Materials Today Bio 32 (2025) 101781

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Recent advances in biomimetic nanodelivery systems for the treatment of depression

Ping Jiang , Jian Li *

General Hospital of Northern Theater Command, Shenyang, 110016, China

ARTICLE INFO

Keywords:
Depression
Nanozyme
Cell membrane
Exosomes
Drug delivery
Nanomedicine

ABSTRACT

Depression and cognitive disorders remain major challenges in healthcare, with conventional treatments often facing limitations such as slow onset, side effects, and poor drug delivery to the brain. Biomimetic nanodelivery systems, including nanozymes, cell membrane-based systems, and exosomes, have emerged as promising solutions to these issues. These systems leverage natural biological processes to enhance drug targeting, improve bioavailability, and regulate complex biological pathways. Nanoenzymes, with their catalytic properties, offer antioxidant and anti-inflammatory benefits, while cell membranes and exosomes provide efficient targeting and immune evasion. However, challenges remain, including the immaturity of large-scale production techniques, stability concerns, and incomplete understanding of their mechanisms of action. Moreover, the long-term safety, pharmacokinetics, and toxicity of these systems require further investigation. Despite these obstacles, the potential of biomimetic nanodelivery systems to revolutionize depression treatment is significant. Future research should focus on optimizing their preparation, improving drug targeting and release, and ensuring clinical safety. Multidisciplinary collaboration will be essential for advancing these systems from the laboratory to clinical practice, offering new therapeutic avenues for depression and other neurological disorders.

1. Introduction

Depression is a complex and prevalent neuropsychiatric disorder that imposes a significant burden on individuals and global healthcare systems [1]. According to recent data from the World Health Organization (WHO), more than 350 million individuals worldwide suffer from depression, with over 75 % of these patients experiencing recurrent and lifelong episodes [2–5]. Depression often manifests early in life and can persist for years, negatively impacting the prognosis of other comorbid diseases. Beyond the mental anguish it causes, depression disrupts essential biological functions, including sleep regulation, appetite, metabolism, autonomic functioning, and neuroendocrine processes. Consequently, the WHO has recognized depression as one of the leading causes of disability globally [6–8].

In recent years, the global burden of depression has intensified, exacerbated by the mental health consequences of the COVID-19 pandemic [9–11]. Depression is now considered one of the most significant public health challenges, second only to cancer in its global impact. The disorder's high prevalence, debilitating nature, and recurrence contribute to substantial economic and social burdens [12–14]. Furthermore, the heterogeneity of depression complicates efforts to identify its precise pathophysiology, making its underlying mechanisms and optimal treatment strategies areas of ongoing investigation [15–17]. Current therapeutic approaches for depression include pharmacotherapy, psychotherapy, and electroconvulsive therapy, with pharmacotherapy being the most commonly employed. However, antidepressant medications often present significant challenges. Many of these drugs suffer from poor bioavailability due to limited solubility and permeability, which significantly diminishes their clinical effectiveness. Additionally, antidepressants are frequently nonspecific in their distribution within the body, leading to a range of side effects, including weight gain, sexual dysfunction, and sleep disturbances [18–20].

Advancements in nanotechnology have opened new avenues for the treatment of central nervous system (CNS) disorders, including depression. Nanodelivery systems can improve drug solubility and bioavailability, prolong circulation time, and, crucially, enhance the permeability of therapeutic agents across the BBB [21–23]. Among these, biomimetic nanodelivery systems have emerged as particularly promising platforms. By mimicking endogenous biological structures

* Corresponding author.
E-mail address: mnwklj0626@163.com (J. Li).

https://doi.org/10.1016/j.mtbio.2025.101781
Received 23 February 2025; Received in revised form 12 April 2025; Accepted 17 April 2025
Available online 17 April 2025

and mechanisms, such systems such as exosomes, cell membrane-coated nanoparticles, and nanozyme-based carriers offer advantages including high biocompatibility, immune evasion, prolonged circulation, and the potential for targeted delivery to diseased regions of the brain [24–26].

This review critically evaluates the recent advances in biomimetic nanodelivery systems for depression treatment, with a particular focus on exosomal-based, cell membrane-based, and nanozyme-based strategies. We explore the principles behind the design and construction of these nanosystems, examining their ex vivo and in vivo efficacy, and assessing their potential for clinical translation. Moreover, we discuss the existing challenges and limitations of these systems in treating depression, highlighting key areas for future research. Ultimately, we provide an outlook on the continued development of biomimetic nanodelivery strategies, emphasizing the importance of interdisciplinary collaboration and ongoing refinement to bridge the gap between laboratory research and clinical application. Our goal is to underscore the transformative potential of biomimetic nanodelivery systems in revolutionizing depression treatment and offer a new perspective for researchers in the field (Fig. 1). By integrating mechanistic insights, emerging strategies, and translational perspectives, this review seeks to offer a timely and comprehensive resource for researchers and clinicians interested in the next generation of antidepressant therapies.

2. Pathogenesis of depression

Significant strides have been made in understanding the pathophysiology of depression over the past few decades, yet its precise pathogenesis remains incompletely understood [27]. Persistent stress is considered a major contributing factor to depression, and multiple biological mechanisms have been implicated in its development. These mechanisms include monoaminergic neuronal underactivity, increased inflammatory responses, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, vascular changes, and diminished neuroplasticity [28–30]. Notably, these processes do not always co-occur in every patient, which suggests that depression may represent a collection of biologically distinct disorders rather than a single, homogeneous condition. Current research on depression mechanisms often focuses on individual biological pathways, without fully considering the complex interplay between them. A more comprehensive understanding of these interactions may provide a more holistic and effective approach to treating depression [31–33].

2.1. Genetic and environmental factors

Depression has a notable hereditary component, with genetic factors contributing to its onset in approximately 8 % of men and 15 % of women [34]. However, the genetic underpinnings of depression

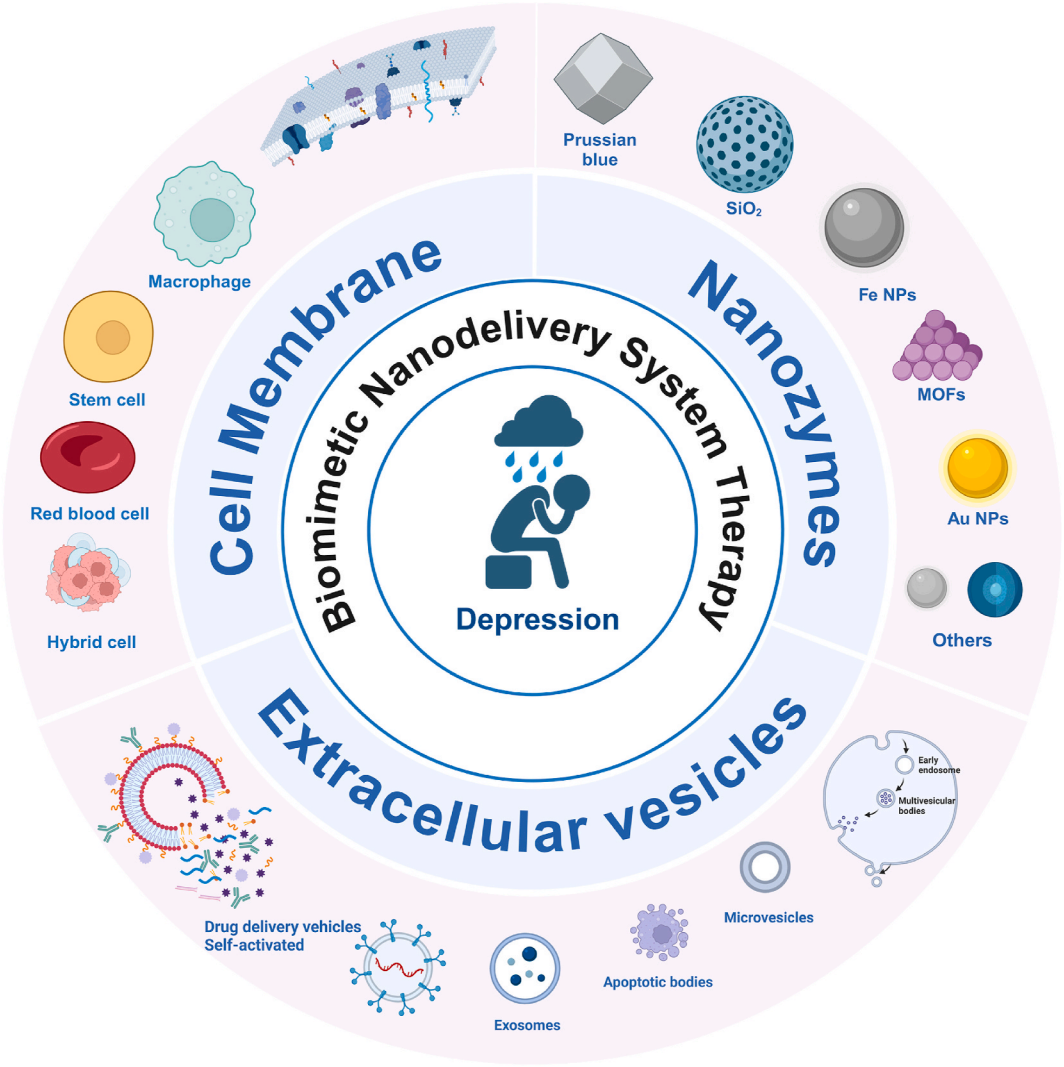

Fig. 1. Schematic representation of a biomimetic nano-delivery system for the treatment of depression.

susceptibility in specific populations are still under active investigation. The field of neuroscience has advanced significantly with the advent of new technologies in genetics, neuroimaging, and molecular biology, allowing researchers to explore genetic material, visualize synaptic structures, and study the electrical activity of neurons, as well as the role of ion channels, neurotransmitters, and receptors in depression [35–37]. These advances have led to the recognition that genetic factors are key contributors to the development of depression. As shown in Fig. 2, environmental stressors, trauma, and adversity in parents can induce epigenetic changes such as DNA methylation, acetylation, and phosphorylation that affect the offspring. During early brain development, offspring are highly sensitive to the effects of these stressors, which can trigger reprogramming of stress-related pathways and result in persistent changes throughout the developmental process. Notably, epigenetic modifications have been identified in the brains and white blood cells of individuals with depression or those who have experienced childhood adversity, highlighting the role of epigenetic mechanisms in depression [38]. The genetic predisposition for major depression is estimated to be between 31 % and 42 %. Moreover, epigenetic phenomena are not confined to childhood but also occur in the adult brain, where they play a crucial role in regulating neural functions. These epigenetic regulatory processes represent interactions between environmental factors and genetic predispositions, and they are long-lasting, often being passed down to future generations.

In addition to genetic factors, environmental influences play a crucial role in the development of depression. Depression arises from a complex interplay between genetic and environmental factors, with gene-environment interactions significantly influencing its onset and progression. Stress, in particular, is a key environmental factor that can trigger depression and affect its incidence, severity, and course [39–41]. The stress response elicits a range of changes in the body, including altered levels of anxiety, a reduction in cognitive and emotional flexibility, and activation of the HPA axis and autonomic nervous system. In extreme cases, stress can inhibit vital trophic processes that are essential for survival such as those regulating sleep, growth, and reproduction which in turn may lead to depression or other neurological disorders. Early life stress (ELS) is a major contributor to brain damage during critical stages of development and has profound effects on the body and mind. The physiological response to ELS is typically divided into three phases: the alarm phase, the resistance phase, and the decay phase. In the alarm phase, the internal balance of the organism is disrupted, and it begins to react to external stressors [42–44]. During the resistance phase, the organism adjusts physiologically and behaviorally to counteract the stressor, while in the decay phase, the organism's adaptive responses become overwhelmed, leading to energy depletion and neurological failure. The longer the organism remains in a state of heightened stress response, the more profound the resulting behavioral and physiological changes, ultimately culminating in an overload of energy that leads to neurological dysfunction. The impact of ELS on the brain, mind, and body increases the organism's sensitivity to stress in adulthood and contributes to the development of a wide range of disorders [45–47]. Furthermore, the effects of environmental factors on genetic predispositions and gene expression continue throughout life. Chronic exposure to stressors induces a variety of biological changes, including the modulation of neuropeptide and classical neurotransmitter systems. These changes may offer new insights into the underlying mechanisms of depression and provide potential avenues for therapeutic intervention.

2.2. *Neurotransmitters*

Beyond genetic and environmental factors, extensive experimental and clinical evidence suggests that dysregulation of neurotransmitter systems is a central contributor to the pathogenesis of depression [48]. Studies have shown that concentrations of key neurotransmitters such as 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA) that are significantly lower in the cerebrospinal fluid (CSF) of individuals with depression, particularly in patients with suicidal tendencies. Additionally, abnormalities in neurotransmitter receptor expression and neurotransmitter reuptake mechanisms have been observed in depressed patients [49]. These findings indicate a direct association between specific neurotransmitter deficiencies or dysfunctions and the clinical features of depression. For example, a deficiency in 5-HT is linked to anxiety and obsessive-compulsive behaviors, reduced NE transmission is associated with symptoms such as low energy, inattention, and cognitive impairments, while DA dysfunction is implicated in disruptions to motivation, pleasure, and reward [50].

5-HT, also known as serotonin, is a monoamine neurotransmitter present throughout the CNS of both vertebrates and invertebrates. Remarkably, only about 5 % of endogenous 5-HT is found in the brain, while approximately 90 % is synthesized and released by enterochromaffin cells in the gastrointestinal tract [51–53]. 5-HT was first discovered in serum over 70 years ago and was originally found to regulate local blood flow. Later, its presence in the brain was identified, where it functions as a behavioral regulator. In the CNS, 5-HT is involved in a range of physiological processes, including sleep, appetite, cognition, and emotional regulation. It also plays a significant role in mediating various social behaviors such as anxiety, depression, and aggression.

The synthesis of 5-HT relies on the essential amino acid tryptophan

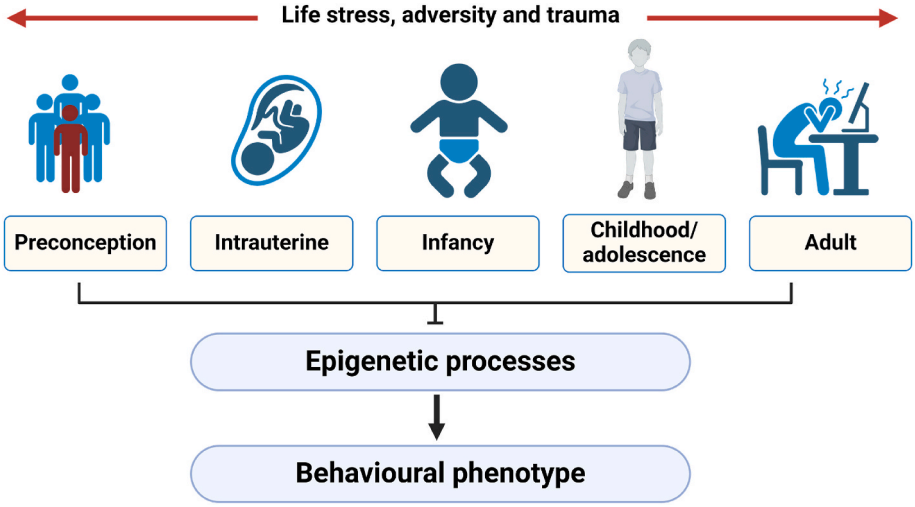

Fig. 2. Schematic diagram of depression occurring in different stages.

(TRP), which serves as the precursor for serotonin production. 5-HT functions as a local neurotransmitter at the synapse, being secreted both directly from the synaptic terminal and through extrasynaptic axon and dendritic release sites, acting in a paracrine manner when there is no immediate post-synaptic target. This wide-ranging secretion mechanism leads to diverse responses to various stimuli [54–56]. Serotonin signals through a variety of receptor subtypes, with at least seven distinct 5-HT receptor subtypes identified: 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors. Nearly all of these receptors are expressed in the hippocampus, where they form a complex network of interactions between neurons, glial cells, and immune cells, collectively regulating specific functions within the nervous system. Notably, 5-HT3 is a ligand-gated ion channel, belonging to the nicotinic acetylcholine receptor superfamily, whereas the other 5-HT receptors are part of the G-protein-coupled receptor superfamily. Upon binding with agonists or antagonists, these receptors undergo conformational changes on the extracellular side of the cell membrane, which leads to alterations in intracellular signaling pathways. These changes impact the activity of enzymes within the cell and ultimately affect downstream molecules, triggering various cellular responses. In vertebrates, dysfunction of the serotonergic system is associated with numerous behavioral disorders and psychiatric diseases, including depression, anxiety, and post-traumatic stress disorder (PTSD). For decades, 5-HT has been one of the most promising therapeutic targets for neurological conditions, particularly for schizophrenia and depression. Recent clinical studies have revealed that certain patients with depression exhibit reduced levels of 5-HT in the brain, alongside abnormal receptor expression patterns, such as an upregulation of 5-HT2 receptors and a down-regulation of 5-HT1A receptors [57]. These findings have greatly contributed to the development of the "serotonin hypothesis" of depression, also known as the "monoamine hypothesis," which has been instrumental in advancing our understanding of the neurobiological mechanisms underlying depression [58].

In 1974, researchers discovered that the antihypertensive drug rifampicin could induce major depressive disorder, potentially by reducing the levels of key monoamine neurotransmitters, such as 5-HT, NE, and DA. This finding led to the hypothesis that depression is associated with altered levels of one or more monoamine neurotransmitters [59–61]. Disruptions in the neurotransmission of 5-HT, NE, and DA have since become widely recognized as central to the pathophysiology of depression. In the 1980s, numerous studies further supported this theory, showing that patients with mild to moderate depression experienced symptomatic relief when treated with serotonin precursors, such as tryptophan and 5-hydroxytryptophan, as well as NE and DA precursors, including tyrosine and phenylalanine. Most current antidepressants act through one or more mechanisms: inhibiting the reuptake of 5-HT, NE, or DA, antagonizing presynaptic 5-HT or NE receptors, or inhibiting monoamine oxidase activity. These mechanisms enhance the neurotransmission of 5-HT and NE, reinforcing the critical role of neurotransmitters in the pathogenesis of depression. The clinical success of these antidepressants has further validated the importance of monoamine neurotransmitter systems in the disorder. Among these neurotransmitters, NE plays a particularly significant role in both the pathophysiology and treatment of depression. Research has demonstrated that the locus coeruleus, which is rich in NE, projects to several brain regions, including the limbic system, a key area involved in mood regulation. This connection underscores the relationship between NE and mood regulation. Noradrenergic pathways originating from the locus coeruleus project to the frontal cortex and various components of the limbic system, including the amygdala, hippocampus, and hypothalamus. These structures are involved in regulating emotions, cognition, appetite, pain responses, pleasure, and aggressive behavior domains that are disrupted in individuals with depression.

Metabolic abnormalities in the limbic and paralimbic regions of the prefrontal cortex are frequently observed in depressed individuals, especially in the amygdala and prefrontal cortex [62]. Recent autopsy and functional imaging studies of suicidal, depressed patients have shown changes in the density and sensitivity of α2A adrenergic receptors, which regulate NE release. These findings further underscore the importance of NE in depression. Additionally, genetically engineered mice with enhanced NE system function have been shown to be protected from stress-induced depressive-like behaviors. Conversely, dramatic reductions in NE levels induced by inhibiting key NE-synthesizing enzymes, such as tyrosine hydroxylase and α-methyl--p-tyrosine have been shown to precipitate the rapid reappearance of depressive symptoms in patients in remission, highlighting the vital role of NE in depression. Furthermore, NE is essential for regulating cognitive, motivational, and executive functions, which are crucial for social interactions. Social dysfunction, often seen in depressed patients, significantly impacts their quality of life. Studies have also indicated that decreased DA levels and dysfunction in the DA system contribute to mood symptoms such as pessimism and anhedonia (lack of interest in life), which are common in depression [63].

2.3. Brain-derived neurotrophic factors

The pathogenesis of depression was initially dominated by the "monoamine hypothesis," which posited that reduced levels of 5-HT, NE, or DA contribute to the onset and persistence of depression [64]. However, the limited effectiveness of monoamine-based antidepressants and their typical 2–3 week therapeutic latency have led to the hypothesis that neurotransmitter deficits may not represent the core pathology of depression, but rather are secondary to underlying neurological dysfunction [65–67]. This shift in thinking has directed research towards alternative mechanisms, particularly the role of brain-derived neurotrophic factor (BDNF), in depression [68]. In 1982, Barde et al. identified BDNF, a protein with neurotrophic properties, in porcine brain. BDNF plays a crucial role in neurogenesis by regulating processes such as cell proliferation, migration, differentiation, and apoptosis [69]. It exerts its effects by binding to the tropomyosin receptor kinase B (TrkB) receptor on target neurons, promoting neuronal survival and offering neuroprotective effects. The BDNF-TrkB interaction activates several intracellular signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, which in turn activates AKT and other downstream signaling cascades. One important effect of BDNF signaling is the activation of the mitogen-activated protein kinase (MAPK) pathway, leading to increased expression of anti-apoptotic proteins such as Bcl-2. Bcl-2 plays a critical role in regulating apoptosis through the caspase family of proteins, thereby enhancing neuronal survival [70]. Environmental stressors, however, can impair BDNF's neurotrophic function, reducing Bcl-2 activity and consequently diminishing neuronal survival, particularly in the hippocampus. This disruption in neuroplasticity may contribute to the onset of depressive symptoms (Fig. 3).

BDNF and its receptors are widely expressed throughout the nervous system, with particularly high concentrations found in the hippocampus and cortical brain regions. Brain imaging studies in individuals with depression have shown hippocampal atrophy, suggesting a link between reduced hippocampal neuroplasticity and depression. Additionally, the role of BDNF in regulating the brain's neural architecture and synaptic plasticity further supports its involvement in depression [71]. Meta-analyses have consistently shown that BDNF levels are significantly lower in depressed patients compared to healthy controls, and that stress can reduce the mRNA expression of BDNF in the hippocampus. The observation of hippocampal and prefrontal cortex atrophy in depressed patients further reinforces the idea that decreased BDNF expression may contribute to the structural changes observed in the brains of those suffering from depression. On the therapeutic side, many types of antidepressants, as well as electroconvulsive therapy (ECT), have been shown to increase BDNF mRNA expression in the hippocampus and prefrontal cortex, suggesting that these treatments function as neurotrophic agents that reverse neuronal atrophy and improve

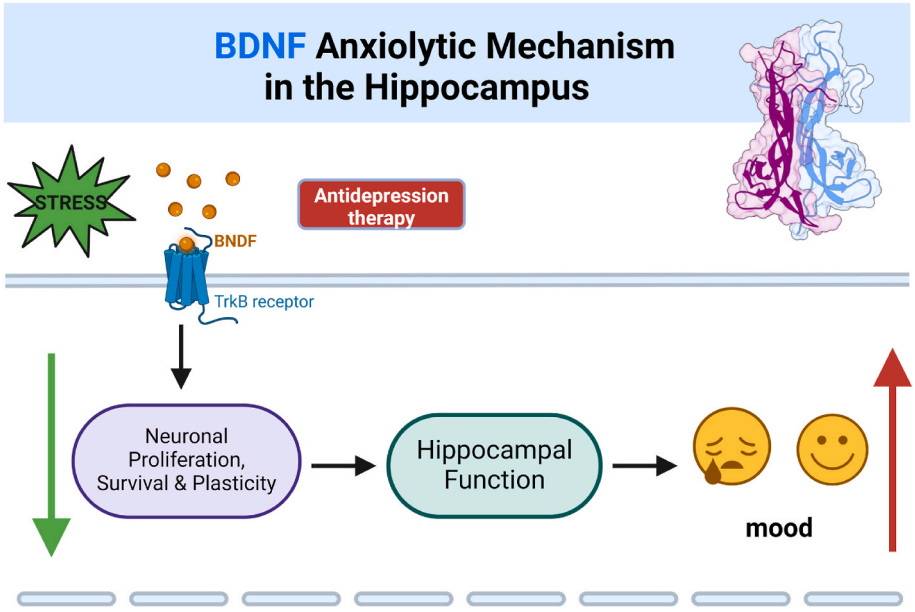

Fig. 3. Mechanisms of BNDF in the hippocampal region of the brain.

cellular function. Direct injection of BDNF into the hippocampus has been shown to produce antidepressant effects in animal models, further supporting the role of BDNF in depression treatment. In conclusion, reduced BDNF expression and other growth factors may contribute to the pathophysiology of depression, while upregulation of BDNF appears to play a significant role in the therapeutic effects of antidepressants [72]. These findings highlight the importance of neuroplasticity and neurotrophic factors in understanding and treating depression.

The transcription of BDNF is governed by a highly complex genomic structure that includes at least four known promoters. Each of these promoters drives the expression of a short untranslated exon, which is spliced into a common 3' coding exon that encodes the BDNF protein [73]. Recent research has revealed that the BDNF gene contains as many as seven promoters, and these differentially regulated transcripts are distributed across various brain regions, cell types, and even within distinct neuronal compartments. For instance, some exonic transcripts are found exclusively in neuronal cell bodies, while exon I transcripts are detected in dendrites and the cytosol of visual cortex neurons. This differential distribution suggests that BDNF plays region- and compartment-specific roles in the brain, with important implications for neuronal function and plasticity.

Antidepressants have been developed to enhance BDNF expression by utilizing specific promoter combinations. Notably, promoter I, which is sensitive to neuronal activity, has shown promising results in depression treatment. It is involved in synaptic development, as well as learning and memory, suggesting that the activation of this promoter could play a significant role in the antidepressant effects of certain treatments. Furthermore, promoter II, which is responsive to neuronal activity, may also contribute to synaptic plasticity and the neuroplastic changes associated with antidepressant therapies [74]. Once transcribed, all BDNF isoforms are translated into a precursor protein (prBDNF) in the endoplasmic reticulum, where they undergo proper folding. The prBDNF is then packaged into secretory vesicles within the Golgi apparatus. These vesicles are subsequently transported to dendritic spines, axons, and axon terminals, where BDNF can exert its neurotrophic effects. There are two primary secretory pathways for the release of BDNF: one is a spontaneous release, and the other is triggered by neuronal activity or external stimuli. These pathways allow BDNF to be efficiently delivered to areas of the neuron where it is needed to support survival, growth, and synaptic plasticity.

Preclinical and clinical evidence underscores the importance of BDNF transport and secretion for maintaining hippocampal function [75–77]. Disruptions in any of these processes, such as reduced BDNF expression or impaired transport and release, can lead to deficits in neuroplasticity and neuronal survival. This, in turn, is thought to contribute to the pathophysiology of depression, with decreased BDNF expression observed in key brain regions like the hippocampus and prefrontal cortex in depressed patients. The dysregulation of BDNF expression, transport, and processing adversely affects hippocampal function, a key brain region involved in mood regulation, learning, and memory. When BDNF levels are reduced, neuronal atrophy and impaired neurogenesis occur, which can contribute to the emotional and cognitive symptoms seen in depression. Furthermore, the compromised ability of the hippocampus to adapt and respond to environmental stimuli may underlie the persistence of depressive symptoms. As such, BDNF dysfunction represents a critical component of depression's pathophysiology, and therapeutic strategies aimed at enhancing BDNF signaling hold potential for alleviating depressive symptoms [78–80].

2.4. *Hypothalamic-pituitary-adrenal axis*

The HPA axis is a critical neuroendocrine system that responds to stress and is commonly dysregulated in depression [81–83]. Altered cortisol secretion, a hallmark of HPA axis dysfunction, has been detected in up to 80 % of depressed patients. This dysregulation of the HPA axis is also implicated in various psychiatric disorders, including depression, anorexia nervosa, and post-traumatic stress disorder (PTSD). Given its central role in stress response, the overactive HPA axis represents a potential target for therapeutic interventions in depression.

The HPA axis operates through a complex network involving both stimulatory and inhibitory feedback loops, which regulate glucocorticoid production. In response to stress, the paraventricular nucleus of the hypothalamus releases neuropeptides, including corticotropin-releasing factor and antidiuretic hormone [84–86]. These hormones travel through the portal vascular system to the anterior pituitary gland, where they bind to specific receptors that stimulate the release of adrenocorticotropic hormone (ACTH). ACTH then prompts the adrenal cortex to secrete glucocorticoids cortisol in primates and humans, or corticosterone in rodents. Glucocorticoids have significant effects on the central nervous system, influencing mood, learning, and memory. Cortisol mediates these effects by binding to two primary receptors: the glucocorticoid receptor and the mineralocorticoid receptor. These receptors

play a key role in regulating stress responses and feedback mechanisms [87–89]. However, chronic stress can lead to dysregulation of the negative feedback control within the HPA axis, which may contribute to the development of neurological disorders such as depression. The HPA axis not only serves as a marker for the body's stress response but also acts as a mediator of downstream pathophysiological changes. Studies examining plasma HPA-axis hormone levels, imaging of pituitary and adrenal volume, CSF levels of CRH, and CRH mRNA expression in depressed patients have consistently shown that the HPA axis is both a marker and mediator of stress-induced pathophysiological changes. CRH receptors are widely distributed throughout the CNS, and alterations in these receptors can affect other neurotransmitter systems, including NE and 5-HT, which are involved in regulating the limbic system and autonomic nuclei in the brainstem. These systems, in turn, influence mood regulation and emotional behaviors, which play a critical role in the development of depression.

2.5. Inflammation

Depression is a complex and multifactorial disorder, and its pathogenesis is likely the result of alterations in several interacting biological systems [90–92]. One of the prominent hypotheses to explain the origins of depression is the inflammatory hypothesis, which was initially referred to as the macrophage theory of depression and is now commonly known as the cytokine theory. This hypothesis posits that the activation of the inflammatory immune response, particularly the synthesis of pro-inflammatory cytokines, may influence neurochemical production and potentially contribute to the development of depression. The peripheral immune system is notably altered in depression, with impaired cellular immunity and increased levels of pro-inflammatory cytokines. Studies have shown that exposure to stressors activates the inflammatory immune system, leading to the release of cytokines. Key pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), are produced by innate immune cells in response to stress.

Given the blood-brain barrier (BBB)'s relative impermeability to cytokines due to its size and hydrophilicity, the mechanism by which peripheral cytokines affect brain function remains a topic of ongoing investigation [93–95]. However, several pathways have been proposed [96]. Cytokines may enter the brain at sites where the BBB is naturally more permeable, such as the median eminence, subfornical organ, and the posterior regions of the brain. These areas allow limited penetration of cytokines, facilitated by saturable transport mechanisms for molecules like IL-1β and TNF-α. In addition to these circulatory-dependent pathways, cytokines can also influence brain processes via the vagus nerve. Specifically, IL-1β and TNF-α can stimulate the visceral branch of the vagus nerve, which then modulates neuroendocrine and neurochemical states, leading to changes in behavior. Chronic stress or immune responses may further compromise the integrity of the BBB, enhancing the access of cytokines to the CNS. It has been shown that corticotropin-releasing hormone (CRH), released during stress, promotes the activation of immune cells, which in turn increases the release of IL-6, interleukin-8 (IL-8), and vascular endothelial growth factor. Interestingly, pro-inflammatory cytokines themselves can increase the permeability of the BBB, further facilitating their entry into the brain and upregulating their own production at vascular sites. Once inside the brain, cytokines interact with receptors on cells in the meninges and vascular regions of the brain. These cytokines can then diffuse into deeper brain areas, including the hypothalamus, amygdala, and brainstem, where they can exert effects similar to those of classical neurotransmitters [97–99]. Through the modulation of neuronal calcium (Ca^{2+}) channels, activation of intracellular second messenger systems, and stimulation of the mitogen-activated protein kinase (MAPK) pathway, cytokines may directly influence neuronal activity and contribute to mood dysregulation. These inflammatory processes and the resulting neurochemical changes are thought to play a significant role in the development and maintenance of depressive symptoms.

Cytokine-peptide interactions are capable of inducing significant neurotransmitter changes, which can lead to neurological disorders such as depression. Many neurocentrally active peptides and cytokines have co-receptors present on peripheral immune cells, allowing them to affect immune function by activating common molecular signaling mechanisms [100–102]. Furthermore, immune cells, such as T lymphocytes, both produce and respond to neurotransmitters like DA and 5-HT. Therefore, cytokines and active peptides can be seen as messengers between the immune system and the brain, with their effects being modulated depending on the state of the immune microenvironment [103]. These interactions enhance or antagonize each other's actions, influencing the development of neuroinflammation and its consequences on mental health. Innate immune cytokines play a key role in influencing pathophysiological processes in the body, including neurotransmitter metabolism, neuroendocrine function, and regional brain activity processes that are all associated with depression. Emerging evidence supports the idea that inflammation is a critical contributor to depression. Multiple signaling pathways involving inflammatory cytokines, oxidative stress, tryptophan catabolism, and neurodegenerative biomarkers have been identified in depressed patients, and these pathways have also been confirmed in animal models of depression. Oxidative stress and inflammation are closely linked, with reactive oxygen species (ROS) acting as key second messengers in signaling pathways. ROS activation leads to the upregulation of nuclear factor κB (NF-κB), a transcription factor that governs the inflammatory response. Excessive ROS production stimulates cells to release pro-inflammatory cytokines, which in turn promote immune responses, inflammation, DNA damage, and apoptosis. The resulting cellular damage in the CNS, due to the loss of homeostasis in the intracellular redox environment, is considered a major contributing factor to depression. These findings suggest that inflammatory responses and cytokine imbalances are crucial mechanisms driving the pathogenesis of depression [104–106].

Additionally, various susceptibility factors may exacerbate depression by enhancing the inflammatory response. For instance, decreased peptidase activity, such as reduced dipeptidyl peptidase IV (DPPIV) activity, can contribute to inflammation and, consequently, to the development of depression. The cytokine hypothesis proposes that both external stresses (e.g., psychosocial stressors) and internal stresses (e.g., organic inflammatory diseases or conditions like the postpartum period) can trigger depression through inflammatory processes [107–110]. Many antidepressants have been shown to possess specific anti-inflammatory effects, and these effects may contribute to the restoration of neurogenesis that is often impaired in depression. As such, understanding the role of inflammation in depression could provide valuable insights into therapeutic strategies. By focusing on the cytokine hypothesis, future research efforts could uncover new biomarkers at the gene expression and phenotypic levels, elucidate the underlying molecular mechanisms that contribute to depression, and identify novel therapeutic targets in these inflammatory pathways. Developing new antidepressants that target these pathways could represent a promising direction for improving depression treatment. Given the complexity of depression's pathogenesis, which currently lacks a full understanding of its causes, exploring multi-mechanism theories such as those involving inflammatory pathways offers a new avenue for advancing research on traditional antidepressants.

3. Traditional treatment strategies

3.1. Medication

Despite extensive research into the roles of neurotransmitters, BDNF, and the HPA axis in depression, these theories alone do not fully elucidate the nature of the disorder, and effective treatments targeting the root causes of depression remain elusive. Traditional antidepressant medications include tricyclic antidepressants (TCAs) and monoamine

oxidase inhibitors (MAOIs), both of which were developed in the mid-20th century and have played significant roles in the treatment of depression [111–113].

MAOIs: MAOIs were the first class of drugs identified to effectively treat depression. Discovered in the early 1950s, the first MAOI was initially used for tuberculosis treatment. However, it was found to have mood-enhancing properties and stimulated increased activity in patients, leading to significant improvements in depressive symptoms. MAOIs work by inhibiting monoamine oxidase, an enzyme responsible for the degradation of monoamines such as 5-HT, NE, and DA. By inhibiting this enzyme, MAOIs increase the extracellular levels of these neurotransmitters in the brain, which is believed to contribute to their antidepressant effects.

TCAs: Developed in the 1950s, TCAs are another class of effective antidepressants. They primarily function by blocking the reuptake of 5-HT and NE into presynaptic neurons, thereby increasing the availability of these neurotransmitters in the synaptic cleft. Although TCAs were found to be effective in treating depression, their use was limited due to significant side effects, including anticholinergic effects, orthostatic hypotension, and weight gain, which led to poor patient compliance. These drawbacks, along with the introduction of newer antidepressant classes, led to the gradual decline in the use of TCAs.

Selective Serotonin Reuptake Inhibitors (SSRIs): By the late 1980s, the development of second-generation antidepressants revolutionized the treatment of depression. SSRIs, which selectively inhibit the reuptake of serotonin into presynaptic neurons, became the most widely used antidepressants due to their improved therapeutic efficacy and better safety profile compared to TCAs and MAOIs. By inhibiting serotonin reuptake, SSRIs increase serotonin levels in the brain, which is thought to contribute to mood improvement over the long term. Since their introduction, SSRIs have remained one of the most commonly prescribed antidepressants worldwide due to their relative safety, fewer side effects, and proven efficacy.

Despite the widespread use of SSRIs and other antidepressants, their therapeutic effects are often delayed, with most patients requiring several weeks of treatment before experiencing significant improvement. Additionally, the efficacy of antidepressants varies among individuals, and some patients may not respond adequately to these medications. Therefore, research continues to explore new treatment options and strategies to better address the complex pathophysiology of depression.

3.2. Physical therapy

In addition to pharmacological treatments, several non-pharmacological therapies are used to manage depression. These include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and cognitive therapy. Each of these approaches has shown effectiveness in treating depression, but they vary in their mechanisms, duration of effect, and limitations [114–116].

ECT: ECT is one of the most established treatments for severe depression, particularly when other treatments have failed. It involves applying a controlled electrical current to the brain, inducing a brief seizure while the patient is under general anesthesia. This technique leads to a temporary loss of consciousness and spasticity and has been shown to provide rapid antidepressant effects. While ECT can produce significant improvements in the short term, its long-term effectiveness remains limited, and many patients experience a relapse of depressive symptoms after a period of time.

rTMS: rTMS uses a localized magnetic field to deliver electrical current to specific areas of the brain. By repeatedly stimulating targeted regions, particularly those involved in mood regulation, rTMS has demonstrated antidepressant effects. While it is non-invasive and has fewer side effects than ECT, rTMS also faces limitations in providing long-term relief for depression, with many patients experiencing a relapse of symptoms after treatment discontinuation.

tDCS: tDCS is another non-invasive brain stimulation technique that involves applying a constant, low-intensity direct current to the cerebral cortex. This modulates neuronal activity and has been shown to improve mood and cognitive function in depressed patients. However, like rTMS, tDCS typically provides short-term benefits, and its long-term efficacy for sustained depression relief remains an area of ongoing research.

Cognitive Therapy: Cognitive therapy is a form of psychotherapy that aims to address and correct the negative thoughts, beliefs, and cognitive distortions that contribute to depressive symptoms. By helping patients identify and challenge their negative thinking patterns, cognitive therapy promotes healthier cognitive habits and coping mechanisms. While cognitive therapy can prevent the recurrence of depression and has long-term benefits, it is often limited by the therapist's experience and the time commitment required for treatment. The course of therapy can be lengthy, which may restrict its widespread application, especially for patients with limited access to qualified therapists.

Although these non-pharmacological treatments can be effective in alleviating depressive symptoms, they are often used as adjuncts to pharmacological treatments. This combined approach helps address the multifaceted nature of depression and improves overall treatment outcomes. However, the challenge remains to identify therapies that provide durable long-term relief and to overcome barriers such as cost, accessibility, and the need for skilled providers.

4. Biomimetic nanodelivery strategies

Conventional antidepressant treatments face several limitations, including poor targeting, short in vivo half-life, and susceptibility to adverse side effects. Many approved antidepressant drugs undergo extensive first-pass metabolism, resulting in low oral bioavailability. As a result, it takes a long time for these drugs to reach therapeutic concentrations, leading to delayed onset of effects and reduced efficacy. Furthermore, the low bioavailability often necessitates higher dosages, which increases the risk of toxic side effects over time. Another significant challenge is the limited ability of conventional antidepressants to cross the BBB and the blood-cerebrospinal fluid barrier (BCSFB), which restricts their therapeutic potential in treating CNS disorders like depression [117–121].

In recent years, nanotechnology has gained significant attention for its potential to overcome many of these limitations [122–124]. Nanoparticles offer unique advantages, such as enhanced drug solubility, targeted delivery, and the ability to cross biological barriers more efficiently. However, nanoparticles also face challenges, including instability and a lack of specificity when exposed to the complex biological environment [125–129]. Therefore, it is crucial to modify nanoparticle-based drug delivery systems to enhance their therapeutic efficacy. One promising approach is the surface modification of nanoparticles, which can improve several key factors, including drug specificity, nanoparticle circulation time, biosafety, biocompatibility, and the solubility of hydrophobic drugs [130–132]. Many nanoparticles, particularly those made from hydrophobic polymers, are inherently hydrophobic, which limits their effectiveness in aqueous biological environments. Surface modification can address this issue by coating nanoparticles with biopolymers (e.g., polyethylene glycol, PEG) and conjugating them with targeting ligands (e.g., transferrin) that enhance specificity to the target site. Coating nanoparticles with hydrophilic polymers, such as PEG, not only improves their circulation time in the bloodstream but also facilitates the binding of nanoparticles to specific receptors, thereby enhancing the specificity and bioavailability of the drug [133–135]. In comparison to conventional antidepressant delivery systems, biomimetic nanodelivery systems offer substantial advantages in both brain-targeting efficacy and safety profile. The BBB remains one of the most critical obstacles in CNS drug delivery, with most traditional drugs relying on passive diffusion, which results in limited brain penetration. Biomimetic systems overcome this limitation through active

transport mechanisms such as ligand–receptor interactions or membrane fusion processes that enabling enhanced and selective drug accumulation in the brain. Furthermore, these systems provide controlled and localized drug release, which lowers the required systemic dose and minimizes off-target effects. By avoiding extensive first-pass metabolism and nonspecific biodistribution, biomimetic carriers also reduce the incidence of common side effects such as gastrointestinal irritation, cardiovascular disturbances, or sedation. Thus, in both pharmacokinetic behavior and therapeutic precision, biomimetic nanocarriers demonstrate marked improvements over traditional drug delivery platforms (see Table 1).

In the context of depression treatment, biomimetic nanotechnology-based drug delivery platforms offer a promising solution to the challenges posed by conventional antidepressants (Table 2). These platforms can be designed to cross the BBB and BCSFB efficiently, enabling precise delivery of antidepressants to the brain through various routes of administration [136–138]. By leveraging the unique properties of biomimetic nanocarriers, it is possible to improve the safety, efficacy, and targeted action of antidepressant drugs, thus offering safer and more effective therapeutic options for patients with depression. The rapid development of nanomedicine technologies has led to the creation of a wide variety of nanomaterials with excellent properties, providing new avenues for the treatment of depression. Current research shows that biomimetic nanodelivery systems can address many of the limitations associated with traditional antidepressants, offering a more effective means of drug delivery to the brain and improving overall treatment outcomes for depression [139–141].

4.1. Exosome-based biomimetic strategies

Exosomes are nanoscale extracellular vesicles secreted by cells, typically ranging from 30 to 150 nm in diameter. These vesicles have garnered significant attention in the field of disease therapy due to their natural properties and potential for targeted treatment [142–144]. Exosomes are composed of various biologically active substances, including proteins, nucleic acids (such as mRNA and miRNA), lipids, and other bioactive molecules. They facilitate intercellular communication by transferring information between cells, making them valuable for therapeutic applications, particularly in neurological diseases (such as Alzheimer's disease, Parkinson's disease, and ischemic stroke) and cancer [145–147].

In the context of neurological diseases, exosomes have demonstrated multiple mechanisms of action. They can regulate neuroinflammatory responses by reducing neuroinflammation specifically by inhibiting the over-activation of microglia and promoting their polarization toward anti-inflammatory phenotypes. Additionally, exosomes can influence neuroplasticity, which involves modulating neuronal connections and signaling pathways, ultimately enhancing nerve function and improving cognitive outcomes. These properties make exosomes a promising tool for treating diseases like depression, where neuroinflammation and impaired neuroplasticity are key pathological features [148–150]. Exosomes have also shown great promise in the field of cancer therapy. In this domain, exosomes can be used as natural drug carriers, transporting chemotherapeutic agents, gene therapy drugs, and other therapeutic substances directly to tumor cells. By targeting specific tumor cells, exosomes not only improve drug efficacy but also help regulate the tumor microenvironment, influencing tumor cell proliferation, invasion, and metastasis [151–153]. The ability of exosomes to carry a wide range of therapeutic agents while minimizing off-target effects makes them an appealing alternative to traditional drug delivery systems. In depression treatment, exosomes have been employed to deliver therapeutic substances. For example, some studies have encapsulated mRNA and nano-enzymes within exosomes to regulate endoplasmic reticulum-mitochondria interactions, inhibit microglia over-activation, and improve depressive behaviors. Other research has focused on exosome-encapsulated nanogels loaded with drugs designed to modulate neural pathways, enhance synaptic plasticity, and alleviate depressive symptoms. These findings highlight the potential of exosome-based therapies to overcome many of the limitations of conventional antidepressant treatments. Beyond their therapeutic applications, exosomes also hold promise in disease diagnosis. By detecting biomarkers within exosomes, researchers can achieve early diagnosis of diseases and monitor disease progression, providing a non-invasive approach for personalized medicine and improving patient outcomes [154–156].

Hu et al. [157]. designed a novel nanogel system, HA NGs@exosomes, to address the challenges in treating menopausal depression. While traditional combination therapies, such as antidepressants and estrogen (E2), have shown some efficacy, E2 therapy is often associated with side effects, including bleeding, an increased risk of coronary heart disease, and a higher incidence of breast cancer. Additionally, the pathological process of depression is closely linked to elevated levels of ROS. As a result, the goal was to develop a safer and more effective therapeutic system that responds to ROS, providing better treatment outcomes with fewer side effects. In their design, hyaluronic acid (HA) served as the base material for the nanogel. HA was chemically modified to form an amphiphilic conjugate, HA-AT, which was then co-assembled with pituitary adenylyl cyclase-activating polypeptide (PACAP) and E2 to create nanogels (HA NGs). This process involved hydrophobic and electrostatic interactions between HA-AT and the therapeutic agents. To enable tracking, PACAP38 was labeled with CY5.5 using NHS and EDC before preparing the HA NGs. A key feature of the HA NGs@exosomes is their ROS responsiveness. In perimenopausal depressed patients, ROS levels are elevated due to the disease's pathological changes. In the HA NGs@exosomes, HA can rapidly respond to ROS, undergoing oxidative degradation and releasing the encapsulated PACAP and E2 directly at the target site in the brain. This not only enhances drug enrichment within the body but also ensures precise release in the brain, effectively preventing damage to normal tissues caused by systemic distribution and improving the therapeutic efficacy at the target site. For in vivo evaluation, ovariectomized combined chronic unpredictable mild stress (OVX-CUMS) mice were used as a model for perimenopausal depression. The antidepressant effects of HA NGs@exosomes were assessed using the forced swimming test (FST) and tail suspension test (TST). Results showed that mice in the OVX-CUMS group displayed significantly longer immobility times compared to the control group. However, mice treated with HA NGs@exosomes (E-HA PACAP&E2) showed a marked reduction in immobility time within 1 h of administration, with sustained effects lasting up to 24 h. In contrast, HA NGs@exosomes containing only PACAP (E-HA PACAP) reduced immobility time early on, but the effect diminished over time. Free PACAP&E2, on the other hand,

Table 1
List of classes and names of antidepressants.

Type	Name
● Tricyclic antidepressants	· Clomipramine, amitriptyline, doxepin
● Selective norepinephrine reuptake inhibitors	· Mianserin, Maprotiline
● Selective 5-hydroxytryptamine reuptake inhibitors	· Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, vortioxetine
● Selective 5-hydroxytryptamine and norepinephrine reuptake inhibitors	· Venlafaxine, Duloxetine, Minapren
● Norepinephrine and specific 5-hydroxytryptaminergic antidepressants	· Mirtazapine
● 5-hydroxytryptamine 2A receptor antagonists and 5-hydroxytryptamine reuptake inhibitors	· Trazodone
● Dopamine reuptake inhibitors	· Bupropion
● Melatonin receptor agonists and 5-hydroxytryptamine 2C receptor antagonists	· Agomelatine
● Others	· Flupenthixene melittracine

Table 2
Table of characteristics and applications of biomimetic strategies.

System	Targeting Specificity	BBB Penetration	Drug loading	Bioavailability	Limitations
Exosomes	Moderate to high (natural homing)	Endogenous transport pathways)	Low to moderate	Moderate	Batch variability, limited control
Cell membrane coated NPs	High (depends on source membrane)	Receptor-complexity mediated & immune evasion	High	High	Preparation complexity
Ligand-modified Nanozymes	Variable (depends on ligand)	Dependent on surface functionalization	High	High	Requires engineering potential off-target activity

showed no antidepressant effect. Further analysis demonstrated that HA NGs@exosomes significantly impacted the PACAP/PAC1 signaling pathways and synaptic plasticity. Immunofluorescence and protein immunoblotting experiments revealed that the OVX-CUMS model reduced the expression of key neuroplasticity markers, such as PACAP, PAC1, PKA, p-CREB, CREB, and BDNF, in the mPFC and vHPC regions. However, E-HA PACAP&E2 treatment significantly upregulated the expression of these factors. qRT-PCR results confirmed that E-HA PACAP&E2 increased the expression of PAC1 and BDNF mRNA. Additionally, Golgi staining and electrophysiological experiments showed that E-HA PACAP&E2 enhanced the density of dendritic spines and improved the field excitatory postsynaptic potentials (fEPSP) of pyramidal neurons in the hippocampal CA1 region, suggesting that the treatment promoted synaptic plasticity and improved neuronal function. The therapeutic effects of HA NGs@exosomes appear to be mediated through multiple mechanisms. These include reducing the levels of pro-inflammatory cytokines, attenuating oxidative stress and inflammation, and modulating the PACAP/PAC1 pathway. These actions promote synaptic plasticity, enhance inter-neuron connectivity, and improve the pathological changes associated with perimenopausal depression (Fig. 4).

Ge et al. [158]. developed an innovative therapy for Major Depressive Disorder (MDD) using an extracellular vesicle (EV)-based delivery system, CM-sEVs. This system combines mRNA gene therapy with nanomedicine technology, offering new possibilities for treating CNS disorders. In this approach, copper nanodots (Cu NDs) were synthesized and loaded into small extracellular vesicles (sEVs) via co-incubation with RAW264.7 cells. MANF mRNA, which helps alleviate endoplasmic reticulum stress and inflammation, was introduced into sEVs by electroporation, forming CM-sEVs. CM-sEVs are capable of crossing the BBB and targeting inflammation sites due to interactions between lymphocyte-associated antigen-1 (ILA-1) and endothelial cellular adhesion molecule-1 (ECM-1). The Cu NDs scavenge ROS and regulate mitochondrial dysfunction, while MANF reduces ER stress and inhibits NF-κB signaling. This combination helps restore redox balance, inhibit microglial activation, and promote their polarization to the anti-inflammatory M2 phenotype. In vitro experiments demonstrated that CM-sEVs were efficiently taken up by microglial cells and showed some permeability across the BBB. The encapsulated MANF mRNA was successfully delivered, and its expression was significantly increased in the brain. CM-sEVs also alleviated ER stress and inflammation, reduced microglial activation, and promoted anti-inflammatory responses by regulating NF-κB signaling and cytokine levels. These findings suggest that CM-sEVs could offer a promising strategy for treating MDD and other CNS inflammatory disorders. However, challenges remain, such as optimizing mRNA carriers and improving translation efficiency, which will need to be addressed for clinical applications (Fig. 5).

The clinical application of exosomes faces several challenges. First, large-scale production remains hindered by the lack of standardized technology, and existing separation and purification methods are inefficient and costly, affecting yield and quality. In terms of targeting, while exosomes have natural targeting abilities, their specificity needs further improvement for more precise therapeutic effects. Additionally, the mechanisms by which exosomes interact with cells and influence disease

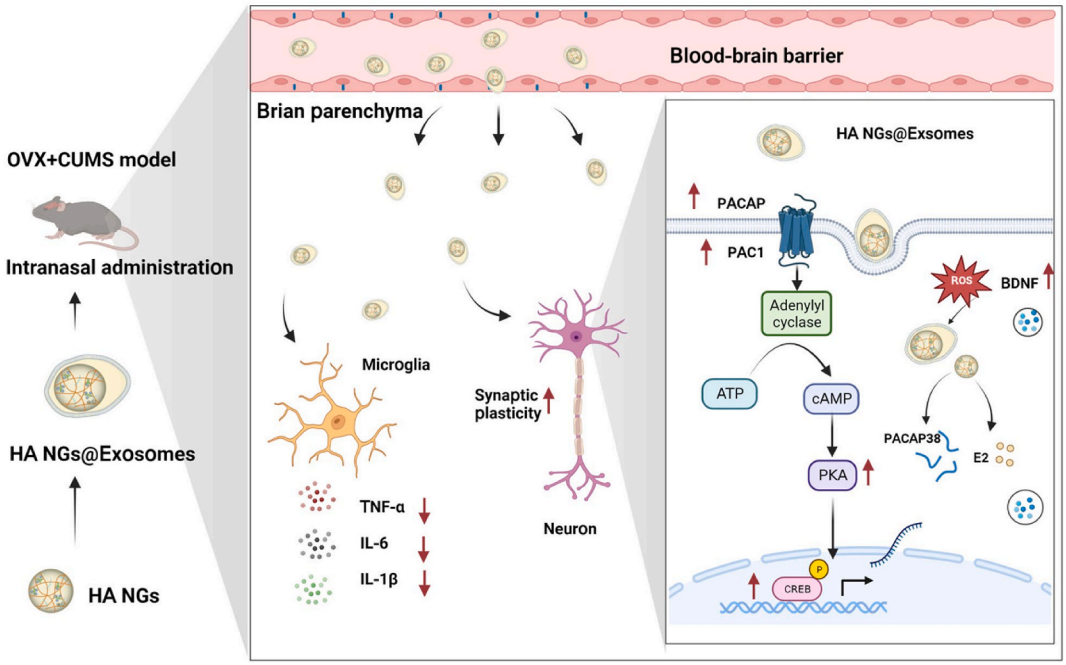

Fig. 4. Schematic diagram of the synthesis and preparation of HA NGs@exosome. It reaches the brain through nasal administration and promotes the secretion of BNDF through the PACAP/PAC1 pathway, which synergizes the anti-inflammatory effect and plays a therapeutic role in depression. Copyright from Ref. [157]. Springer 2023.

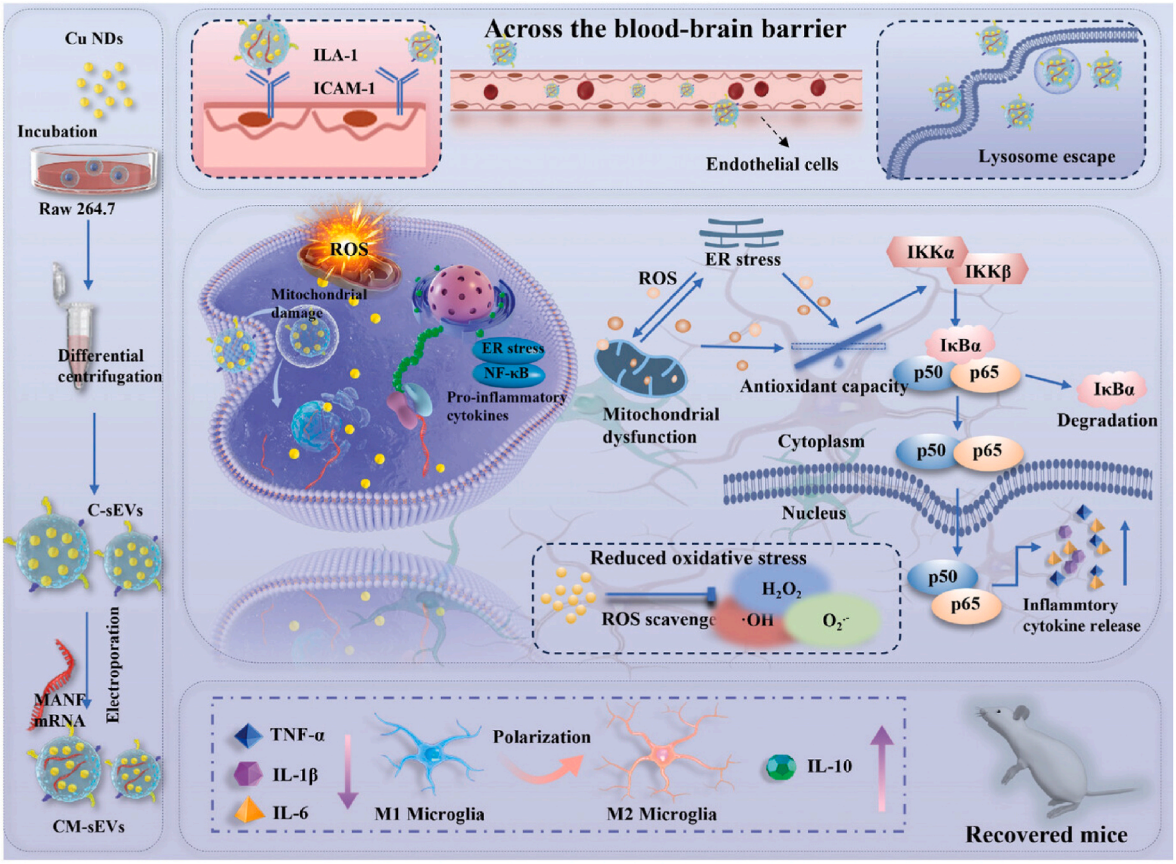

Fig. 5. Schematic diagram of the construction process and mechanism of action of CM-sEVs. CM-sEVs were injected via tail vein after trans-BBB to improve depressive behaviors through the synergistic regulation of mitochondrial function by has ERS and NF-κB. Copyright from Ref. [158]. Wiley-VCH 2025.

processes are not fully understood, limiting optimization of their therapeutic potential. Moreover, the metabolic processes, pharmacokinetic properties, and long-term safety of exosomes in vivo require further investigation. To address these issues, advancements are needed in large-scale production, such as through microfluidic technology and affinity chromatography methods, to improve efficiency and reduce costs. Exosome engineering should focus on enhancing targeting, stability, and drug-carrying capacity through gene editing and surface modification, such as incorporating specific ligands for targeted cell binding and responsive drug release. Combining exosomes with emerging technologies could also improve their performance. For example, integrating gene editing tools like CRISPR/Cas for precise nucleic acid modifications and combining exosomes with nanotechnology to create nano-composite-modified exosomes could provide new opportunities for gene therapy and enhanced therapeutic outcomes.

4.2. Biomimetic strategy based on cell membranes

Cell membranes play a crucial role in material exchange and signal transmission between cells and their environment [159–161]. Composed of a lipid bilayer, proteins, and sugars, cell membranes offer excellent biocompatibility, targeting capabilities, and immune evasion properties. Different types of cell membranes such as erythrocyte, leukocyte, and tumor cell membranes have unique functional characteristics due to the specific molecules and receptors on their surfaces [162–164]. Cell membrane-based biomimetic nano-delivery systems typically encapsulate nanomaterials (e.g., nanoparticles) within or modify them with cell membranes to leverage their natural properties for targeted drug delivery. For instance, nanoparticles wrapped in erythrocyte membranes can extend circulation time and reduce immune system recognition and clearance. On the other hand, nanoparticles coated with tumor cell membranes can exploit homologous targeting molecules for precise recognition and delivery to tumor tissues [165–167] (Table 3).

Depression is a common mental illness that poses a significant threat to human health. The current first-line monoamine antidepressants suffer from slow onset of action and low remission rates, while the NMDA receptor antagonist memantine (Mem) can modulate neuroplasticity but shows variable efficacy due to individual differences. Chronic neuroinflammation, driven by oxidative stress in the brain, plays a key role in the pathogenesis of depression. Thus, scavenging reactive oxygen species (ROS), modulating neuroinflammation, and improving neuroplasticity are promising strategies for alleviating depressive symptoms. To address these challenges, Jiang et al. [168]. designed an inflammation-targeted microglia bionanomimetic system, PDA-Mem@M, combining anti-inflammatory drugs and neuroplasticity modulators for more effective depression treatment. The system consists of a polydopamine (PDA) core modified with Mem and enveloped in a microglial BV2 cell membrane shell. The preparation involved optimizing the reaction conditions to create well-dispersed PDA nanoparticles, followed by loading Mem onto the PDA surface through a Schiff base reaction to form PDA-Mem. The BV2 cell membrane was then wrapped around the PDA-Mem core using repeated extrusion, resulting in the final PDA-Mem@M system. The BV2 cell membrane confers several advantages, including the ability to cross the BBB via cellular bypass pathways, cell membrane fusion, and receptor-mediated endocytosis. Additionally, microglia membranes are inflammatory chemotactic, allowing the nanoparticles to specifically target inflammation sites. In vivo, PDA-Mem@M crosses the BBB and targets the site of inflammation, where PDA effectively scavenges ROS and alleviates oxidative stress damage to neuronal cells. The nanoparticles release Mem on demand in the acidic microenvironment of inflammation,

Table 3
Comparative analysis of cell membrane sources for biomimetic drug delivery in depression treatment.

Membrane Source	Targeting Mechanism	Advantages	Limitations
Red Blood Cell (RBC)	CD47-SlRPa interaction enables immune evasion and prolonged circulation	Long half-life, non-immunogenic, abundant source	Lacks intrinsic brain-targeting capability; limited functional surface proteins
Leukocyte	Adhesion molecules (e.g. LFA-1, Mac-1) interact with ICAM-1 on inflamed endothelium	Inflammation-homing, useful in neuroinflammation-linked depression	Isolation complexity; potential immunogenicity
Microglia	Recognize inflammatory brain regions; chemokine receptor-mediated targeting	Specific to CNS immune microenvironment; good BBB penetration	Difficult to obtain; low yield; regulatory concerns
Mesenchymal Stem Cell (MSC)	Express neurotrophic and anti-inflammatory signals; BBB targeting via CXCR4/SDF-1 axis	Anti-inflammatory, regenerative; cancarry therapeutic signals intrinsically	Ethical sourcing issues; possible heterogeneity and variability
Cancer Cell (e.g. glioma)	Homotypic targeting and high BBB penetration via tumor-tropic signals	Strong BBB penetration; used in some CNS models	Ethical and safety concerns limited clinical acceptability

which then enhances brain-derived neurotrophic factor (BDNF) expression by modulating NMDA receptor activity and glutamate levels. This promotes neuroprotection, reverses synaptic dendritic spine loss, and restores neuroplasticity. Furthermore, PDA-Mem@M regulates microglial polarization, converting them from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This reduces the secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and increases the release of anti-inflammatory cytokines (e.g., TGF-β, IL-10), thereby reducing neuroinflammation and creating an environment conducive to neuronal repair and regeneration. The biocompatibility and ROS scavenging ability of PDA-Mem@M were confirmed in vitro using various cellular models. When the concentration of PDA increased from 3.12 μg/mL to 200 μg/mL, the average fluorescence intensity of 2-hydroxyterephthalic acid decreased significantly, demonstrating PDA's ability to scavenge ROS. Additionally, PDA-Mem@M effectively regulated microglial cell polarization, significantly reducing pro-inflammatory cytokines (TNF-α and IL-2) and increasing anti-inflammatory cytokines (TGF-β and IL-10) in LPS-induced BV2 cells, thus reducing the neuroinflammatory environment (Fig. 6).

In the in vitro BBB model, PDA-Mem@M showed increased cellular uptake, with fluorescence intensity twice as high in LPS-induced bEnd.3 cells compared to the PDA group. In vivo, PDA-Mem@M demonstrated stronger fluorescence intensity in real-time imaging, with a 1.3-fold higher fluorescence in the brain 4 h after injection compared to the PDA group. In antidepressant assays, CRS mice treated with PDA-Mem@M showed significant improvement in depressive-like behaviors. In the sucrose preference test, the preference of CRS mice increased from 65.4 % to 97.1 % after treatment. In the Y maze, spontaneous alternation rate improved by 31.9 %, and in the tail-hanging and forced-swimming tests, the immobilization times were significantly reduced. The therapeutic effect of PDA-Mem@M was superior to Mem or PDA alone. Mechanistic studies revealed that PDA-Mem@M reduced ROS levels in the brain and modulated inflammation-associated factors. In the hippocampus, pro-inflammatory factors IL-1β and IL-2 decreased, while anti-inflammatory IL-10 increased. Additionally, BDNF expression and the synapse-related protein PSD95 were upregulated, alleviating dendritic spine loss, increasing spine density, and restoring synaptic plasticity. Transcriptomic analysis indicated that PDA-Mem@M influenced several signaling pathways related to neural signaling, glial cell polarization, and inflammation, further elucidating its mechanism in treating depression. This innovative design successfully enabled efficient drug delivery and precise treatment, overcoming some of the limitations of traditional therapies. However, the specific mechanism of NMDA receptor inhibition by PDA-Mem@M remains unclear, and its rapid therapeutic potential requires further exploration. Future research should address these aspects and optimize the PDA-Mem@M design, potentially combining it with other therapeutic methods for more effective depression treatments.

In response to the limitations of traditional therapies and the challenges associated with ketamine (KA) use, Ge et al. [169]. developed a nanocarrier system (AC-RM@HA-MS) that can cross the BBB and specifically target the NMDA receptor (NMDAR) site, enhancing ketamine efficacy while reducing side effects in the treatment of depression. The AC-RM@HA-MS system has a multilayered core-shell structure. Initially, KA-loaded aminated mesoporous silica (MS) nanoparticles were prepared with an average particle size of about 160 nm, featuring a high surface area, porosity, and a loading capacity of 22.05 wt%. Hyaluronic acid (HA) was then conjugated to the surface of the MS-KA nanoparticles, acting as a "pore guardian" to prevent premature release of KA. HA is degraded by hyaluronidase (Hya) at the target site, enabling controlled drug release. Next, the red blood cell membrane (RM) was wrapped around the surface of HA-MS-KA nanoparticles to evade clearance by the reticuloendothelial system (RES) and prolong circulation time. RM membranes, enriched with proteins like CD47, contribute to immune evasion. Additionally, a bifunctional peptide (Ang-2-Con-G, AC) was labeled on the surface of the nanoparticles. Ang-2 binds specifically to low-density lipoprotein receptor-associated protein (LRP) on the BBB, facilitating transcytosis across endothelial cells and enhancing delivery of KA to the target regions in the brain. In vivo, the AC-RM@HA-MS system crosses the BBB and selectively targets NMDAR-rich regions like the hippocampus and prefrontal cortex, while minimizing KA entry into addiction-related areas such as the ventral tegmental area (VTA) and nucleus accumbens (NAc). After reaching the target site, KA is gradually released as HA is degraded by Hya, allowing KA to act as a non-competitive NMDAR channel blocker. This promotes synaptic protein expression, increases dendritic spine density and length, and enhances neuronal dendritic growth, ultimately improving synaptic plasticity and alleviating depressive symptoms. The RM membrane helps to reduce immune recognition, decrease complement activation, and avoid macrophage phagocytosis, ensuring that the nanoparticles successfully reach the target site. In vitro experiments confirmed the functionality of the nanoparticles, showing controlled KA release upon Hya addition and reduced phagocytosis of RM@MS nanoparticles by RAW264.7 cells compared to MS nanoparticles. Future research should focus on optimizing the nanocarriers to improve drug delivery efficiency, evaluating the duration of cognitive and behavioral improvements, and expanding the application of this system to other brain disorders, advancing nanotechnology for treating depression and related neurological diseases (Fig. 7).

4.3. Biomimetic strategies based on nanozymes

As a class of nanomaterials with enzyme catalytic activity, nanozymes have shown great potential for application in the biomedical field due to their unique physicochemical properties and biological characteristics, bringing a new light to the treatment of depression [170–172]. Nanozymes have good biocompatibility and can exist more stably in the

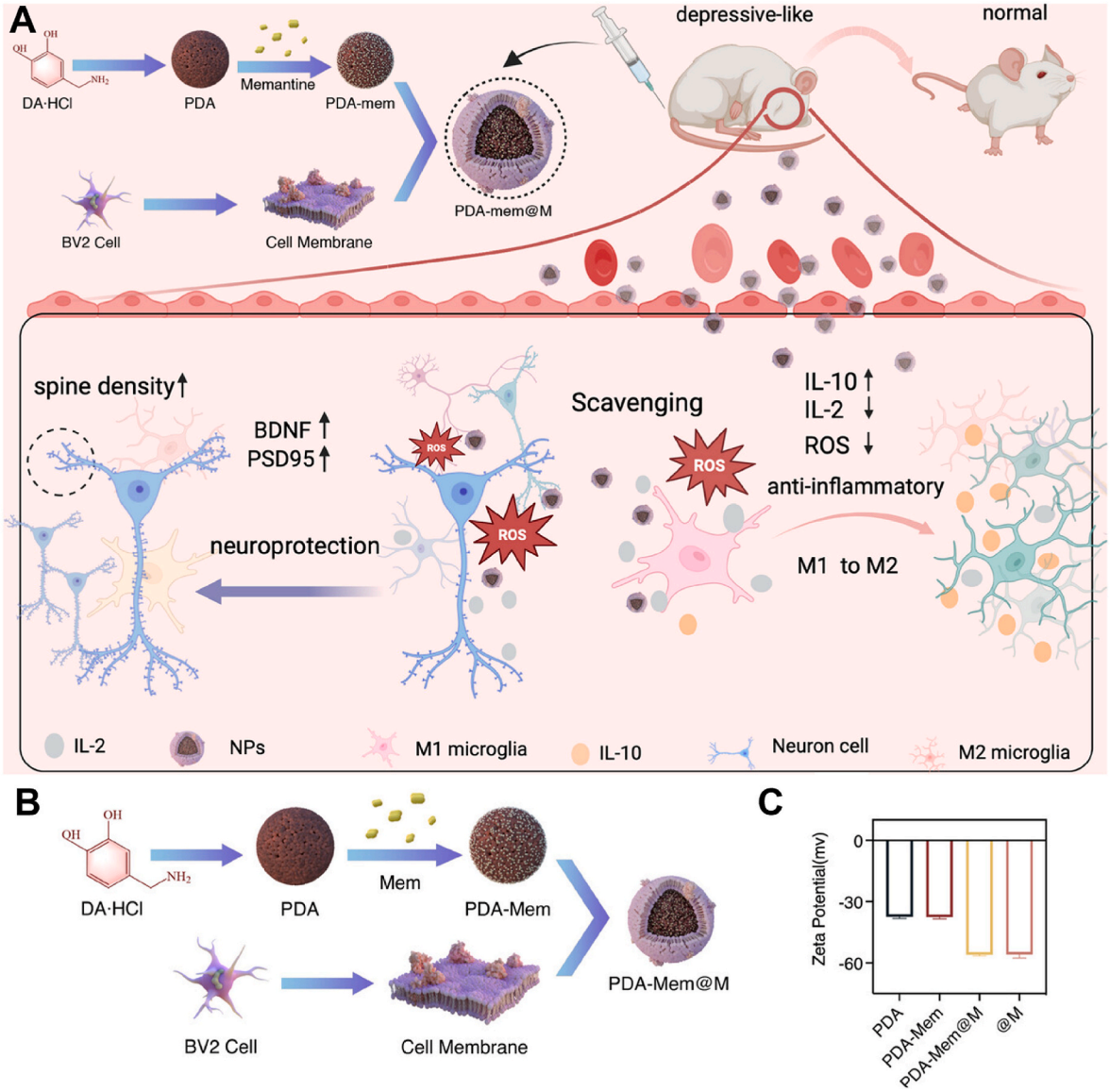

Fig. 6. (A) Schematic representation of PDA-Mem@M synthesis and regulation of neuroinflammation and neuroplasticity in depression. (B) Construction process of PDA-Mem@M. (C) Particle size distribution diagram of each nanosystem. Copyright from Ref. [168]. Wiley-VCH 2025.

body, reducing immune stimulation to the organism. Their size is usually at the nanometer level, which is similar to the size of biomolecules, and is conducive to interaction with cells and biomolecules to achieve efficient material delivery and signal transduction. Nanozymes can also mimic the activity of a variety of natural enzymes, such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD). Depressed patients often have an imbalance of oxidative stress in their bodies and elevated levels of ROS, which cause damage to nerve cells [173–175]. By mimicking the activities of SOD, CAT and other enzymes, nanozymes can effectively remove excessive ROS, regulate the redox balance, and protect nerve cells from oxidative damage, which provides a new target and therapeutic idea for the treatment of depression.

Depression and cognitive impairment significantly affect the quality of life for millions worldwide. The pathogenesis of these conditions is often linked to dysregulation of the monoamine transporter pathway. While current first-line drugs provide some relief, they suffer from slow onset, side effects, and poor BBB penetration. Additionally, iron, crucial for tyrosine hydroxylase and dopamine receptor D_2, is linked to anxiety, depression, and cognitive dysfunction, but traditional iron supplementation struggles to cross the BBB effectively. To address these challenges, Hu et al. [176]. designed a novel nanocarrier, CFs@DP, which combines the unique properties of nanozymes with dual responsiveness to near-infrared (NIR) light and magnetic fields for precise drug delivery. The CFs are derived from the carbonization of MIL-100 (Fe), with iron predominantly in the form of Fe_3O_4 and γ-Fe_2O_3. This structure provides CFs with excellent paramagnetism, allowing them to be precisely guided by a magnetic field, essential for targeted therapy. CFs also exhibit photothermal effects under NIR irradiation, increasing their temperature and enabling controlled disintegration for drug release. When stimulated by NIR and catecholamine-induced complexation, CFs@DP releases ferric ions and dopamine precursors (DP), which regulate dopamine receptors, activate the AC/cAMP/CREB signaling pathway, and increase BDNF expression. Treatment with CFs@DP enhanced dopamine receptor densities in key brain areas such as the prefrontal cortex (PFC) and hippocampus, leading to antidepressant and cognitive-enhancing effects. These changes continued post-treatment, enhancing synaptic plasticity and neuronal function. In vivo experiments demonstrated that CFs@DP improved behavior in various tests. Mice treated with CFs@DP showed increased movement distance in the open field test and more time spent in the open arm in the elevated cross

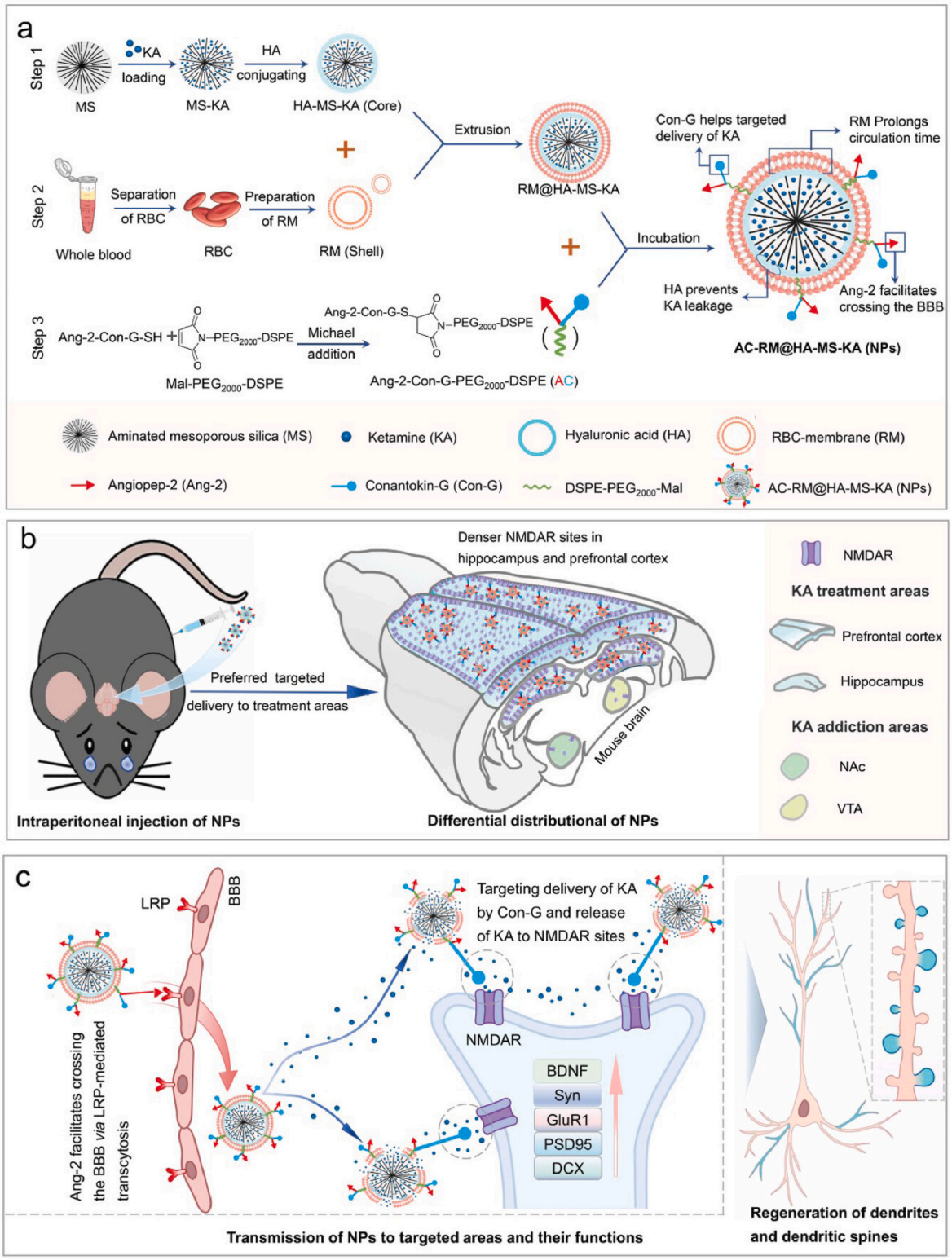

Fig. 7. Diagrams depicting the synthesis method and therapeutic mechanism of AC-RM@HA-MS-KA NPs. (A) The synthesis procedure and functions associated with AC-RM@HA-MS-KA NPs. (B) These NPs are directed towards the N-methyl-D-aspartate receptor (NMDAR) sites located in the hippocampus and prefrontal cortex. This targeting serves to augment the therapeutic impacts while simultaneously avoiding the VTA and NAc, thus preventing the development of dependence or addiction. (C) The mechanism by which the NPs penetrate the BBB and accumulate at the NMDAR site for the treatment of depression and the improvement of cognitive function. Copyright from Ref. [169]. Wiley-VCH 2023.

maze test, indicating reduced anxiety and enhanced exploration. In the Morris water maze, CFs@DP-treated mice exhibited superior cognitive performance, spending more time in the target quadrant. Additionally, in vitro studies confirmed that CFs@DP did not inhibit cell activity at a concentration of 200 μg/mL, indicating good biocompatibility. Immunofluorescence and Western blot analyses revealed that CFs@DP treatment upregulated dopamine receptor densities and activated relevant signaling pathways in the PFC, increasing the expression of p-CREB, p-CaMKII, and BDNF. This nanozyme-based design of CFs@DP opens new possibilities for treating depression and cognitive disorders, offering enhanced drug delivery, controlled release, and improved therapeutic efficacy (Fig. 8).

Burn injuries often lead to prolonged oxidative stress, inflammatory pain, and can contribute to the development of depressive disorders, significantly affecting the patient's quality of life. Traditional burn treatments focus on infection control and tissue repair but fail to address inflammatory pain and post-burn depression. Nanozymes, with their unique catalytic activity and multifunctionality, offer promising solutions for these challenges. Zhao et al. [177]. developed a novel nanozyme-integrated hydrogel, H@EFCP, combining Prussian blue nanoparticles (HMPB) with a microenvironment-adaptive matrix to promote burn healing, alleviate pain, and prevent post-burn depression.

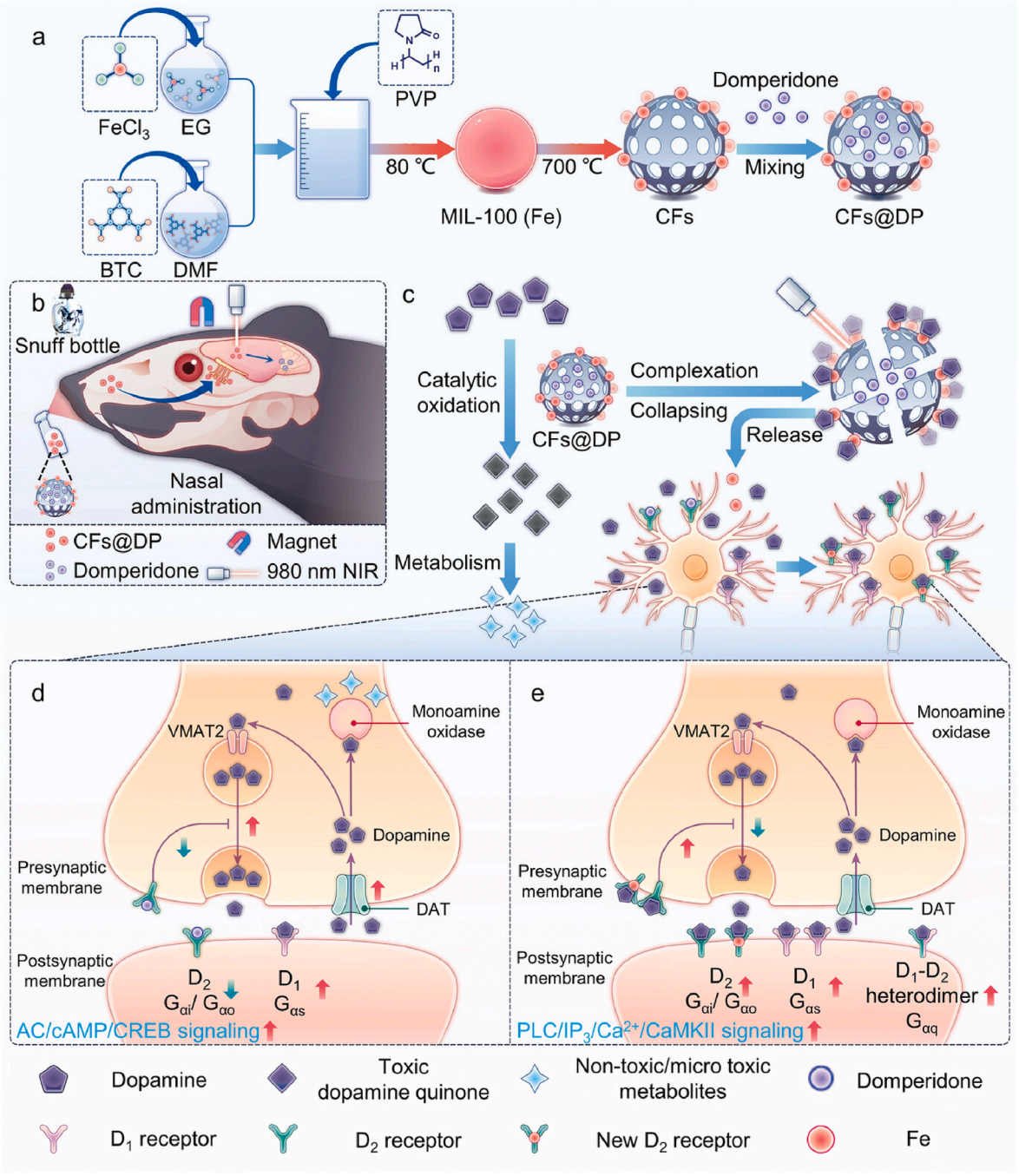

Fig. 8. The preparation of CFs@DP and its utilization in magnetic - target - based drug delivery and neurotherapeutic applications. a) Preparation process of CFs@DP. b) A magnetic - targeted nasal administration delivery system of CFs@DP. c) The mechanisms underlying toxicity reduction and controlled release. The mechanisms of the therapeutic effects in (d) the "treatment - in - progress phase" and (e) the "post - drug - withdrawal phase". Copyright from Ref. [176]. Wiley-VCH 2024.

HMPB, a nanozyme with superoxide dismutase (SOD)-like activity, is stabilized in the hydrogel system and plays a key role in scavenging ROS. The hydrogel, consisting of carboxymethyl chitosan, polyvinyl alcohol, and borate chelates (formed by EGCG and 4-FPBA), is designed to degrade under high ROS and low pH conditions, releasing HMPB and EGCG at the burn site. HMPB effectively scavenges ROS, reducing oxidative stress and inflammatory markers such as TNF-α and IL-1β, while increasing anti-inflammatory cytokines like IL-4. This helps regulate the inflammatory microenvironment, reducing peripheral inflammation and limiting the entry of inflammatory factors into the brain, thus protecting the central nervous system. In vivo studies showed that H@EFCP treatment reduced pro-inflammatory mediators in the brain, inhibited microglia and astrocyte activation, and promoted the normal function of neurons, which lowered the risk of depression. HMPB's antioxidant and anti-inflammatory properties provide significant antidepressant benefits. By alleviating oxidative stress and regulating the inflammatory microenvironment, it helps protect nerve cells and relieve inflammatory pain, reducing the incidence of depression. Behavioral tests on burned mice treated with H@EFCP showed improved outcomes, including reduced anxiety and depression-like behaviors, demonstrated by increased movement and activity in open-field, tail-hanging, and forced-swimming tests. While the promising results suggest that HMPB-based hydrogel can effectively prevent post-burn depression, further research is needed to understand its long-term mechanisms, potential side effects, and optimize its application across varying burn severities and individual patient differences. Future studies could explore combining this treatment with other antidepressants to enhance therapeutic outcomes in clinical burn care (Fig. 9).

Despite progress in the application of nanozymes for depression treatment, the understanding of their mechanisms of action remains limited. The ways in which nanozymes interact with neuronal receptors, neurotransmitter transporters, and intracellular signaling pathways are not fully understood. For example, how nanozymes regulate neuroplasticity-related genes and affect neural circuits in different brain regions still requires in-depth investigation. This lack of clarity hinders the optimization of therapeutic regimens and improvement in efficacy. Nanozymes face several challenges in the complex physiological environment. Their stability needs improvement, as interactions with proteins, enzymes, and ions in the blood can alter their structure and

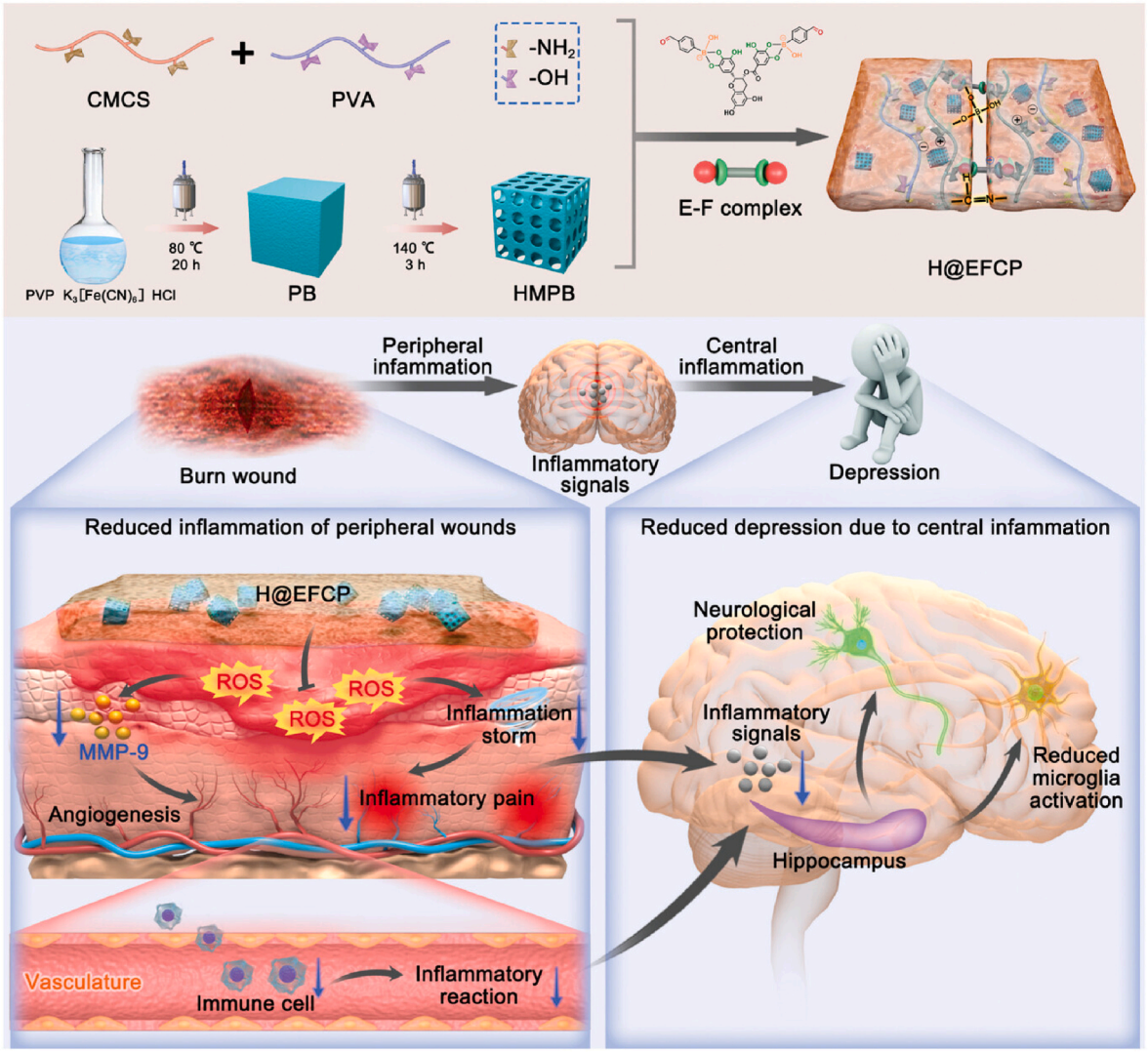

Fig. 9. H@EFCP is applied to the repair of burn wounds and the intervention therapy for post - burn depression. The hydrogel mainly consists of CMCS and PVA as its structural components. Subsequently, an E − F complex is utilized to dynamically cross - link these components, resulting in the formation of H@EFCP. H@EFCP can accelerate wound healing and alleviate the pain response triggered by the inflammatory microenvironment. By doing so, it reduces the impact of the inflammatory infiltration in the peripheral circulation on the brain and suppresses the depressive pathologies and behaviors that are present in burn patients. Copyright from Ref. [177]. Wiley-VCH 2025.

function, potentially diminishing their therapeutic effects. Additionally, the long-term safety of nanozymes remains a concern. There is insufficient research on their metabolic pathways, excretion, and potential toxicity, including the risks of accumulation in vital organs like the liver and kidneys or triggering immune responses. To address these challenges, future research should focus on optimizing nanozyme design based on a deeper understanding of their mechanisms. Strategies could include precisely modifying their composition, structure, and surface properties to improve stability, enzymatic activity, and targeting. For example, designing nanozymes with multiple enzyme activities to regulate various biological processes related to depression, integrating functional genes via gene editing to endow new biological functions, and developing smart-responsive nanozymes for controlled drug release based on microenvironment changes (e.g., pH, temperature, ROS levels) are promising directions for enhancing therapeutic efficacy.

5. Design and clinical translation challenges of biomimetic nanodelivery systems

Biomimetic nanodelivery systems have emerged as a transformative approach in the treatment of depression, offering unique advantages in targeting the CNS, modulating neurobiological pathways, and mimicking endogenous vesicles or interfaces. However, despite encouraging preclinical progress, the translation of these systems into clinically viable therapies remains limited. Multiple barriers spanning from manufacturing and quality control to long-term safety and ethical oversight must be addressed before biomimetic nanocarriers can become a realistic option in psychiatry. In this section, we present a comprehensive and integrated discussion of the major translational challenges, aiming to provide a strategic overview for researchers and clinicians working to bridge the laboratory-to-clinic divide.

5.1. Scalability and manufacturing constraints

The scale-up of biomimetic nanocarrier production presents significant challenges that affect the reproducibility, quality, and economic feasibility of future clinical applications. In laboratory environments, most biomimetic systems are synthesized using small-scale, highly controlled processes, which involve meticulous conditions for pH, temperature, stirring rates, and material ratios. These parameters are often highly sensitive and difficult to standardize across batches. For example, nanozymes require stringent control over redox reactions and surface engineering to maintain catalytic activity, but such precision becomes exponentially more difficult in large-volume production. Similarly, the isolation of cell membranes—whether from red blood cells, leukocytes, microglia, or mesenchymal stem cells—must ensure protein integrity, membrane orientation, and compatibility with nanoparticle cores. Minor deviations in centrifugation speed or membrane–core ratio can result in significant batch-to-batch variability. The situation is even more complex with exosomes, where secretion rates are inherently low, and isolation methods such as ultracentrifugation, tangential flow filtration, or immunoaffinity capture are labor-intensive and poorly scalable. Furthermore, these biomaterials often have limited shelf-lives and require cold-chain logistics, further complicating production planning. Microfluidic technologies and continuous-flow systems have been proposed as potential solutions, enabling high-throughput synthesis with better process control. However, these platforms are still under optimization and have yet to be validated for clinical-grade production. Therefore, developing automated, GMP-compliant, and economically scalable manufacturing pipelines remains one of the most urgent tasks in the field.

5.2. Stability and storage issues

Long-term stability is a critical factor in the clinical viability of any nanomedicine. Biomimetic nanocarriers, particularly those constructed from biological materials, pose unique challenges in this regard. Exosomes, though naturally secreted and stable in vivo, are highly sensitive to freeze–thaw cycles, pH shifts, and ionic strength during storage. Structural degradation of lipid bilayers or cargo leakage during storage can result in the loss of functionality. Cell membrane-coated nanoparticles, while more robust than pure biological vesicles, also suffer from oxidation, hydrolysis, and aggregation over time, especially when stored at room temperature. Additionally, membrane proteins responsible for targeting and immune evasion may denature, losing bioactivity and potentially triggering adverse immune responses. Nanozymes are generally more stable due to their inorganic composition, yet surface modifications such as PEGylation, peptide ligands, or antibody conjugates can degrade under physiological or storage conditions. The development of stabilizing strategies such as lyophilization with cryoprotectants, encapsulation within hydrogel matrices, or storage in inert gas environments has shown promise but remains formulation-specific and often reduces biological activity. Furthermore, regulatory approval requires long-term stability data under various storage and transport conditions, including accelerated aging and stress testing. Establishing universally applicable stability protocols and identifying formulation-specific degradation mechanisms will be essential for future product registration.

5.3. Biocompatibility and long-term safety

While biomimetic nanocarriers are often presumed to be safe due to their endogenous origins, comprehensive evaluations of their biocompatibility and long-term safety are largely lacking. For chronic diseases like depression, where treatment duration may span months or even years, it is crucial to understand the cumulative biological impact of repeated administration. One major concern is the potential for systemic accumulation. Exosomes and cell membrane-coated particles may be taken up by phagocytes and accumulate in the liver, spleen, or lungs, leading to RES overload and immunological disturbances. Although exosomes generally evade the immune system, non-autologous sources (e.g., allogeneic stem cells or tumor cells) may provoke antigenic responses or trigger off-target effects. Nanozymes containing transition metals or redox-active centers can catalyze unintended oxidative reactions, particularly in off-target tissues, raising concerns of genotoxicity or mitochondrial dysfunction. Additionally, hybrid systems that incorporate both organic and inorganic elements pose complex degradation and excretion challenges. For gene-delivering exosomes, the long-term risk of insertional mutagenesis, gene silencing, or uncontrolled expression remains theoretical but must be rigorously excluded. Chronic exposure could also affect the host microbiome or neuroimmune balance in unpredictable ways. Toxicological evaluations should not only involve acute and subchronic studies but also incorporate multi-organ histopathology, neurobehavioral testing, immune profiling, and genotoxicity assays. Regulatory agencies will require a complete toxicological package prior to first-in-human trials, and building such a dataset should be prioritized in preclinical development.

5.4. Cost-effectiveness and economic viability

Economic feasibility plays a decisive role in whether a biomedical technology is adopted into standard clinical practice. Biomimetic nanomedicines, by nature of their complexity and reliance on biological components, are currently among the most expensive nanotherapeutic platforms. The costs associated with cell culture (e.g., mesenchymal stem cells, immune cells), isolation (e.g., exosomes, membranes), and purification (e.g., chromatography, ultrafiltration) far exceed those of conventional drugs or synthetic nanoparticles. In addition, maintaining GMP compliance, sterile production environments, and qualified personnel further increases operational costs. From a payer perspective, high development and production costs may translate into elevated treatment prices, limiting access and reimbursement potential. This is

particularly problematic in psychiatry, where most antidepressants are generic and inexpensive. Therefore, biomimetic systems must demonstrate not only superior efficacy but also clear cost–benefit advantages. Strategies to reduce cost include developing off-the-shelf biomimetic systems using universal donor cells, plant-derived vesicles, or semi-synthetic mimics. Hybrid platforms that combine synthetic backbones with minimal biologics could also reduce complexity without sacrificing function. Furthermore, economic modeling should be integrated into preclinical and clinical study design, evaluating how biomimetic systems influence hospitalization rates, relapse frequency, treatment adherence, and quality-adjusted life years (QALYs). Only by aligning scientific innovation with economic pragmatism can biomimetic nanomedicine become a sustainable part of depression management.

5.5. Standardization, regulation, and ethical considerations

The lack of regulatory clarity is one of the most formidable barriers facing biomimetic nanomedicine. Traditional frameworks were developed for small molecules and biologics, not for hybrid systems that blur the lines between drugs, devices, and biological products. For example, it is unclear whether an exosome loaded with an antidepressant is a biologic, a drug–device combination, or a novel entity requiring a bespoke pathway. Furthermore, standardization of manufacturing processes, product characterization, and release criteria is still in its infancy. There is no consensus on what constitutes an acceptable exosome preparation in terms of size distribution, cargo integrity, surface marker expression, or potency. Similar issues exist for cell membrane-coated particles and nanozymes, particularly in defining batch consistency and functional reproducibility. In addition, ethical concerns must be addressed transparently. The use of human-derived materials requires donor consent, genetic screening, and compliance with bioethical standards. The use of animal-derived components may conflict with religious or cultural beliefs, and the therapeutic use of stem cells continues to face moral scrutiny. Traceability, biobanking, and responsible sourcing protocols are essential to ensure public trust and regulatory acceptance. Importantly, early and proactive dialogue with regulatory agencies can help align development strategies with approval requirements, ultimately accelerating time to market.

5.6. Personalized design and clinical readiness

Personalized medicine is increasingly viewed as the future of depression treatment, and biomimetic nanodelivery systems are well positioned to support this paradigm. Depression is a highly heterogeneous disorder with subtypes characterized by distinct neurobiological signatures ranging from inflammation and oxidative stress to neurotransmitter depletion and neuroplasticity deficits. Biomimetic nanocarriers can be engineered to selectively address these subtypes by incorporating specific surface ligands, cargo molecules, and environmental responsiveness. For instance, carriers targeting inflammatory depression could deliver anti-cytokine siRNAs or anti-inflammatory drugs and respond to elevated levels of TNF-α or IL-6 in the brain. Similarly, oxidative-stress-responsive nanozymes could be deployed in subtypes marked by ROS dysregulation. Exosomes could be loaded with neurotrophic factors or synapse-modulating miRNAs in patients with reduced BDNF or impaired hippocampal connectivity. Moreover, AI-driven design tools can help match patient biomarker profiles with optimal carrier formulations, improving response prediction and minimizing trial-and-error dosing. To translate these innovations into clinical reality, robust companion diagnostics must be developed, including blood-based biomarker assays and neuroimaging readouts. Clinical trial design should also reflect the personalized approach, employing stratified patient enrollment and outcome measures such as patient-reported outcomes, functional capacity, and relapse rates. Importantly, the success of personalized nanomedicine will depend not only on scientific advances but also on the alignment of regulatory, economic, and societal frameworks that support individualized care.

6. Conclusion and perspectives

Biomimetic nanodelivery systems including those based on cell membranes, exosomes, and nanozymes have emerged as promising innovations in the field of depression therapeutics, offering unprecedented opportunities to enhance drug delivery, targeting precision, and neurobiological regulation. These nanocarriers are engineered to leverage biological features such as immune evasion, tissue-specific homing, and responsive drug release to address the multifaceted pathogenesis of depression. Their demonstrated ability to traverse the BBB, regulate oxidative stress, and modulate neuroinflammatory and synaptic pathways places them at the forefront of next-generation antidepressant strategies. However, as highlighted in Section 5, the path to clinical translation remains complex and requires the systematic resolution of several interrelated challenges. In this concluding section, we propose concrete, forward-looking solutions to address the specific translational barriers identified, with the aim of providing a more actionable roadmap for future research and development.

To overcome the critical challenge of scalability and manufacturing, a shift from manual, laboratory-scale preparation toward automated and modular production platforms is imperative. The integration of microfluidic reactors, programmable synthesis pipelines, and GMP-compatible bioreactor systems can significantly improve the yield, consistency, and sterility of biomimetic nanocarriers. For example, microfluidic-assisted fusion of cell membranes with nanoparticle cores can ensure precise size control and membrane orientation, while high-density bioreactor systems can boost exosome secretion rates by optimizing cell viability and metabolic output. In parallel, machine learning algorithms can be used to monitor and adjust synthesis parameters in real-time, enabling predictive control over product attributes. The implementation of these technologies can bridge the current production gap, bringing laboratory innovation closer to clinical feasibility. Addressing stability and storage issues will require formulation science to play a central role. Innovative lyophilization protocols using customized cryoprotectants (e.g., trehalose, dextran, mannitol) in combination with amphiphilic stabilizers can improve the shelf-life of delicate biological structures such as exosomes and membrane proteins. Additionally, the encapsulation of nanocarriers within protective matrices like lipid–polymer hybrid shells or thermoresponsive hydrogels can prevent cargo degradation and maintain membrane integrity during transportation and long-term storage. These strategies must be supported by systematic stability testing under various environmental conditions (e.g., temperature, humidity, light exposure) to generate regulatory-grade stability profiles. Establishing standardized protocols for accelerated aging studies, real-time monitoring, and reconstitution validation will facilitate the regulatory evaluation and industrial deployment of these nanocarriers. For biocompatibility and long-term safety, comprehensive toxicological profiling must become a mandatory component of early-phase development. Preclinical studies should go beyond basic cytotoxicity and include advanced models such as organ-on-a-chip systems, humanized mice, and long-term neurobehavioral assays. Special attention must be paid to the biodistribution, accumulation, and clearance patterns of nanocarriers in the brain, liver, spleen, kidneys, and lymphatic system. Immunogenicity should be assessed not only by antibody titers and cytokine release assays but also by transcriptomic and proteomic profiling of immune cells after repeated exposure. For nanozymes, long-term redox activity and metal ion leaching should be evaluated using oxidative DNA damage assays and mitochondrial function tests. Only through multilayered, multi-organ safety assessments can we ensure that these platforms will be well tolerated in clinical populations, particularly in chronic-use scenarios typical for antidepressant therapy. To improve cost-effectiveness and economic viability, strategic simplification of carrier composition is key. Hybrid systems that retain biomimetic functionality while

minimizing biological complexity such as polymer-supported membranes or synthetic exosome mimetics can reduce dependency on scarce or ethically sensitive materials. In parallel, the use of universally compatible donor cells, plant-derived vesicles, or bioengineered membrane analogs can offer scalable alternatives to primary human or animal-derived components. From a health economics perspective, it is critical to integrate pharmacoeconomic modeling into clinical trial planning. Models that capture not only direct treatment costs but also long-term benefits such as improved remission rates, reduced hospitalization, and enhanced patient productivity can help justify investment in these advanced therapies and support reimbursement decisions by healthcare systems. The issue of standardization and regulatory clarity calls for immediate attention through collaborative guideline development. Regulatory bodies such as the FDA and EMA should work closely with academic researchers and industry partners to establish evaluation frameworks that define product categories, quality control benchmarks, and potency assays for biomimetic nanocarriers. For example, exosomes may be defined not only by size and surface markers (CD9, CD63, CD81) but also by cargo composition (miRNA, proteins) and functional activity (e.g., anti-inflammatory or neurogenic effects). Similarly, nanozyme products should include catalytic efficiency metrics, stability indices, and toxicity limits. Ethical sourcing protocols covering donor consent, biosafety, and cultural acceptability must be transparently documented and traceable throughout the production pipeline. The adoption of blockchain-based supply chain systems may further enhance accountability and public trust. In the context of personalized medicine and clinical readiness, biomimetic nanocarriers offer a unique platform for individualized intervention in depression subtypes. For example, exosomes can be loaded with specific miRNAs (e.g., miR-124, miR-139-5p) or proteins (e.g., BDNF, GDNF) tailored to patients with neuroplasticity impairments, while nanozymes responsive to elevated ROS or pro-inflammatory cytokines can target oxidative and inflammatory depression phenotypes. Integration with companion diagnostics such as blood-based biomarker panels, neuroimaging biomarkers, or genetic polymorphism profiling can further refine patient stratification. Artificial intelligence tools can be leveraged to identify optimal treatment combinations, delivery timings, and formulation profiles based on longitudinal clinical and molecular data. Future clinical trials should move beyond homogenous study populations and adopt stratified, biomarker-informed designs with adaptive endpoints and patient-centered outcome measures (e.g., fatigue, cognitive function, emotional reactivity).

In conclusion, the transition of biomimetic nanodelivery systems from preclinical promise to clinical reality in depression therapy demands an integrated, multidisciplinary, and solution-focused approach. Each of the key barriers identified ranging from production and stability to safety, regulation, cost, and personalization has actionable strategies that are increasingly supported by technological and methodological advances. By aligning scientific innovation with clinical need, economic viability, and ethical responsibility, biomimetic nanocarriers can evolve into next-generation therapeutics capable of addressing the unmet challenges of depression. The future of this field lies not merely in discovery but in deliberate and coordinated efforts to translate these discoveries into safe, effective, and accessible treatments that improve patient outcomes on a global scale.

CRediT authorship contribution statement

Ping Jiang: Writing – original draft. **Jian Li:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the General Hospital of Northern Theater Command (NTGS-023).

Data availability

No data was used for the research described in the article.

References

[1] A. Thapar, O. Eyre, V. Patel, D. Brent, Depression in young people, Lancet 400 (10352) (2022) 617–631.
[2] N. Racine, E. Hetherington, B.A. McArthur, S. McDonald, S. Edwards, S. Tough, S. Madigan, Maternal depressive and anxiety symptoms before and during the COVID-19 pandemic in Canada: a longitudinal analysis, Lancet Psychiatry 8 (5) (2021) 405–415.
[3] A. Rogers, S. Obst, S.J. Teague, L. Rossen, E.A. Spry, J.A. Macdonald, M. Sunderland, C.A. Olsson, G. Youssef, D. Hutchinson, Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis, JAMA Pediatr. 174 (11) (2020) 1082–1092.
[4] Z.I. Santini, P.E. Jose, E.Y. Cornwell, A. Koyanagi, L. Nielsen, C. Hinrichsen, C. Meilstrup, K.R. Madsen, V. Koushede, Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis, Lancet Public Health 5 (1) (2020) e62–e70.
[5] D.F. Santomauro, A.M.M. Herrera, J. Shadid, P. Zheng, C. Ashbaugh, D.M. Pigott, C. Abbafati, C. Adolph, J.O. Amlag, A.Y. Aravkin, Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic, Lancet 398 (10312) (2021) 1700–1712.
[6] N. Racine, B.A. McArthur, J.E. Cooke, R. Eirich, J. Zhu, S. Madigan, Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis, JAMA Pediatr. 175 (11) (2021) 1142–1150.
[7] M. Ridley, G. Rao, F. Schilbach, V. Patel, Poverty, depression, and anxiety: Causal evidence and mechanisms, Science 370 (6522) (2020) eaay0214.
[8] N.A.L. Ruiz, D.S. Del Ángel, H.J. Olguín, M.L. Silva, Neuroprogression: the hidden mechanism of depression, Neuropsychiatric Dis. Treat. (2018) 2837–2845.
[9] G. Aalbers, R.J. McNally, A. Heeren, S. De Wit, E.I. Fried, Social media and depression symptoms: a network perspective, J. Exp. Psychol. Gen. 148 (8) (2019) 1454.
[10] G.S. Alexopoulos, Mechanisms and treatment of late-life depression, Transl. Psychiatry 9 (1) (2019) 188.
[11] A. Aprilia, D. Aminatun, Investigating memory loss: how depression affects students' memory endurance, J. English Lang. Teach. Learn 3 (1) (2022) 1–11.
[12] H. Cai, J. Han, Y. Chen, X. Sha, Z. Wang, B. Hu, J. Yang, L. Feng, Z. Ding, Y. Chen, A pervasive approach to EEG-based depression detection, Complexity 2018 (1) (2018) 5238028.
[13] C.M. Celano, A.C. Villegas, A.M. Albanese, H.K. Gaggin, J.C. Huffman, Depression and anxiety in heart failure: a review, Harv. Rev. Psychiatr. 26 (4) (2018) 175–184.
[14] F. Chen, D. Zheng, J. Liu, Y. Gong, Z. Guan, D. Lou, Depression and anxiety among adolescents during COVID-19: a cross-sectional study, Brain Behav. Immun. 88 (2020) 36.
[15] R.K. Bailey, J. Mokonogho, A. Kumar, Racial and ethnic differences in depression: current perspectives, Neuropsychiatric Dis. Treat. (2019) 603–609.
[16] I.O. Bergfeld, M. Mantione, M. Figee, P.R. Schuurman, A. Lok, D. Denys, Treatment-resistant depression and suicidality, J. Affect. Disord. 235 (2018) 362–367.
[17] J.E.R. Bernard, Depression: a review of its definition, MOJ Addict. Med. Therap. 5 (1) (2018) 6–7.
[18] E. Beurel, M. Toups, C.B. Nemeroff, The bidirectional relationship of depression and inflammation: double trouble, Neuron 107 (2) (2020) 234–256.
[19] S. Bhatt, A.N. Nagappa, C.R. Patil, Role of oxidative stress in depression, Drug Discov. Today 25 (7) (2020) 1270–1276.
[20] T.H. Bisgaard, K.H. Allin, L. Keefer, A.N. Ananthakrishnan, T. Jess, Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment, Nat. Rev. Gastroenterol. Hepatol. 19 (11) (2022) 717–726.
[21] M. Alberto, A.C. Paiva-Santos, F. Veiga, P.C. Pires, Lipid and polymeric nanoparticles: successful strategies for nose-to-brain drug delivery in the treatment of depression and anxiety disorders, Pharmaceutics 14 (12) (2022) 2742.
[22] T.H. Baryakova, B.H. Pogostin, R. Langer, K.J. McHugh, Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems, Nat. Rev. Drug Discov. 22 (5) (2023) 387–409.
[23] L. Battaglia, P.P. Panciani, E. Muntoni, M.T. Capucchio, E. Biasibetti, P. De Bonis, S. Mioletti, M. Fontanella, S. Swaminathan, Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery, Expet Opin. Drug Deliv. 15 (4) (2018) 369–378.
[24] V.N. Bharadwaj, D.T. Nguyen, V.D. Kodibagkar, S.E. Stabenfeldt, Nanoparticle-based therapeutics for brain injury, Adv. Healthcare Mater. 7 (1) (2018) 1700668.
[25] H. Chen, M. Zhou, Y. Zeng, T. Miao, H. Luo, Y. Tong, M. Zhao, R. Mu, J. Gu, S. Yang, Biomimetic lipopolysaccharide-free bacterial outer membrane-

functionalized nanoparticles for brain-targeted drug delivery, Adv. Sci. 9 (16) (2022) 2105854.
[26] S. Chi, L. Zhang, H. Cheng, Y. Chang, Y. Zhao, X. Wang, Z. Liu, Biomimetic nanocomposites camouflaged with hybrid cell membranes for accurate therapy of early-stage glioma, Angew. Chem. 135 (29) (2023) e202304419.
[27] E.P.H. Choi, B.P.H. Hui, E.Y.F. Wan, Depression and anxiety in Hong Kong during COVID-19, Int. J. Environ. Res. Publ. Health 17 (10) (2020) 3740.
[28] Z.D. Cohen, R.J. DeRubeis, Treatment selection in depression, Annu. Rev. Clin. Psychol. 14 (1) (2018) 209–236.
[29] P. Cuijpers, S. Quero, C. Dowrick, B. Arroll, Psychological treatment of depression in primary care: recent developments, Curr. Psychiatry Rep. 21 (2019) 1–10.
[30] P. Cuijpers, A. Stringaris, M. Wolpert, Treatment outcomes for depression: challenges and opportunities, Lancet Psychiatry 7 (11) (2020) 925–927.
[31] S. Cunningham, C.C. Hudson, K. Harkness, Social media and depression symptoms: a meta-analysis, Res. Child Adolescent Psychopathol. 49 (2) (2021) 241–253.
[32] R.K. Dagher, H.E. Bruckheim, L.J. Colpe, E. Edwards, D.B. White, Perinatal depression: challenges and opportunities, J. Wom. Health 30 (2) (2021) 154–159.
[33] M. Daly, E. Robinson, Depression and anxiety during COVID-19, Lancet 399 (10324) (2022) 518.
[34] M. Daly, A.R. Sutin, E. Robinson, Depression reported by US adults in 2017–2018 and March and April 2020, J. Affect. Disord. 278 (2021) 131–135.
[35] D.G. Dillon, D.A. Pizzagalli, Mechanisms of memory disruption in depression, Trends Neurosci. 41 (3) (2018) 137–149.
[36] L. Dobrek, K. Głowacka, Depression and its phytopharmacotherapy—a narrative review, Int. J. Mol. Sci. 24 (5) (2023) 4772.
[37] R.S. Eid, A.R. Gobinath, L.A. Galea, Sex differences in depression: insights from clinical and preclinical studies, Prog. Neurobiol. 176 (2019) 86–102.
[38] H. Fang, S. Tu, J. Sheng, A. Shao, Depression in sleep disturbance: a review on a bidirectional relationship, mechanisms and treatment, J. Cell Mol. Med. 23 (4) (2019) 2324–2332.
[39] J. Firth, W. Marx, S. Dash, R. Carney, S.B. Teasdale, M. Solmi, B. Stubbs, F. B. Schuch, A.F. Carvalho, F. Jacka, The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials, Psychosom. Med. 81 (3) (2019) 265–280.
[40] J. Firth-Cozens, A Perspective on Stress and Depression, Understanding Doctors' Performance, CRC Press, 2023, pp. 22–37.
[41] E.I. Fried, J.K. Flake, D.J. Robinaugh, Revisiting the theoretical and methodological foundations of depression measurement, Nat. Rev. Psychol. 1 (6) (2022) 358–368.
[42] S. Fulton, L. Décarie-Spain, X. Fioramonti, B. Guiard, S. Nakajima, The menace of obesity to depression and anxiety prevalence, Trends Endocrinol. Metabol. 33 (1) (2022) 18–35.
[43] M.J. Gardner, H.J. Thomas, H.E. Erskine, The association between five forms of child maltreatment and depressive and anxiety disorders: a systematic review and meta-analysis, Child Abuse Negl. 96 (2019) 104082.
[44] B.N. Gaynes, L. Lux, G. Gartlehner, G. Asher, V. Forman-Hoffman, J. Green, E. Boland, R.P. Weber, C. Randolph, C. Bann, Defining treatment-resistant depression, Depress. Anxiety 37 (2) (2020) 134–145.
[45] M.A. Gebara, N. Siripong, E.A. DiNapoli, R.D. Maree, A. Germain, C.F. Reynolds, J.W. Kasckow, P.M. Weiss, J.F. Karp, Effect of insomnia treatments on depression: a systematic review and meta-analysis, Depress. Anxiety 35 (8) (2018) 717–731.
[46] S.M. Gold, O. Köhler-Forsberg, R. Moss-Morris, A. Mehnert, J.J. Miranda, M. Bullinger, A. Steptoe, M.A. Whooley, C. Otte, Comorbid depression in medical diseases, Nat. Rev. Dis. Primers 6 (1) (2020) 69.
[47] A. Gururajan, A. Reif, J.F. Cryan, D.A. Slattery, The future of rodent models in depression research, Nat. Rev. Neurosci. 20 (11) (2019) 686–701.
[48] J. Harro, Animal models of depression: pros and cons, Cell Tissue Res. 377 (1) (2019) 5–20.
[49] H. Herrman, V. Patel, C. Kieling, M. Berk, C. Buchweitz, P. Cuijpers, T. A. Furukawa, R.C. Kessler, B.A. Kohrt, M. Maj, Time for united action on depression: a lancet–world psychiatric association commission, Lancet 399 (10328) (2022) 957–1022.
[50] E. Hoare, E. Callaly, M. Berk, Can depression be prevented? If so, how? JAMA Psychiatry 77 (11) (2020) 1095–1096.
[51] L. Hull, L. Levy, M.-C. Lai, K. Petrides, S. Baron-Cohen, C. Allison, P. Smith, W. Mandy, Is social camouflaging associated with anxiety and depression in autistic adults? Mol. Autism 12 (2021) 1–13.
[52] W.W. IsHak, R.Y. Wen, L. Naghdechi, B. Vanle, J. Dang, M. Knosp, J. Dascal, L. Marcia, Y. Gohar, L. Eskander, Pain and depression: a systematic review, Harv. Rev. Psychiatr. 26 (6) (2018) 352–363.
[53] M.F. Juruena, M. Bocharova, B. Agustini, A.H. Young, Atypical depression and non-atypical depression: is HPA axis function a biomarker? A systematic review, J. Affect. Disord. 233 (2018) 45–67.
[54] M.A. Kebede, B. Anbessie, G. Ayano, Prevalence and predictors of depression and anxiety among medical students in Addis Ababa, Ethiopia, Int. J. Ment. Health Syst. 13 (2019) 1–8.
[55] P. Koutsimani, A. Montgomery, K. Georganta, The relationship between burnout, depression, and anxiety: a systematic review and meta-analysis, Front. Psychol. 10 (2019) 429219.
[56] J.H. Krystal, C.G. Abdallah, G. Sanacora, D.S. Charney, R.S. Duman, Ketamine: a paradigm shift for depression research and treatment, Neuron 101 (5) (2019) 774–778.
[57] J. LeMoult, I.H. Gotlib, Depression: a cognitive perspective, Clin. Psychol. Rev. 69 (2019) 51–66.
[58] G.Y. Lim, W.W. Tam, Y. Lu, C.S. Ho, M.W. Zhang, R.C. Ho, Prevalence of depression in the community from 30 countries between 1994 and 2014, Sci. Rep. 8 (1) (2018) 2861.
[59] L. Liu, H. Wang, X. Chen, Y. Zhang, H. Zhang, P. Xie, Gut microbiota and its metabolites in depression: from pathogenesis to treatment, EBioMedicine 90 (2023).
[60] C.J. Lynch, F.M. Gunning, C. Liston, Causes and consequences of diagnostic heterogeneity in depression: paths to discovering novel biological depression subtypes, Biol. Psychiatry 88 (1) (2020) 83–94.
[61] S. Marwaha, E. Palmer, T. Suppes, E. Cons, A.H. Young, R. Upthegrove, Novel and emerging treatments for major depression, Lancet 401 (10371) (2023) 141–153.
[62] D.M. Maurer, T.J. Raymond, B.N. Davis, Depression: screening and diagnosis, Am. Fam. Physician 98 (8) (2018) 508–515.
[63] Y. Milaneschi, F. Lamers, M. Berk, B.W. Penninx, Depression heterogeneity and its biological underpinnings: toward immunometabolic depression, Biol. Psychiatry 88 (5) (2020) 369–380.
[64] L. Miller, J.V. Campo, Depression in adolescents, N. Engl. J. Med. 385 (5) (2021) 445–449.
[65] A. Correia, A. Monteiro, R. Silva, J. Moreira, J.S. Lobo, A. Silva, Lipid nanoparticles strategies to modify pharmacokinetics of central nervous system targeting drugs: crossing or circumventing the blood–brain barrier (BBB) to manage neurological disorders, Adv. Drug Deliv. Rev. 189 (2022) 114485.
[66] D. Deepika, H.K. Dewangan, L. Maurya, S. Singh, Intranasal drug delivery of Frovatriptan succinate–loaded polymeric nanoparticles for brain targeting, J. Pharmaceut. Sci. 108 (2) (2019) 851–859.
[67] S. Ding, A.I. Khan, X. Cai, Y. Song, Z. Lyu, D. Du, P. Dutta, Y. Lin, Overcoming blood–brain barrier transport: advances in nanoparticle-based drug delivery strategies, Mater. Today 37 (2020) 112–125.
[68] F. Moir, J. Yielder, J. Sanson, Y. Chen, Depression in medical students: current insights. Advances in Medical Education and Practice, 2018, pp. 323–333.
[69] M.L. Okun, R.A. Mancuso, C.J. Hobel, C.D. Schetter, M. Coussons-Read, Poor sleep quality increases symptoms of depression and anxiety in postpartum women, J. Behav. Med. 41 (2018) 703–710.
[70] J. Ormel, S.D. Hollon, R.C. Kessler, P. Cuijpers, S.M. Monroe, More treatment but no less depression: the treatment-prevalence paradox, Clin. Psychol. Rev. 91 (2022) 102111.
[71] L.T. Park, C.A. Zarate Jr., Depression in the primary care setting, N. Engl. J. Med. 380 (6) (2019) 559–568.
[72] A. Pitman, S. Suleman, N. Hyde, A. Hodgkiss, Depression and anxiety in patients with cancer, Br. Med. J. 361 (2018).
[73] D.A. Pizzagalli, A.C. Roberts, Prefrontal cortex and depression, Neuropsychopharmacology 47 (1) (2022) 225–246.
[74] B. Planchez, A. Surget, C. Belzung, Animal models of major depression: drawbacks and challenges, J. Neural Transm. 126 (2019) 1383–1408.
[75] A. Priya, S. Garg, N.P. Tigga, Predicting anxiety, depression and stress in modern life using machine learning algorithms, Procedia Comput. Sci. 167 (2020) 1258–1267.
[76] E. Sarno, A.J. Moeser, A.J. Robison, Neuroimmunology of depression, Adv. Pharmacol. (2021) 259–292. Elsevier.
[77] N. Sartorius, Depression and diabetes, Dialogues Clin. Neurosci. 20 (1) (2018) 47–52.
[78] Y. Duan, M. Wu, D. Hu, Y. Pan, F. Hu, X. Liu, N. Thakor, W.H. Ng, X. Liu, Z. Sheng, Biomimetic nanocomposites cloaked with bioorthogonally labeled glioblastoma cell membrane for targeted multimodal imaging of brain tumors, Adv. Funct. Mater. 30 (38) (2020) 2004346.
[79] M. Ehsanifar, A.A. Tameh, M. Farzadkia, R.R. Kalantari, M.S. Zavareh, H. Nikzaad, A.J. Jafari, Exposure to nanoscale diesel exhaust particles: oxidative stress, neuroinflammation, anxiety and depression on adult male mice, Ecotoxicol. Environ. Saf. 168 (2019) 338–347.
[80] G. Erel-Akbaba, L.A. Carvalho, T. Tian, M. Zinter, H. Akbaba, P.J. Obeid, E. A. Chiocca, R. Weissleder, A.G. Kantarci, B.A. Tannous, Radiation-induced targeted nanoparticle-based gene delivery for brain tumor therapy, ACS Nano 13 (4) (2019) 4028–4040.
[81] F.B. Schuch, B. Stubbs, The role of exercise in preventing and treating depression, Curr. Sports Med. Rep. 18 (8) (2019) 299–304.
[82] M. Shadrina, E.A. Bondarenko, P.A. Slominsky, Genetics factors in major depression disease, Front. Psychiatr. 9 (2018) 334.
[83] S. Shorey, E.D. Ng, C.H. Wong, Global prevalence of depression and elevated depressive symptoms among adolescents: a systematic review and meta-analysis, Br. J. Clin. Psychol. 61 (2) (2022) 287–305.
[84] S. Fu, H. Chen, W. Yang, X. Xia, S. Zhao, X. Xu, P. Ai, Q. Cai, X. Li, Y. Wang, ROS-targeted depression therapy via BSA-incubated ceria nanoclusters, Nano Lett. 22 (11) (2022) 4519–4527.
[85] D. Gonzalez-Carter, X. Liu, T.A. Tockary, A. Dirisala, K. Toh, Y. Anraku, K. Kataoka, Targeting nanoparticles to the brain by exploiting the blood–brain barrier impermeability to selectively label the brain endothelium, Proc. Natl. Acad. Sci. 117 (32) (2020) 19141–19150.
[86] G. Graverini, V. Piazzini, E. Landucci, D. Pantano, P. Nardiello, F. Casamenti, D. E. Pellegrini-Giampietro, A.R. Bilia, M.C. Bergonzi, Solid lipid nanoparticles for delivery of andrographolide across the blood-brain barrier: in vitro and in vivo evaluation, Colloids Surf. B Biointerfaces 161 (2018) 302–313.
[87] C.A. Smith, M. Armour, M.S. Lee, L.Q. Wang, P.J. Hay, Acupuncture for depression, Cochrane Database Syst. Rev. (3) (2018).
[88] A. Steiger, M. Pawlowski, Depression and sleep, Int. J. Mol. Sci. 20 (3) (2019) 607.

[89] D.E. Stewart, S.N. Vigod, Postpartum depression: pathophysiology, treatment, and emerging therapeutics, Annu. Rev. Med. 70 (1) (2019) 183–196.
[90] L.M. Tomfohr-Madsen, N. Racine, G.F. Giesbrecht, C. Lebel, S. Madigan, Depression and anxiety in pregnancy during COVID-19: a rapid review and meta-analysis, Psychiatry Res. 300 (2021) 113912.
[91] R. Troubat, P. Barone, S. Leman, T. Desmidt, A. Cressant, B. Atanasova, B. Brizard, W. El Hage, A. Surget, C. Belzung, Neuroinflammation and depression: a review, Eur. J. Neurosci. 53 (1) (2021) 151–171.
[92] M.S. Van Niel, J.L. Payne, Perinatal depression: a review, Cleve. Clin. J. Med. 87 (5) (2020) 273–277.
[93] J.V. Gregory, P. Kadiyala, R. Doherty, M. Cadena, S. Habeel, E. Ruoslahti, P. R. Lowenstein, M.G. Castro, J. Lahann, Systemic brain tumor delivery of synthetic protein nanoparticles for glioblastoma therapy, Nat. Commun. 11 (1) (2020) 5687.
[94] X. Guo, G. Deng, J. Liu, P. Zou, F. Du, F. Liu, A.T. Chen, R. Hu, M. Li, S. Zhang, Thrombin-responsive, brain-targeting nanoparticles for improved stroke therapy, ACS Nano 12 (8) (2018) 8723–8732.
[95] H. He, Q. Qin, F. Xu, Y. Chen, S. Rao, C. Wang, X. Jiang, X. Lu, C. Xie, Oral polyphenol-armored nanomedicine for targeted modulation of gut microbiota–brain interactions in colitis, Sci. Adv. 9 (21) (2023) eadf3887.
[96] S.J. Van Rooij, A.R. Arulpragasam, W.M. McDonald, N.S. Philip, Accelerated TMS-moving quickly into the future of depression treatment, Neuropsychopharmacology 49 (1) (2024) 128–137.
[97] W. He, X. Li, M. Morsch, M. Ismail, Y. Liu, F.U. Rehman, D. Zhang, Y. Wang, M. Zheng, R. Chung, Brain-targeted codelivery of Bcl-2/Bcl-xl and Mcl-1 inhibitors by biomimetic nanoparticles for orthotopic glioblastoma therapy, ACS Nano 16 (4) (2022) 6293–6308.
[98] X.-L. He, L. Yang, Z.-J. Wang, R.-Q. Huang, R.-R. Zhu, L.-M. Cheng, Solid lipid nanoparticles loading with curcumin and dexanabinol to treat major depressive disorder, Neural Regenerat. Res. 16 (3) (2021) 537–542.
[99] Y. Islam, A.G. Leach, J. Smith, S. Pluchino, C.R. Coxon, M. Sivakumaran, J. Downing, A.A. Fatokun, M. Teixidò, T. Ehtezazi, Physiological and pathological factors affecting drug delivery to the brain by nanoparticles, Adv. Sci. 8 (11) (2021) 2002085.
[100] A.M. Jimenez, A.A. Krauskopf, R.A. Pérez-Camargo, D. Zhao, J. Pribyl, J. Jestin, B.C. Benicewicz, A.J. Müller, S.K. Kumar, Effects of hairy nanoparticles on polymer crystallization kinetics, Macromolecules 52 (23) (2019) 9186–9198.
[101] L. Jin, P. Hu, Y. Wang, L. Wu, K. Qin, H. Cheng, S. Wang, B. Pan, H. Xin, W. Zhang, Fast-acting black-phosphorus-assisted depression therapy with low toxicity, Adv. Mater. 32 (2) (2020) 1906050.
[102] Y.A. Khadrawy, E.N. Hosny, M. Magdy, H.S. Mohammed, Antidepressant effects of curcumin-coated iron oxide nanoparticles in a rat model of depression, Eur. J. Pharmacol. 908 (2021) 174384.
[103] D. Voineskos, Z.J. Daskalakis, D.M. Blumberger, Management of treatment-resistant depression: challenges and strategies, Neuropsychiatric Dis. Treat. (2020) 221–234.
[104] J. Kong, R. Zou, G.-L. Law, Y. Wang, Biomimetic multifunctional persistent luminescence nanoprobes for long-term near-infrared imaging and therapy of cerebral and cerebellar gliomas, Sci. Adv. 8 (10) (2022) eabm7077.
[105] K. Kucharz, K. Kristensen, K.B. Johnsen, M.A. Lund, M. Lønstrup, T. Moos, T. L. Andresen, M.J. Lauritzen, Post-capillary venules are the key locus for transcytosis-mediated brain delivery of therapeutic nanoparticles, Nat. Commun. 12 (1) (2021) 4121.
[106] B. Lee, K. Lee, S. Panda, R. Gonzales-Rojas, A. Chong, V. Bugay, H.M. Park, R. Brenner, N. Murthy, H.Y. Lee, Nanoparticle delivery of CRISPR into the brain rescues a mouse model of fragile X syndrome from exaggerated repetitive behaviours, Nat. Biomed. Eng. 2 (7) (2018) 497–507.
[107] S. Li, X. Li, N. Wang, C. Zhang, Y. Sang, Y. Sun, X. Xia, M. Zheng, Brain targeted biomimetic siRNA nanoparticles for drug resistance glioblastoma treatment, J. Contr. Release 376 (2024) 67–78.
[108] Y.-J. Li, J.-Y. Wu, J. Liu, X. Qiu, W. Xu, T. Tang, D.-X. Xiang, From blood to brain: blood cell-based biomimetic drug delivery systems, Drug Deliv. 28 (1) (2021) 1214–1225.
[109] H.-J. Liu, P. Xu, Strategies to overcome/penetrate the BBB for systemic nanoparticle delivery to the brain/brain tumor, Adv. Drug Deliv. Rev. 191 (2022) 114619.
[110] Y. Liu, Z. Zhou, J. Hou, W. Xiong, H. Kim, J. Chen, C. Zheng, X. Jiang, J. Yoon, J. Shen, Tumor selective metabolic reprogramming as a prospective PD-L1 depression strategy to reactivate immunotherapy, Adv. Mater. 34 (41) (2022) 2206121.
[111] J.Q. Wang, L. Mao, The ERK pathway: molecular mechanisms and treatment of depression, Mol. Neurobiol. 56 (2019) 6197–6205.
[112] Y.-H. Wang, J.-Q. Li, J.-F. Shi, J.-Y. Que, J.-J. Liu, J.M. Lappin, J. Leung, A. V. Ravindran, W.-Q. Chen, Y.-L. Qiao, Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies, Mol. Psychiatr. 25 (7) (2020) 1487–1499.
[113] S. Yoon, M. Kleinman, J. Mertz, M. Brannick, Is social network site usage related to depression? A meta-analysis of Facebook–depression relations, J. Affect. Disord. 248 (2019) 65–72.
[114] Y. Liu, Y. Zou, C. Feng, A. Lee, J. Yin, R. Chung, J.B. Park, H. Rizos, W. Tao, M. Zheng, Charge conversional biomimetic nanocomplexes as a multifunctional platform for boosting orthotopic glioblastoma RNAi therapy, Nano Lett. 20 (3) (2020) 1637–1646.
[115] Y. Luo, H. Yang, Y.-F. Zhou, B. Hu, Dual and multi-targeted nanoparticles for site-specific brain drug delivery, J. Contr. Release 317 (2020) 195–215.
[116] A. Marino, O. Tricinci, M. Battaglini, C. Filippeschi, V. Mattoli, E. Sinibaldi, G. Ciofani, A 3D real-scale, biomimetic, and biohybrid model of the blood-brain barrier fabricated through two-photon lithography, Small 14 (6) (2018) 1702959.
[117] X. Men, X. Geng, Z. Zhang, H. Chen, M. Du, Z. Chen, G. Liu, C. Wu, Z. Yuan, Biomimetic semiconducting polymer dots for highly specific NIR-II fluorescence imaging of glioma, Mater. Today Bio 16 (2022) 100383.
[118] D. Mendanha, J.V. de Castro, H. Ferreira, N. Neves, Biomimetic and cell-based nanocarriers–new strategies for brain tumor targeting, J. Contr. Release 337 (2021) 482–493.
[119] H.P. Modarres, M. Janmaleki, M. Novin, J. Saliba, F. El-Hajj, M. RezayatiCharan, A. Seyfoori, H. Sadabadi, M. Vandal, M.D. Nguyen, In vitro models and systems for evaluating the dynamics of drug delivery to the healthy and diseased brain, J. Contr. Release 273 (2018) 108–130.
[120] T. Musumeci, A. Bonaccorso, G. Puglisi, Epilepsy disease and nose-to-brain delivery of polymeric nanoparticles: an overview, Pharmaceutics 11 (3) (2019) 118.
[121] R. Qiao, C. Fu, H. Forgham, I. Javed, X. Huang, J. Zhu, A.K. Whittaker, T.P. Davis, Magnetic iron oxide nanoparticles for brain imaging and drug delivery, Adv. Drug Deliv. Rev. 197 (2023) 114822.
[122] N. Rabiee, S. Ahmadi, R. Afshari, S. Khalaji, M. Rabiee, M. Bagherzadeh, Y. Fatahi, R. Dinarvand, M. Tahriri, L. Tayebi, Polymeric nanoparticles for nasal drug delivery to the brain: relevance to Alzheimer's disease, Adv. Therapeut. 4 (3) (2021) 2000076.
[123] U.M. Rajadurai, A. Hariharan, S. Durairaj, F. Ameen, T. Dawoud, S. Alwakeel, I. Palanivel, L.P. Azhagiyamanavalan, J.A. Jacob, Assessment of behavioral changes and antitumor effects of silver nanoparticles synthesized using diosgenin in mice model, J. Drug Deliv. Sci. Technol. 66 (2021) 102766.
[124] I. Rana, N. Khan, M.M. Ansari, F.A. Shah, F. ud Din, S. Sarwar, M. Imran, O. S. Qureshi, H.-I. Choi, C.-H. Lee, Solid lipid nanoparticles-mediated enhanced antidepressant activity of duloxetine in lipopolysaccharide-induced depressive model, Colloids Surf. B Biointerfaces 194 (2020) 111209.
[125] Y. Li, J. Liao, L. Xiong, Z. Xiao, F. Ye, Y. Wang, T. Chen, L. Huang, M. Chen, Z.-S. Chen, Stepwise targeted strategies for improving neurological function by inhibiting oxidative stress levels and inflammation following ischemic stroke, J. Contr. Release 368 (2024) 607–622.
[126] Y. Li, Y. Luo, J. Wang, H. Shi, J. Liao, Y. Wang, Z. Chen, L. Xiong, C. Zhang, T. Wang, Discovery of novel danshensu derivatives bearing pyrazolone moiety as potential anti-ischemic stroke agents with antioxidant activity, Bioorg. Chem. 131 (2023) 106283.
[127] J. Liao, W. He, S. Zhang, J. Wang, H. Cheng, L. Gong, Y. Li, Y. Sun, D. Lu, C. Zhang, Magnetic field driven ceria nanosystems for mitochondria targeted therapy of ischemic stroke, Adv. Funct. Mater. (2025) 2423291.
[128] C. Xie, J. Liao, Y. Li, Y. Zhang, Z. Xiao, Y. Wang, T. Chen, L. Xiong, T. Pang, X. Jiang, Synergistic anti-inflammatory effect of cascade nanozymes for neural recovery in ischemic stroke, Chin. Chem. Lett. (2025) 110956.
[129] J. Liao, W. He, L. Li, J. Wang, L. Gong, Q. Zhang, Z. Lin, Mitochondria in brain diseases: bridging structural-mechanistic insights into precision-targeted therapies, Cell Biomater. (2025).
[130] M.S. Rodrigues, G.C. de Paula, M.B. Duarte, V.L. de Rezende, J.C. Possato, H. R. Farias, E.B. Medeiros, P.E. Feuser, E.L. Streck, R.A.M. de Ávila, Nanotechnology as a therapeutic strategy to prevent neuropsychomotor alterations associated with hypercholesterolemia, Colloids Surf. B Biointerfaces 201 (2021) 111608.
[131] S.J. Rosenthal, Nanotechnology in neuroscience reveals membrane mobility matters, ACS Chem. Neurosci. 10 (1) (2018) 30–32.
[132] S. Rubab, K. Naeem, I. Rana, N. Khan, M. Afridi, I. Ullah, F.A. Shah, S. Sarwar, F. ud Din, H.-I. Choi, Enhanced neuroprotective and antidepressant activity of curcumin-loaded nanostructured lipid carriers in lipopolysaccharide-induced depression and anxiety rat model, Int. J. Pharm. 603 (2021) 120670.
[133] L.H. Salem, G.S. El-Feky, R.H. Fahmy, O.N. El Gazayerly, A. Abdelbary, Coated lipidic nanoparticles as a new strategy for enhancing nose-to-brain delivery of a hydrophilic drug molecule, J. Pharmaceut. Sci. 109 (7) (2020) 2237–2251.
[134] J. Su, Z. Yao, Z. Chen, S. Zhou, Z. Wang, H. Xia, S. Liu, Y. Wu, TfR aptamer enhanced blood-brain barrier penetration of biomimetic nanocomplexes for intracellular transglutaminase 2 imaging and silencing in glioma, Small 18 (40) (2022) 2203448.
[135] S. Tang, A. Wang, X. Yan, L. Chu, X. Yang, Y. Song, K. Sun, X. Yu, R. Liu, Z. Wu, Brain-targeted intranasal delivery of dopamine with borneol and lactoferrin co-modified nanoparticles for treating Parkinson's disease, Drug Deliv. 26 (1) (2019) 700–707.
[136] Z. Tang, S. Meng, Z. Song, X. Yang, X. Li, H. Guo, M. Du, J. Chen, Y.Z. Zhu, X. Wang, Neutrophil membrane fusogenic nanoliposomal leonurine for targeted ischemic stroke therapy via remodeling cerebral niche and restoring blood-brain barrier integrity, Mater. Today Bio 20 (2023) 100674.
[137] H. Tian, J. Yao, Q. Ba, Y. Meng, Y. Cui, L. Quan, W. Gong, Y. Wang, Y. Yang, M. Yang, Cerebral biomimetic nano-drug delivery systems: a frontier strategy for immunotherapy, J. Contr. Release 376 (2024) 1039–1067.
[138] N. Tran, W. Zhao, F. Carlson, J.H. Davidson, A. Stein, Metal nanoparticle–carbon matrix composites with tunable melting temperature as phase-change materials for thermal energy storage, ACS Appl. Nano Mater. 1 (4) (2018) 1894–1903.
[139] G. Valle, N. Katic Secerovic, D. Eggemann, O. Gorskii, N. Pavlova, F.M. Petrini, P. Cvancara, T. Stieglitz, P. Musienko, M. Bumbasirevic, Biomimetic computer-to-brain communication enhancing naturalistic touch sensations via peripheral nerve stimulation, Nat. Commun. 15 (1) (2024) 1151.
[140] A. van Teijlingen, S.A. Davis, S.R. Hall, Size-dependent melting point depression of nickel nanoparticles, Nanoscale Adv. 2 (6) (2020) 2347–2351.

[141] C. Vitorino, S. Silva, F. Gouveia, J. Bicker, A. Falcão, A. Fortuna, QbD-driven development of intranasal lipid nanoparticles for depression treatment, Eur. J. Pharm. Biopharm. 153 (2020) 106–120.
[142] C. Wang, B. Wu, Y. Wu, X. Song, S. Zhang, Z. Liu, Camouflaging nanoparticles with brain metastatic tumor cell membranes: a new strategy to traverse blood–brain barrier for imaging and therapy of brain tumors, Adv. Funct. Mater. 30 (14) (2020) 1909369.
[143] C. Wang, Y. Xue, T. Markovic, H. Li, S. Wang, Y. Zhong, S. Du, Y. Zhang, X. Hou, Y. Yu, Blood–brain-barrier-crossing lipid nanoparticles for mRNA delivery to the central nervous system, Nat. Mater. (2025) 1–11.
[144] L. Wang, L. Bai, S. Wang, J. Zhou, Y. Liu, C. Zhang, S. Yao, J. He, C. Liu, D. Li, Biomimetic design and integrated biofabrication of an in-vitro three-dimensional multi-scale multilayer cortical model, Mater. Today Bio 28 (2024) 101176.
[145] R. Wang, W. Song, J. Zhu, X. Shao, C. Yang, W. Xiong, B. Wang, P. Zhao, M. Chen, Y. Huang, Biomimetic nano-chelate diethyldithiocarbamate Cu/Fe for enhanced metalloimmunity and ferroptosis activation in glioma therapy, J. Contr. Release 368 (2024) 84–96.
[146] X. Wang, P. Li, Q. Ding, C. Wu, W. Zhang, B. Tang, Illuminating the function of the hydroxyl radical in the brains of mice with depression phenotypes by two-photon fluorescence imaging, Angew. Chem. Int. Ed. 58 (14) (2019) 4674–4678.
[147] H. Wu, T. Zhang, N. Li, J. Gao, Cell membrane-based biomimetic vehicles for effective central nervous system target delivery: insights and challenges, J. Contr. Release 360 (2023) 169–184.
[148] C. Xie, J. Liao, N. Zhang, Y. Sun, Y. Li, L. Xiong, Y. Zhang, X. Liu, W. Su, H. Chen, Advanced nano drug delivery systems for neuroprotection against ischemic stroke, Chin. Chem. Lett. 35 (2) (2024) 109149.
[149] J. Yang, L. Guo, J. Liao, H. Yi, Nano-enhanced nature medicine for ischemic stroke: opportunities and challenges, Biomed. Technol. 7 (2024) 32–45.
[150] S. Yang, H. Chen, W. Su, Y. Luo, J. Liao, Y. Wang, L. Xiong, C. Zhang, F. Li, Z.-S. Chen, Protective effects of Salvianic acid A against multiple-organ ischemia-reperfusion injury: a review, Front. Pharmacol. 14 (2023) 1297124.
[151] H. Wu, X. Zhu, Microstructures, magnetic, and dielectric properties of Ba-doped BiFeO3 nanoparticles synthesized via molten salt route, J. Am. Ceram. Soc. 102 (8) (2019) 4698–4709.
[152] D. Xu, L.-N. Gao, X.-J. Song, Q.-W. Dong, Y.-B. Chen, Y.-L. Cui, Q. Wang, Enhanced antidepressant effects of BDNF-quercetin alginate nanogels for depression therapy, J. Nanobiotechnol. 21 (1) (2023) 379.
[153] J. Ye, Y. Fan, Y. She, J. Shi, Y. Yang, X. Yuan, R. Li, J. Han, L. Liu, Y. Kang, Biomimetic self-propelled asymmetric nanomotors for cascade-targeted treatment of neurological inflammation, Adv. Sci. 11 (22) (2024) 2310211.
[154] T. Yin, Y. Liu, B. He, B. Gong, J. Chu, C. Gao, W. Liang, M. Hao, W. Sun, J. Zhuang, Cell primitive-based biomimetic nanomaterials for Alzheimer's disease targeting and therapy, Mater. Today Bio 22 (2023) 100789.
[155] L. You, J. Wang, T. Liu, Y. Zhang, X. Han, T. Wang, S. Guo, T. Dong, J. Xu, G. J. Anderson, Targeted brain delivery of rabies virus glycoprotein 29-modified deferoxamine-loaded nanoparticles reverses functional deficits in parkinsonian mice, ACS Nano 12 (5) (2018) 4123–4139.
[156] D. Zhang, Y. Sun, S. Wang, Y. Zou, M. Zheng, B. Shi, Brain-targeting metastatic tumor cell membrane cloaked biomimetic nanomedicines mediate potent chemodynamic and RNAi combinational therapy of glioblastoma, Adv. Funct. Mater. 32 (51) (2022) 2209239.
[157] Y. Hu, M. Zhao, H. Wang, Y. Guo, X. Cheng, T. Zhao, H. Wang, Y. Zhang, Y. Ma, W. Tao, Exosome-sheathed ROS-responsive nanogel to improve targeted therapy in perimenopausal depression, J. Nanobiotechnol. 21 (1) (2023) 261.
[158] K. Ge, Z. Bai, J. Wang, Z. Li, F. Gao, S. Liu, L. Zhang, F. Gao, C. Xie, Engineering EVs-mediated mRNA delivery regulates microglia function and alleviates depressive-like behaviors, Adv. Mater. (2025) 2418872.
[159] H. Zhang, W. Jiao, H. Cui, Q. Sun, H. Fan, Combined exposure of alumina nanoparticles and chronic stress exacerbates hippocampal neuronal ferroptosis via activating IFN-γ/ASK1/JNK signaling pathway in rats, J. Hazard Mater. 411 (2021) 125179.
[160] W. Zhang, A. Mehta, Z. Tong, L. Esser, N.H. Voelcker, Development of polymeric nanoparticles for blood–brain barrier transfer—strategies and challenges, Adv. Sci. 8 (10) (2021) 2003937.
[161] P. Zhao, J. Zhang, A. Wu, M. Zhang, Y. Zhao, Y. Tang, B. Wang, T. Chen, F. Li, Q. Zhao, Biomimetic codelivery overcomes osimertinib-resistant NSCLC and brain metastasis via macrophage-mediated innate immunity, J. Contr. Release 329 (2021) 1249–1261.
[162] Y. Zhou, Z. Peng, E.S. Seven, R.M. Leblanc, Crossing the blood-brain barrier with nanoparticles, J. Contr. Release 270 (2018) 290–303.
[163] Z. Zhou, J. Chen, Y. Liu, C. Zheng, W. Luo, L. Chen, S. Zhou, Z. Li, J. Shen, Cascade two-stage tumor re-oxygenation and immune re-sensitization mediated by self-assembled albumin-sorafenib nanoparticles for enhanced photodynamic immunotherapy, Acta Pharm. Sin. B 12 (11) (2022) 4204–4223.
[164] Z. Zhou, Y. Liu, W. Song, X. Jiang, Z. Deng, W. Xiong, J. Shen, Metabolic reprogramming mediated PD-L1 depression and hypoxia reversion to reactivate tumor therapy, J. Contr. Release 352 (2022) 793–812.
[165] J. Liao, Y. Li, Y. Luo, S. Meng, C. Zhang, L. Xiong, T. Wang, Y. Lu, Recent advances in targeted nanotherapies for ischemic stroke, Mol. Pharm. 19 (9) (2022) 3026–3041.
[166] Y. Pan, L. Li, N. Cao, J. Liao, H. Chen, M. Zhang, Advanced nano delivery system for stem cell therapy for Alzheimer's disease, Biomaterials (2024) 122852.
[167] L. Wang, M. Gu, X. Zhang, T. Kong, J. Liao, D. Zhang, J. Li, Recent advances in nanoenzymes based therapies for glioblastoma: overcoming barriers and enhancing targeted treatment, Adv. Sci. (2025) 2413367.
[168] C. Jiang, X. Yang, Q. Huang, T. Lei, H. Luo, D. Wu, Z. Yang, Y. Xu, Y. Dou, X. Ma, Microglial-biomimetic memantine-loaded polydopamine nanomedicines for alleviating depression, Adv. Mater. (2025) 2417869.
[169] J. Ge, R. Tan, Q. Gao, R. Li, P. Xu, H. Song, S. Wang, Y. Wan, L. Zhou, A multifunctional nanocarrier system for highly efficient and targeted delivery of ketamine to NMDAR sites for improved treatment of depression, Adv. Healthcare Mater. 12 (21) (2023) 2300154.
[170] L. Zhu, Y. Zhong, S. Wu, M. Yan, Y. Cao, N. Mou, G. Wang, D. Sun, W. Wu, Cell membrane camouflaged biomimetic nanoparticles: focusing on tumor theranostics, Mater. Today Bio 14 (2022) 100228.
[171] T.-t. Zhu, H. Wang, H.-w. Gu, L.-s. Ju, X.-m. Wu, W.-t. Pan, M.-m. Zhao, J.-j. Yang, P.-m. Liu, Melanin-like polydopamine nanoparticles mediating anti-inflammatory and rescuing synaptic loss for inflammatory depression therapy, J. Nanobiotechnol. 21 (1) (2023) 52.
[172] A. Zinger, S. Soriano, G. Baudo, E. De Rosa, F. Taraballi, S. Villapol, Biomimetic nanoparticles as a theranostic tool for traumatic brain injury, Adv. Funct. Mater. 31 (30) (2021) 2100722.
[173] J. Liao, L. Fan, Y. Li, Q.-Q. Xu, L.-Y. Xiong, S.-S. Zhang, J.-H. Liu, Z.-C. Xiao, C. Zhang, J. Yang, Recent advances in biomimetic nanodelivery systems: new brain-targeting strategies, J. Contr. Release 358 (2023) 439–464.
[174] J. Liao, L. Gong, Q. Xu, J. Wang, Y. Yang, S. Zhang, J. Dong, K. Lin, Z. Liang, Y. Sun, Revolutionizing neurocare: biomimetic nanodelivery via cell membranes, Adv. Mater. 36 (26) (2024) 2402445.
[175] J. Liao, Y. Li, L. Fan, Y. Sun, Z. Gu, Q.-Q. Xu, Y. Wang, L. Xiong, K. Xiao, Z.-s. Chen, Bioactive ceria nanoenzymes target mitochondria in reperfusion injury to treat ischemic stroke, ACS Nano 18 (7) (2024) 5510–5529.
[176] J. Hu, Z. Lian, Z. Weng, Z. Xu, J. Gao, Y. Liu, T. Luo, X. Wang, Intranasal delivery of near-infrared and magnetic dual-response nanospheres to rapidly produce antidepressant-like and cognitive enhancement effects, Adv. Mater. 36 (31) (2024) 2405547.
[177] W. Zhao, X. Chen, Z. Han, Z. Xun, Y. Qi, H. Wang, C. Chen, Z. Gong, X. Xue, Nanoenzymes-integrated and microenvironment self-adaptive hydrogel for the healing of burn injury and post-burn depression, Adv. Sci. 12 (7) (2025) 2413032.