-resistant mania, catatonia, and severe, occasionally life-threatening depression episodes in unipolar and bipolar illnesses can all be effectively treated with electroconvulsive therapy (ECT). These particular ECT indications have been approved by the National Institute for Health and Care Excellence in the UK.[99]

ECT enhances gamma-aminobutyric acid (GABA) levels in the brain and serotonergic functioning. The dexamethasone suppression test outcomes are normalized since the hypothalamic-pituitary-adrenal axis is also affected.[100] Treatment-resistant depression is the most frequent indication for ECT in Western industrialized countries, where it is administered to over 1.4 million patients annually.[99] Table 5 lists some ECT clinical trials.

Table 5: clinical trials of ECT for depression.

Status and Study Starts	Study Title	Enrollments and Treatments	Conditions	References
Completed June 2011	Neurorestorative effects of electroconvulsive therapy (ECT) in patients with severe late-life depression	110 participants; ECT was administered twice a week with a constant-current brief-pulse device.	Depression	http://cuts2.com/rXoJd
Recruiting October 29, 2018	Ketamine versus ECT in depression	240 participants For three to four weeks, participants underwent ECT therapy three times per week. If the individual responds, they will continue to receive ECT for the duration of the trial, at the treating physician's discretion and in accordance with best practice recommendations for frequency.	Depressive disorder, major, bipolar depression	http://cuts2.com/FXxhi
Completed January 2008	Randomized controlled trials of electroconvulsive therapy (ECT) in relapse prevention in depression	56 participants Unilateral brief pulse ECT weekly for the first 6 weeks and thereafter every 2 weeks for a total of one year.	Depressive disorder, major	http://cuts2.com/JvDQy
Completed August 2012	A study comparing magnetic seizure therapy (MCT) to electroconvulsive therapy (ECT) for depression in older adults	18 participants Brain stimulation by magnetic means versus electrical standard unilateral electroconvulsive therapy. Treatment will be administered 3 times a week.	Depression, major depressive episodes, bipolar disorder	http://cuts2.com/AhCjr
Completed April 2008	A randomized controlled trial for treatment-resistant depression in bipolar disorder	73 participants	Bipolar disorder	http://cuts2.com/NDkEO

Cognitive therapy:

The introduction of cognitive therapy, created by Aaron T. Beck during the past 40+ years, has been one of the key advancements in managing depression.[101] The basis of cognitive therapy is that cognition, or the process of learning new information and creating beliefs, is a major factor in mood and behavior. The writers review the fundamental theories of cognitive therapy before discussing how it can be used to treat depression. The typical length of treatment for cognitive therapy is 12 to 20 sessions. During the first few weeks of therapy, twice-weekly sessions may be planned, followed by weekly sessions. Those who are severely depressed, however, may require three or more sessions of therapy each week.[102] According to research, CT is occasionally better than other psychotherapies but is roughly equivalent to behavior treatments. There have been numerous randomized clinical trials of cognitive treatment for depression over the years.[103] In Table 6, a few cognitive therapy clinical trials are mentioned.

Table 6: Clinical trials of cognitive therapy for depression.

Status	Study Title	Enrollment and Treatments	Conditions	References
Completed October 2010	Mindfulness-based cognitive therapy (MBTC) for chronic depression	106 participants Following a first introduction session, an instructor leads eight weekly 2.5-hour group sessions for the MBCT program.	Chronic major depression	https://clinicaltrials.gov/ct2/show/NCT01065311?term=cognitive+therapy&cond=depression&draw=2&rank=5
Completed October 2016	Clinical and biological markers response to cognitive behavioral therapy for depression	41 participants 20 individual 60-minute appointments for 16 weeks.	Depression	https://clinicaltrials.gov/ct2/show/NCT02883257?term=cognitive+therapy&cond=depression&draw=2&rank=6
Completed September 2016	Efficacy of trial-based cognitive therapy and behavioral activation in the treatment of depression	76 participants Patients with MDD using antidepressants plus trial-based cognitive therapy.	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT02624102?term=cognitive+therapy&cond=depression&draw=3&rank=11
Completed August 10, 2018	Effectiveness of cognitive behavior therapy for a person with depression	148 participants One session per week. 6-8 sessions.	Depression	https://clinicaltrials.gov/ct2/show/NCT05724680?term=cognitive+therapy&cond=depression&draw=5&rank=38
Completed June 2013	Computer-assisted cognitive behavioral therapy for adolescent depression	216 participants	Depression	http://cuts2.com/DsZtU

Gene therapy:

Although gene therapy is a new technology, it has some proven effective therapies, such as for ophthalmologic disorders and muscular dystrophies. Regarding neurological illnesses, the complexity of the BBB and CNS makes it difficult to produce new medications, but gene therapy could get around these problems. Nonetheless, it continues to have CNS cell targeting and vector delivery issues. Now, aromatic L-amino acid decarboxylase (AADC) has been successfully treated using integrating (LV) and nonintegrating (AAV) vectors, giving us fantastic examples to modify the TPH2 gene in depressive patients. Later, the transposon system emerges as it is shown to have a greater capacity to transport therapeutic genes than viral vectors. RNA interference is another potential choice. One investigation suggests that siRNAs can be transmitted into the human brain by directly injecting lipopolymeric nanoparticle siRNAs into mouse brain tumors. This significantly slows the growth of tumors. On the other hand, a 5-HT breakdown can be inhibited by siRNAs that target the 5-HT uptake 2 transporters, serotonin transporter, or monoamine oxidase enzymes on the membranes of non-serotonergic neurons. These studies suggest that gene therapy for depressive disorder is a real possibility.[104] Some clinical trials of gene therapy are mentioned in Table 7.

Table 7: clinical trials of gene therapy for depression.

Status	Study Title	Actual Enrollment and Treatment	Conditions	References
Completed June 2015	Pharmacogenomics decision support with gene sight psychotropic to guide the treatment of a major depressive disorder	542 participants All participants' patient DNA will be obtained, and variations in both medication target genes and drug-metabolizing genes will be analyzed.	Depressive disorder major, depression	https://clinicaltrials.gov/ct2/show/NCT02466477?term=gene+therapy&cond=depression&draw=2&rank=7
Completed May 23, 2018	Pharmacogenetics-informed tricyclic antidepressant dosing (PITA)	125 participants All patients who meet the inclusion requirements will have their CYP2C19 and CYP2D6 gene genotypes determined. Patients will be assigned to one of four metabolization phenotypes (UM, EM, IM, or PM) based on the findings of the genetic test.	Depressive disorder- major	https://clinicaltrials.gov/ct2/show/NCT03548675?term=gene+therapy&cond=depression&draw=4&rank=22
Completed April 2014	Genomics used to improve depression decisions (GUIDED)	1398 participants Subjects being tested with GeneSight Psychotropic	Major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT02109939?term=gene+therapy&cond=depression&draw=5&rank=31

Completed July 2003	Serotonin transporter genetic variation and amygdalar activation correlate with antidepressant response	80 participants	Depression	https://clinicaltrials.gov/ct2/show/NCT00456430?term=gene+therapy&cond=depression&draw=8&rank=61
Completed February 2011	Pioglitazone and quetiapine XR pharmacogenetic study	42 participants Genetic markers in PPARG, 5-HT2A, CYP3A4, and CYP2C8 genes known to be related in the pharmacodynamics and pharmacokinetics of pioglitazone or quetiapine XR will be associated with treatment response.	Bipolar disorder, major depressive disorder	https://clinicaltrials.gov/ct2/show/NCT01342380?term=gene+therapy&cond=depression&draw=4&rank=62

Examples of other applications of nanotechnology:

Nanotechnology in other medical areas

Nanoparticles may be used in the medical field for therapeutic and diagnostic purposes.[108] Its ability to easily infiltrate human body cells due to its nanoscale size makes it favorable for several types of cell target therapy, such as efficient drug delivery to the target cell and accurate disease diagnosis. One further positive aspect discovered by studies is that nanoparticles can also shelter drugs from degradation due to their shield-like characteristics. The usage of nanoparticles in medicine spans many different types and forms.[109] The field of nano psychiatry focuses on using nanoparticles to develop medications, therapies, and diagnostic equipment for various neurological and mental conditions.[5] The herb Hypericum perforatum L., sometimes known as St. John's Wort, has been used for decades in traditional medicine, and it contains a naturally occurring red plant pigment called hypericin (HYP). In-depth biochemical studies conducted over the past three decades have demonstrated that HYP is a multifunctional drug with medicinal applications, including antidepressants and antineoplastics.[110]

Immunology

Nanotechnology takes advantage of the special qualities of small things that work together as a unit. To create new immunomodulatory drugs, materials with nanostructures, such as nanoparticles, nanoemulsions, or nanotubes, offers considerable potential because these nanostructures can be used to more efficiently control or distribute immunologically active components to target areas. New generations of vaccinations, adjuvants, and immunomodulatory medications will be possible with successful uses of nanotechnology in immunology.[105]

Food industry

Nanotechnology has become increasingly important in the food industry in the twenty-first decade. Nano and nano-bio sensors in food applications are being investigated to enhance food safety and identify pathogens. Nanotechnology is also employed in food packaging to increase the shelf life of produce and reduce bacterial counts.[106] Citrus essential oils have several qualities that are greatly valued in the food and agri-food industry and promote wellness. Citrus essential oils are widely used in the food sector, pharmaceuticals, and cosmetics due to their potent antioxidant, antifungal, antibacterial, insecticidal, anticancer, and antidepressant characteristics.[107]

Agriculture:

Nanodevices for plant genetic modification, diseases of plants diagnosis, treatment of animals, breeding animals, poultry production, and after-harvest care are some of the applications

of nanotechnology in agriculture. Nano formulations of agricultural chemicals are used to apply pesticides and fertilizers to enhance crops.[111]

Conclusion

In this review, we address various drug carriers, ligands, and biopolymers that can enhance the therapeutic efficiency and bioavailability of antidepressants by lowering unfavorable adverse effects and dose frequency to reach safe, desirable clinical benefits. Although more in vivo research is required to confirm the safety of the biopolymers and nanocarriers, in vitro and in vivo experiments using nanomedicines showed promising results in managing depression. Hence, the application of nanocontainer systems for the administration of antidepressants, antipsychotics, and medications for the management of neurodegenerative illnesses can help to enhance patient quality of life and contribute to more effective therapy. Several antidepressant medications with nanoformulations are now being tested in laboratories. According to research statistics, nanotechnology will soon be used frequently in psychiatry.

Different nanoparticle-based approaches have been used extensively for diagnosis, including polymeric micelles, liposomes, and inorganic nanoparticles with different organic or inorganic components. Although this method has improved imaging capabilities *in vitro*, *in vivo* targeted distribution still poses the biggest challenge for many nanoparticles. The development of stimuli-responsive delivery systems, which can change their modality only in response to certain biological and chemical alterations in the disease site's microenvironment, such as temperature, pH, enzyme levels, and oxygen concentration, has received a great deal of attention in recent years as a means of overcoming these limitations.[112] Scale-up of nanocarriers, the investments needed for advanced instrumentation, the viability of developing patient-friendly oral formulation, the reproducibility of physical characteristics and *in vitro/in vivo* efficacy for large-scale batches, the cost-to-benefit ratio for nanocarriers, and the significant variations in human population pharmacokinetics are just a few of the many factors that must be taken into consideration. Only formulations that spontaneously emulsify and nanosuspension have overcome these obstacles and entered the pharmaceutical market.[113] Selegiline is a medicine now available on the market and used clinically via transdermal patches.[114]

Conflict of Interest

The authors declare no conflicts of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

Quote this article as Yadav K, Rani A, Tyagi P, Malakapogu Ravindra Babu MR, The Application of Nanotechnology and Nanomaterials in Depression: An Updated Review, Precis. Nanomed. 2023, 6(2):1023-1047, https://doi.org/10.33218/001c.82215

References:

(1) Safayari, A.; Bolhasani, H. Depression Diagnosis by Deep Learning Using EEG Signals: A Systematic Review. *Med Nov Technol Devices* **2021**, *12*, 100102.

(2) Ma, J.; Zhou, H.; Fu, Q.; Lu, G. Facilitators and Barriers in the Development and Implementation of Depression Prevention and Treatment Policies in China: A Qualitative Study. *BMC Public Health* **2023**, *23* (1), 1–11.

(3) Kessler, R. C.; Berglund, P.; Demler, O. Mood Disorders: Bipolar and Major Depressive Disorders. *JAMA* **2003**, *289* (23), 3095–3105.

(4) Ekong, M. B.; Iniodu, C. F. Nutritional Therapy Can Reduce the Burden of Depression Management in Low Income Countries: A Review. *IBRO Neurosci Rep* **2021**, *11*, 15–28.

(5) Harini, K.; Girigoswami, K.; Girigoswami, A. Nanopsychiatry: Engineering of Nanoassisted Drug Delivery Systems to Formulate Antidepressants. *International Journal of Nano Dimension* **2022**, *13* (3), 256–266.

(6) Hasler, G. Pathophysiology of Depression: Do We Have Any Solid Evidence of Interest to Clinicians? *World Psychiatry* **2010**, *9* (3), 155.

(7) Gbadamosi, I. T.; Henneh, I. T.; Aluko, O. M.; Yawson, E. O.; Fokoua, A. R.; Koomson, A.; Torbi, J.; Olorunnado, S. E.; Lewu, F. S.; Yusha'u, Y. Depression in Sub-Saharan Africa. *IBRO Neurosci Rep* **2022**, *12*, 309–322.

(8) Kaiser, T.; Volkmann, C.; Volkmann, A.; Karyotaki, E.; Cuijpers, P.; Brakemeier, E.-L. Heterogeneity of Treatment Effects in Trials on Psychotherapy of Depression. *Clinical Psychology: Science and Practice* **2022**, *29* (3), 294.

(9) Jeevanandam, J.; San Chan, Y.; Danquah, M. K. Nano-Formulations of Drugs: Recent Developments, Impact and Challenges. *Biochimie* **2016**, *128*, 99–112.

(10) Patel, R. B.; Rao, H. R.; Thakkar, D. v; Patel, M. R. Comprehending the Potential of Metallic, Lipid, and Polymer-Based Nanocarriers for Treatment and Management of Depression. *Neurochem Int* **2022**, *153*, 105259.

(11) Zorkina, Y.; Abramova, O.; Ushakova, V.; Morozova, A.; Zubkov, E.; Valikhov, M.; Melnikov, P.; Majouga, A.; Chekhonin, V. Nano Carrier Drug Delivery Systems for the Treatment of Neuropsychiatric Disorders: Advantages and Limitations. *Molecules* **2020**, *25* (22), 5294.

(12) Nguyen, T. T.; Nguyen, T. T. D.; Vo, T. K.; Nguyen, M. K.; Van Vo, T.; Van Vo, G. Nanotechnology-Based Drug Delivery for Central Nervous System Disorders. *Biomedicine & Pharmacotherapy* **2021**, *143*, 112117.

(13) Lin, C.-H.; Chen, C.-H.; Lin, Z.-C.; Fang, J.-Y. Recent Advances in Oral Delivery of Drugs and Bioactive Natural Products Using Solid Lipid Nanoparticles as the Carriers. *J Food Drug Anal* **2017**, *25* (2), 219–234.

(14) Kilts, C. D. Potential New Drug Delivery Systems for Antidepressants: An Overview. *Journal of Clinical Psychiatry* **2003**, *64*, 31–33.

(15) Dimitrijevic, I.; Pantic, I. APPLICATION OF NANOPARTICLES IN PSYCHOPHYSIOLOGY AND PSYCHIATRY RESEARCH. *Reviews on Advanced Materials Science* **2014**, *38* (1).

(16) Swain, S.; Behera, A.; Dinda, S. C.; Patra, C. N.; Jammula, S.; Beg, S.; Rao, M. E. B. Formulation Design, Optimization and Pharmacodynamic Evaluation of Sustained Release Mucoadhesive Microcapsules of Venlafaxine HCl. *Indian J Pharm Sci* **2014**, *76* (4), 354.

(17) Pires, P. C.; Paiva-Santos, A. C.; Veiga, F. Nano and Microemulsions for the Treatment of Depressive and Anxiety Disorders: An Efficient Approach to Improve Solubility, Brain Bioavailability and Therapeutic Efficacy. *Pharmaceutics* **2022**, *14* (12), 2825.

(18) Garg, H.; Mittal, S.; Ashhar, M. U.; Kumar, S.; Dang, S.; Nigam, K.; Ali, J.; Baboota, S. Bioavailability Enhancement of Paroxetine Loaded Self Nanoemulsifying Drug Delivery System (SNEDDS) to Improve Behavioural Activities for the Management of Depression. *J Clust Sci* **2022**, 1–14.

(19) Xu, J.; Tao, J.; Wang, J. Design and Application in Delivery System of Intranasal Antidepressants. *Front Bioeng Biotechnol* **2020**, *8*, 626882.

(20) Alberto, M.; Paiva-Santos, A. C.; Veiga, F.; Pires, P. C. Lipid and Polymeric Nanoparticles: Successful Strategies for Nose-to-Brain Drug Delivery in the Treatment of Depression and Anxiety Disorders. *Pharmaceutics* **2022**, *14* (12), 2742.

(21) Tong, G.-F.; Qin, N.; Sun, L.-W. Development and Evaluation of Desvenlafaxine Loaded PLGA-Chitosan Nanoparticles for Brain Delivery. *Saudi pharmaceutical journal* **2017**, *25* (6), 844–851.

(22) Pandey, Y. R.; Kumar, S.; Gupta, B. K.; Ali, J.; Baboota, S. Intranasal Delivery of Paroxetine Nanoemulsion via the Olfactory Region for the Management of Depression: Formulation, Behavioural and Biochemical Estimation. *Nanotechnology* **2015**, *27* (2), 025102.

(23) Alam, M. I.; Baboota, S.; Ahuja, A.; Ali, M.; Ali, J.; Sahni, J. K.; Bhatnagar, A. Pharmacoscintigraphic Evaluation of Potential of Lipid Nanocarriers for Nose-to-Brain Delivery of Antidepressant Drug. *Int J Pharm* **2014**, *470* (1–2), 99–106.

(24) Zhang, J.; Xie, Z.; Zhang, N.; Zhong, J. Nanosuspension Drug Delivery System: Preparation, Characterization, Postproduction Processing, Dosage Form, and Application. In *Nanostructures for Drug Delivery*; Elsevier, 2017; pp 413–443.

(25) Zhang, T.-Y.; Chen, D.-Q.; Gao, J.-Q.; Hu, Y.-L. Preparation of Sertraline-Loaded Chitosan Nanoparticles and the Pharmacokinetics Studies. *Afr J Pharm Pharmacol* **2016**, *10* (3), 26–33.

(26) Alabsi, A.; Khoudary, A. C.; Abdelwahed, W. The Antidepressant Effect of L-Tyrosine-Loaded Nanoparticles: Behavioral Aspects. *Ann Neurosci* **2016**, *23* (2), 89–99.

(27) Erden, Y. J. ICT Implants, Nanotechnology, and Some Reasons for Caution. *BioCentre, accessed March* **2016**, *2*.

(28) Alshawwa, S. Z.; Kassem, A. A.; Farid, R. M.; Mostafa, S. K.; Labib, G. S. Nanocarrier Drug Delivery Systems: Characterization, Limitations, Future Perspectives and Implementation of Artificial Intelligence. *Pharmaceutics* **2022**, *14* (4), 883.

(29) Fu, S.; Chen, H.; Yang, W.; Xia, X.; Zhao, S.; Xu, X.; Ai, P.; Cai, Q.; Li, X.; Wang, Y. ROS-Targeted Depression Therapy via BSA-Incubated Ceria Nanoclusters. *Nano Lett* **2022**, *22* (11), 4519–4527.

(30) Kamali, H.; Nosrati, R.; Malaekeh-Nikouei, B. Nanostructures and Their Associated Challenges for Drug Delivery. In *Hybrid nanomaterials for drug delivery*; Elsevier, 2022; pp 1–26.

(31) Zhang, W.; Mehta, A.; Tong, Z.; Esser, L.; Voelcker, N. H. Development of Polymeric Nanoparticles for Blood–Brain Barrier Transfer—Strategies and Challenges. *Advanced Science* **2021**, *8* (10), 2003937.

(32) Barenholz, Y. C. Doxil®—The First FDA-Approved Nano-Drug: Lessons Learned. *Journal of controlled release* **2012**, *160* (2), 117–134.

(33) Khalid, M.; El-Sawy, H. S. Polymeric Nanoparticles: Promising Platform for Drug Delivery. *Int J Pharm* **2017**, *528* (1–2), 675–691.

(34) Teleanu, D. M.; Chircov, C.; Grumezescu, A. M.; Volceanov, A.; Teleanu, R. I. Blood-Brain Delivery Methods Using Nanotechnology. *Pharmaceutics* **2018**, *10* (4), 269.

(35) Nagpal, K.; Singh, S. K.; Mishra, D. N. Nanoparticle Mediated Brain Targeted Delivery of Gallic Acid: In Vivo Behavioral and Biochemical Studies for Improved Antioxidant and Antidepressant-like Activity. *Drug Deliv* **2012**, *19* (8), 378–391.

(36) Rajput, R.; Kumar, S.; Nag, P.; Singh, M. Fabrication and Characterization of Chitosan Based Polymeric Escitalopram Nanoparticles. *J Appl Pharm Sci* **2016**, *6* (7), 171–177.

(37) Li, X.; Tsibouklis, J.; Weng, T.; Zhang, B.; Yin, G.; Feng, G.; Cui, Y.; Savina, I. N.; Mikhalovska, L. I.; Sandeman, S. R. Nano Carriers for Drug Transport across the Blood–Brain Barrier. *J Drug Target* **2017**, *25* (1), 17–28.

(38) Sharma, P.; Baisoya, D.; Chauhan, D.; Mishra, D.; Sharma, M.; Chandra, A. Recent Progress, Therapeutic Concepts And Pharmaceutical Challenges Of Dendrimer Based Drug Delivery System. *J Pharm Negat Results* **2023**, 6865–6873.

(39) Gauro, R.; Nandave, M.; Jain, V. K.; Jain, K. Advances in Dendrimer-Mediated Targeted Drug Delivery to the Brain. *Journal of Nanoparticle Research* **2021**, *23*, 1–20.

(40) Yang, H.; Lopina, S. T. Extended Release of a Novel Antidepressant, Venlafaxine, Based on Anionic Polyamidoamine Dendrimers and Poly (Ethylene Glycol)-containing Semi-interpenetrating Networks. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* **2005**, *72* (1), 107–114.

(41) Samimi, S.; Maghsoudnia, N.; Eftekhari, R. B.; Dorkoosh, F. Lipid-Based Nanoparticles for Drug Delivery Systems. *Characterization and biology of nanomaterials for drug delivery* **2019**, 47–76.

(42) Fonseca-Santos, B.; Gremião, M. P. D.; Chorilli, M. Nanotechnology-Based Drug Delivery Systems for the Treatment of Alzheimer's Disease. *Int J Nanomedicine* **2015**, *10*, 4981.

(43) Noack, A.; Hause, G.; Mäder, K. Physicochemical Characterization of Curcuminoid-Loaded Solid Lipid Nanoparticles. *Int J Pharm* **2012**, *423* (2), 440–451.

(44) Fathi, M.; Varshosaz, J.; Mohebbi, M.; Shahidi, F. Hesperetin-Loaded Solid Lipid Nanoparticles and Nanostructure Lipid Carriers for Food Fortification: Preparation, Characterization, and Modeling. *Food Bioproc Tech* **2013**, *6*, 1464–1475.

(45) Vijayanand, P.; Jyothi, V.; Aditya, N.; Mounika, A. Development and Characterization of Solid Lipid Nanoparticles Containing Herbal Extract: In Vivo Antidepressant Activity. *J Drug Deliv* **2018**, *2018*.

(46) Kakkar, V.; Kaur, I. P. Antidepressant Activity of Curcumin Loaded Solid Lipid Nanoparticles (C-SLNs) in Mice. *Am J Pharm Res* **2012**, *2* (3), 729–736.

(47) Rahman, M. A.; Harwansh, R. K.; Iqbal, Z. Systematic Development of Sertraline Loaded Solid Lipid Nanoparticle (SLN) by Emulsification-Ultrasonication Method and Pharmacokinetic Study in Sprague-Dawley Rats. *Pharm Nanotechnol* **2019**, *7* (2), 162–176.

(48) Sabir, F.; Asad, M. I.; Qindeel, M.; Afzal, I.; Dar, M. J.; Shah, K. U.; Zeb, A.; Khan, G. M.; Ahmed, N.; Din, F. Polymeric Nanogels as Versatile Nanoplatforms for Biomedical Applications. *J Nanomater* **2019**, *2019*.

(49) Poovaiah, N.; Davoudi, Z.; Peng, H.; Schlichtmann, B.; Mallapragada, S.; Narasimhan, B.; Wang, Q. Treatment of Neurodegenerative Disorders through the Blood–Brain Barrier Using Nanocarriers. *Nanoscale* **2018**, *10* (36), 16962–16983.

(50) Aderibigbe, B. A.; Naki, T. Design and Efficacy of Nanogels Formulations for Intranasal Administration. *Molecules* **2018**, *23* (6), 1241.

(51) Yetisgin, A. A.; Cetinel, S.; Zuvin, M.; Kosar, A.; Kutlu, O. Therapeutic Nanoparticles and Their Targeted Delivery Applications. *Molecules* **2020**, *25* (9), 2193.

(52) Malhotra, N.; Audira, G.; Chen, J.-R.; Siregar, P.; Hsu, H.-S.; Lee, J.-S.; Ger, T.-R.; Hsiao, C.-D. Surface Modification of Magnetic Nanoparticles by Carbon-Coating Can Increase Its Biosafety: Evidences from Biochemical and Neurobehavioral Tests in Zebrafish. *Molecules* **2020**, *25* (9), 2256.

(53) Mirza, S.; Ahmad, M. S.; Shah, M. I. A.; Ateeq, M. Magnetic Nanoparticles: Drug Delivery and Bioimaging Applications. In *Metal nanoparticles for drug delivery and diagnostic applications*; Elsevier, 2020; pp 189–213.

(54) Veiseh, O.; Gunn, J. W.; Zhang, M. Design and Fabrication of Magnetic Nanoparticles for Targeted Drug Delivery and Imaging. *Adv Drug Deliv Rev* **2010**, *62* (3), 284–304.

(55) Xiong, F.; Huang, S.; Gu, N. Magnetic Nanoparticles: Recent Developments in Drug Delivery System. *Drug Dev Ind Pharm* **2018**, *44* (5), 697–706.

(56) Luan, D.; Zhao, M.-G.; Shi, Y.-C.; Li, L.; Cao, Y.-J.; Feng, H.-X.; Zhang, Z.-J. Mechanisms of Repetitive Transcranial Magnetic Stimulation for Anti-Depression: Evidence from Preclinical Studies. *World J Psychiatry* **2020**, *10* (10), 223.

(57) Chen, Y.; Zhang, Q.; Chen, Z.; Wang, L.; Yao, J.; Kovalenko, V. Study on the Element Segregation and Laves Phase Formation in the Carbon Nanotubes Reinforced IN718 Superalloy by Laser Cladding. *Powder Technol* **2019**, *355*, 163–171.

(58) Alkandari, S. *SYNTHESIS AND ENCAPSULATION OF ANTIDEPRESSANTS IN BIODEGRADABLE POLYMERIC, LIPID NANOPARTICLES TO BYPASS THE BLOOD BRAIN BARRIER*; 2022.

(59) Gorwade, S.; Wilson, B. POTENTIAL OF NANOPARTICLES FOR THE DELIVERY OF ANTIDEPRESSANTS. **2022**.

(60) Nodari, C. H.; de Quadros, N. D.; Chiarentin, R.; da Silva, F. P.; Morisso, F. D. P.; Charão, M. F.; Fleck, J. D.; de Mattos, C. B.; Betti, A. H.; Verza, S. G. Vortioxetine Liposomes as a Novel Alternative to Improve Drug Stability under Stress Conditions: Toxicity Studies and Evaluation of Antidepressant-like Effect. *Pharmacological Reports* **2022**, *74* (5), 969–981.

(61) Fatouh, A. M.; Elshafeey, A. H.; Abdelbary, A. Intranasal Agomelatine Solid Lipid Nanoparticles to Enhance Brain Delivery: Formulation, Optimization and in Vivo Pharmacokinetics. *Drug Des Devel Ther* **2017**, 1815–1825.

(62) Nguyen, T.-T.-L.; Maeng, H.-J. Pharmacokinetics and Pharmacodynamics of Intranasal Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Nose-to-Brain Delivery. *Pharmaceutics* **2022**, *14* (3), 572.

(63) Singh, D.; Rashid, M.; Hallan, S. S.; Mehra, N. K.; Prakash, A.; Mishra, N. Pharmacological Evaluation of Nasal Delivery of Selegiline Hydrochloride-Loaded Thiolated Chitosan Nanoparticles for the Treatment of Depression. *Artif Cells Nanomed Biotechnol* **2016**, *44* (3), 865–877.

(64) Vitorino, C.; Silva, S.; Bicker, J.; Falcão, A.; Fortuna, A. Antidepressants and Nose-to-Brain Delivery: Drivers, Restraints, Opportunities and Challenges. *Drug Discov Today* **2019**, *24* (9), 1911–1923.

(65) El-Nabarawi, M. A.; Bendas, E. R.; el Rehem, R. T. A.; Abary, M. Y. S. Transdermal Drug Delivery of Paroxetine through Lipid-Vesicular Formulation to Augment Its Bioavailability. *Int J Pharm* **2013**, *443* (1–2), 307–317.

(66) Sharma, A.; Arora, S.; Gupta, A.; Mittal, R. Percutaneous Delivery of Antidepressant Drug: Venlafaxine Using Elastic Liposomal Formulation. *J Pharm Res* **2011**, *4* (11), 3875–3879.

(67) Sercombe, L.; Veerati, T.; Moheimani, F.; Wu, S. Y.; Sood, A. K.; Hua, S. Advances and Challenges of Liposome Assisted Drug Delivery. *Front Pharmacol* **2015**, *6*, 286.

(68) Jani, P.; Vanza, J.; Pandya, N.; Tandel, H. Formulation of Polymeric Nanoparticles of Antidepressant Drug for Intranasal Delivery. *Ther Deliv* **2019**, *10* (11), 683–696.

(69) Costa, C. P.; Moreira, J. N.; Lobo, J. M. S.; Silva, A. C. Intranasal Delivery of Nanostructured Lipid Carriers, Solid Lipid Nanoparticles and Nanoemulsions: A Current Overview of in Vivo Studies. *Acta Pharm Sin B* **2021**, *11* (4), 925–940.

(70) Rana, I.; Khan, N.; Ansari, M. M.; Shah, F. A.; ud Din, F.; Sarwar, S.; Imran, M.; Qureshi, O. S.; Choi, H.-I.; Lee, C.-H. Solid Lipid Nanoparticles-Mediated Enhanced Antidepressant Activity of Duloxetine in Lipopolysaccharide-Induced Depressive Model. *Colloids Surf B Biointerfaces* **2020**, *194*, 111209.

(71) Salah, E.; Abouelfetouh, M. M.; Pan, Y.; Chen, D.; Xie, S. Solid Lipid Nanoparticles for Enhanced Oral Absorption: A Review. *Colloids Surf B Biointerfaces* **2020**, *196*, 111305.

(72) Vitorino, C.; Silva, S.; Gouveia, F.; Bicker, J.; Falcão, A.; Fortuna, A. QbD-Driven Development of Intranasal Lipid Nanoparticles for Depression Treatment. *European Journal of Pharmaceutics and Biopharmaceutics* **2020**, *153*, 106–120.

(73) D'Souza, A. A.; Kutlehria, S.; Huang, D.; Bleier, B. S.; Amiji, M. M. Nasal Delivery of Nanotherapeutics for CNS Diseases: Challenges and Opportunities. *Nanomedicine* **2021**, *16* (30), 2651–2655.

(74) Shinde, M.; Salve, P.; Rathod, S. Development and Evaluation of Nanoparticles Based Transdermal Patch of Agomelatine for the Treatment of Depression. *Journal of Drug Delivery and Therapeutics* **2019**, *9* (4-s), 126–144.

(75) Haque, S.; Md, S.; Fazil, M.; Kumar, M.; Sahni, J. K.; Ali, J.; Baboota, S. Venlafaxine Loaded Chitosan NPs for Brain Targeting: Pharmacokinetic and Pharmacodynamic Evaluation. *Carbohydr Polym* **2012**, *89* (1), 72–79.

(76) Mohammed, M. A.; Syeda, J. T. M.; Wasan, K. M.; Wasan, E. K. An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery. *Pharmaceutics* **2017**, *9* (4), 53.

(77) Alam, M.; Zameer, S.; Najmi, A. K.; Ahmad, F. J.; Imam, S. S.; Akhtar, M. Thymoquinone Loaded Solid Lipid Nanoparticles Demonstrated Antidepressant-like Activity in Rats via Indoleamine 2, 3-Dioxygenase Pathway. *Drug Res* **2020**, *70* (05), 206–213.

(78) Satapathy, M. K.; Yen, T.-L.; Jan, J.-S.; Tang, R.-D.; Wang, J.-Y.; Taliyan, R.; Yang, C.-H. Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB. *Pharmaceutics* **2021**, *13* (8), 1183.

(79) Sapre, A. S.; Parikh, R. K. Design of a Buccal Mucoadhesive, Nanoparticles Based Delivery System of Fluoxetine. *JPSBR* **2012**, *2* (3), 148–161.

(80) Sur, S.; Rathore, A.; Dave, V.; Reddy, K. R.; Chouhan, R. S.; Sadhu, V. Recent Developments in Functionalized Polymer Nanoparticles for Efficient Drug Delivery System. *Nanostructures & Nano-Objects* **2019**, *20*, 100397.

(81) Gupta, A.; Aggarwal, G.; Singla, S.; Arora, R. Transfersomes: A Novel Vesicular Carrier for Enhanced Transdermal Delivery of Sertraline: Development, Characterization, and Performance Evaluation. *Sci Pharm* **2012**, *80* (4), 1061–1080.

(82) Kondiah, P. P. D.; Mdanda, S.; Makhathini, S. S.; Rants'o, T. A.; Choonara, Y. E. Development of a Eudragit-Chitosan Nanosystem for the PH-Dependent Transport of Duloxetine to the Brain: Synthesis, Characterization and In Silico Modeling Analysis. *Nanofabrication* **2022**, *7*, 195–216.

(83) el Henawee, M.; Saleh, H.; Attia, A. K.; Hussien, E. M.; Derar, A. R. Carbon Nanotubes Bulk Modified Printed Electrochemical Sensor for Green Determination of Vortioxetine Hydrobromide by Linear Sweep Voltammetry. *Measurement* **2021**, *177*, 109239.

(84) Porwal, M.; Rastogi, V.; Kumar, A. An Overview on Carbon Nanotubes. *MOJ Bioequiv Availab* **2017**, *3* (5), 114–116.

(85) Duarte, E. H.; dos Santos, W. P.; Hudari, F. F.; Neto, J. L. B.; Sartori, E. R.; Dall, L. H.; Pereira, A. C.; Tarley, C. R. T. A Highly Improved Method for Sensitive Determination of Amitriptyline in Pharmaceutical Formulations Using an Unmodified Carbon Nanotube Electrode in the Presence of Sulfuric Acid. *Talanta* **2014**, *127*, 26–32.

(86) Qizilbash, F. F.; Ashhar, M. U.; Zafar, A.; Qamar, Z.; Ali, J.; Baboota, S.; Ghoneim, M. M.; Alshehri, S.; Ali, A. Thymoquinone-Enriched Naringenin-Loaded Nanostructured Lipid Carrier for Brain Delivery via Nasal Route: In Vitro Prospect and In Vivo Therapeutic Efficacy for the Treatment of Depression. *Pharmaceutics* **2022**, *14* (3), 656.

(87) Kaur, P.; Garg, T.; Vaidya, B.; Prakash, A.; Rath, G.; Goyal, A. K. Brain Delivery of Intranasal in Situ Gel of Nanoparticulated Polymeric Carriers Containing Antidepressant Drug: Behavioral and Biochemical Assessment. *J Drug Target* **2015**, *23* (3), 275–286.

(88) Ashraf, A.; Mahmoud, P. A.; Reda, H.; Mansour, S.; Helal, M. H.; Michel, H. E.; Nasr, M. Silymarin and Silymarin Nanoparticles Guard against Chronic Unpredictable Mild Stress Induced Depressive-like Behavior in Mice: Involvement of Neurogenesis and NLRP3 Inflammasome. *Journal of Psychopharmacology* **2019**, *33* (5), 615–631.

(89) Akbari, J.; Saeedi, M.; Ahmadi, F.; Hashemi, S. M. H.; Babaei, A.; Yaddollahi, S.; Rostamkalaei, S. S.; Asare-Addo, K.; Nokhodchi, A. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: A Review of the Methods of Manufacture and Routes of Administration. *Pharm Dev Technol* **2022**, *27* (5), 525–544.

(90) Rajendran, V. Effect of Niosomes in the Transdermal Delivery of Antidepressant Sertraline Hydrochloride. *Journal of Scientific and Innovative Research* **2016**, *5* (4), 138–148.

(91) Das Kurmi, B.; Tekchandani, P.; Paliwal, R.; Rai Paliwal, S. Transdermal Drug Delivery: Opportunities and Challenges for Controlled Delivery of Therapeutic Agents Using Nanocarriers. *Curr Drug Metab* **2017**, *18* (5), 481–495.

(92) Park, W.; Na, K. Advances in the Synthesis and Application of Nanoparticles for Drug Delivery. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **2015**, *7* (4), 494–508.

(93) Mudshinge, S. R.; Deore, A. B.; Patil, S.; Bhalgat, C. M. Nanoparticles: Emerging Carriers for Drug Delivery. *Saudi pharmaceutical journal* **2011**, *19* (3), 129–141.

(94) Kabra, A.; Garg, R.; Brimson, J.; Živković, J.; Almawash, S.; Ayaz, M.; Nawaz, A.; Hassan, S. S. U.; Bungau, S. Mechanistic Insights into the Role of Plant Polyphenols and Their Nano-Formulations in the Management of Depression. *Front Pharmacol* **2022**, *13*, 4731.

(95) Hartmann, M.; Mavrolampados, A.; Toiviainen, P.; Saarikallio, S.; Foubert, K.; Brabant, O.; Snape, N.; Ala-Ruona, E.; Gold, C.; Erkkilä, J. Musical Interaction in Music Therapy for Depression Treatment. *Psychol Music* **2023**, *51* (1), 33–50.

(96) Albornoz, Y. The Effects of Group Improvisational Music Therapy on Depression in Adolescents and Adults with Substance Abuse: A Randomized Controlled Trial. *Nord J Music Ther* **2011**, *20* (3), 208–224.

(97) Ewing, E. S. K.; Diamond, G.; Levy, S. Attachment-Based Family Therapy for Depressed and Suicidal Adolescents: Theory, Clinical Model and Empirical Support. *Attach Hum Dev* **2015**, *17* (2), 136–156.

(98) Garoff, F. F.; Heinonen, K.; Pesonen, A.; Almqvist, F. Depressed Youth: Treatment Outcome and Changes in Family Functioning in Individual and Family Therapy. *J Fam Ther* **2012**, *34* (1), 4–23.

(99) Kirov, G.; Jauhar, S.; Sienaert, P.; Kellner, C. H.; McLoughlin, D. M. Electroconvulsive Therapy for Depression: 80 Years of Progress. *The British Journal of Psychiatry* **2021**, *219* (5), 594–597.

(100) Lisanby, S. H. Electroconvulsive Therapy for Depression. *New England Journal of Medicine* **2007**, *357* (19), 1939–1945.

(101) Young, J. E.; Rygh, J. L.; Weinberger, A. D.; Beck, A. T. Cognitive Therapy for Depression. **2014**.

(102) Wright, J. H.; Beck, A. T. Cognitive Therapy of Depression: Theory and Practice. *Psychiatric Services* **1983**, *34* (12), 1119–1127.

(103) Wampold, B. E.; Minami, T.; Baskin, T. W.; Tierney, S. C. A Meta-(Re) Analysis of the Effects of Cognitive Therapy versus 'Other Therapies' for Depression. *J Affect Disord* **2002**, *68* (2–3), 159–165.

(104) Zhang, X.; Wang, Y. TPH2: A Key Gene Risk Factor and Potential Therapy Target in Depression. In *E3S Web of Conferences*; EDP Sciences, 2021; Vol. 271, p 03070.

(105) Smith, D. M.; Simon, J. K.; Baker Jr, J. R. Applications of Nanotechnology for Immunology. *Nat Rev Immunol* **2013**, *13* (8), 592–605.

(106) Rai, M.; Ribeiro, C.; Mattoso, L.; Duran, N. *Nanotechnologies in Food and Agriculture*; Springer, 2015; Vol. 33.

(107) Oprea, I.; Fărcaș, A. C.; Leopold, L. F.; Diaconeasa, Z.; Coman, C.; Socaci, S. A. Nano-Encapsulation of Citrus Essential Oils: Methods and Applications of Interest for the Food Sector. *Polymers (Basel)* **2022**, *14* (21), 4505.

(108) Navalakhe, R. M.; Nandedkar, T. D. Application of Nanotechnology in Biomedicine. **2007**.

(109) Saxena, S. K.; Nyodu, R.; Kumar, S.; Maurya, V. K. Current Advances in Nanotechnology and Medicine. *Nanobiomedicine (Rij)* **2020**, 3–16.

(110) Calixto, G. M. F.; Bernegossi, J.; De Freitas, L. M.; Fontana, C. R.; Chorilli, M. Nanotechnology-Based Drug Delivery Systems for Photodynamic Therapy of Cancer: A Review. *Molecules* **2016**, *21* (3), 342.

(111) Chhipa, H. Applications of Nanotechnology in Agriculture. In *Methods in microbiology*; Elsevier, 2019; Vol. 46, pp 115–142.

(112) Park, W.; Na, K. Advances in the Synthesis and Application of Nanoparticles for Drug Delivery. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **2015**, *7* (4), 494–508.

(113) Desai, P. P.; Date, A. A.; Patravale, V. B. Overcoming Poor Oral Bioavailability Using Nanoparticle Formulations–Opportunities and Limitations. *Drug Discov Today Technol* **2012**, *9* (2), e87–e95.

(114) Al Hanbali, O. A.; Khan, H. M. S.; Sarfraz, M.; Arafat, M.; Ijaz, S.; Hameed, A. Transdermal Patches: Design and Current Approaches to Painless Drug Delivery. *Acta Pharmaceutica* **2019**, *69* (2), 197–215.