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A comprehensive review on the impact of polyphenol supplementation and exercise on depression and brain function parameters

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Abstract
The objective of this review study is to examine the combined antidepressant effects of exercise and polyphenol supplementation, with a focus on specific polyphenolic compounds such as crocin, curcumin, and quercetin, as well as different forms of physical exercise, including aerobic and resistance training. The research examines how these interventions influence depressive-like behaviors, cognitive function, and neurochemical markers in animal models and human participants. The findings demonstrate that both exercise and polyphenols independently contribute to mood enhancement, reduced anxiety, and improved cognitive function through mechanisms such as neurogenesis, neurotransmitter modulation, and anti-inflammatory effects. Notably, the combined interventions showed a synergistic effect, providing more significant benefits in reducing symptoms of depression and anxiety, enhancing cognitive performance, and supporting overall mental well-being. These results suggest that integrating exercise and polyphenol supplementation could be a promising non-pharmacological approach to managing depression and related disorders.

Keywords Exercise, Polyphenols, Neuroprotection, Anxiety, Depression

Introduction

Depression is among the most prevalent mental disorders, significantly disrupting emotional control, thought processes, and daily functioning. It is a leading contributor to disability, affecting one in eight individuals globally. Depression manifests through persistent sadness, lack of motivation, and cognitive impairments, requiring effective interventions [1]. In 2020, the COVID-19 pandemic led to a substantial rise in the prevalence of anxiety and depressive disorders. Preliminary data indicate a 26% increase in anxiety disorders and a 28% increase in major depressive disorders within a single year [2]. Although there are effective methods for preventing and treating mental disorders, the majority of affected individuals lack access to appropriate care. Additionally, many people with mental disorders face stigma, discrimination, and human rights violations [3]. Depression is a widespread

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mental health condition marked by enduring sadness, diminished interest in activities once found enjoyable, and a variety of cognitive and physical symptoms that greatly hinder everyday functioning. As reported by the World Health Organization (WHO), depression impacts more than 280 million individuals globally, establishing it as a major contributor to disability worldwide [4]. The origins of depression are multifaceted, involving a complex interaction of genetic, biological, environmental, and psychological factors. Biological aspects particularly include imbalances in neurotransmitters, inflammation, and oxidative stress, which play significant roles in the development and progression of depression [5]. Brain health includes cognitive abilities, emotional stability, and general mental well-being. It is shaped by a variety of factors, such as lifestyle choices, diet, exercise, and genetic predispositions. Depression significantly influences mood and emotional well-being and negatively impacts cognitive functions, including memory, attention, and executive functioning. Long-term depression is linked to structural and functional alterations in the brain, such as a decrease in hippocampal volume, disrupted neural network connectivity, and reduced neurogenesis [6]. Conventional approaches to treating depression usually involve using antidepressant medications and different types of psychotherapy. Although these therapies can be beneficial, they frequently have drawbacks like side effects, inconsistent effectiveness across individuals, and challenges related to accessibility. As a result, there is an increasing focus on exploring alternative and complementary methods for treating depression, especially those centered around lifestyle adjustments. Notably, dietary changes and consistent physical exercise have become prominent areas of study for their ability to enhance mental health without significant adverse effects [7].

Polyphenols are recognized for their antioxidant properties, which play a crucial role in reducing oxidative stress, a significant factor in the onset of depression and neurodegenerative conditions [8]. These compounds exert neuroprotective effects by influencing signaling pathways related to inflammation, oxidative stress, and the generation of new nerve cells in the brain [9]. Polyphenols have emerged as potential natural interventions for depression, influencing brain function through multiple pathways. Flavonoids, for instance, penetrate the blood-brain barrier and exert neuroprotective effects by enhancing synaptic plasticity, decreasing neuroinflammation, and stimulating neurogenesis [10]. Several studies have underscored the potential of polyphenols to enhance mood and cognitive function. Research conducted by Vauzour, Vafeiadou [11] showed that diets rich in flavonoids can improve memory and learning abilities by influencing the signaling pathways crucial for synaptic plasticity [11]. In a study conducted by Lin et al., it was demonstrated that supplementation with polyphenols notably decreased symptoms associated with anxiety and depression among clinical populations [12]. These results imply that incorporating polyphenols into treatment strategies could offer substantial benefits in managing depression and promoting overall brain health.

Regular physical exercise is widely recognized for its positive impact on mental health, enhancing mood, reducing stress, and improving cognitive function. Exercise triggers the release of neurotrophic factors, endorphins, and various neurotransmitters that play crucial roles in maintaining brain health and regulating emotions [13]. Engaging in regular physical activity stands out as a highly effective lifestyle intervention for enhancing mental health. Exercise not only lowers the likelihood of depression but also alleviates its symptoms while boosting cognitive function [14]. These benefits arise from complex interactions involving physiological, psychological, and neurobiological mechanisms. From a physiological perspective, physical exercise boosts cerebral blood flow, thereby improving the supply of oxygen and essential nutrients crucial for optimal brain performance. Additionally, exercise triggers the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which play pivotal roles in fostering neurogenesis and synaptic plasticity [15].

From a psychological perspective, engaging in exercise fosters feelings of accomplishment, diminishes stress levels, and encourages social engagement, all of which collectively enhance mood and overall mental well-being [13]. At the neurobiological level, exercise influences neurotransmitter concentrations, particularly serotonin, dopamine, and norepinephrine, which play pivotal roles in mood regulation. These neurotransmitter changes contribute to secondary benefits, including reduced oxidative stress and neuroinflammation, further promoting brain health and emotional stability [16]. Regarding these advantages, incorporating consistent physical activity into the treatment of depression can markedly improve therapeutic results and promote overall brain well-being. While polyphenols and exercise individually provide substantial benefits for depression and brain health, recent studies indicate that their combined effects could be even more powerful. These interventions intersect in influencing oxidative stress, inflammation, and neurotransmitter function, suggesting synergistic potential in enhancing mental well-being and cognitive function. Given their benefits, integrating polyphenol supplementation with regular exercise presents a promising strategy for optimizing mental health outcomes. These interventions may enhance each other's effects, improving mood and cognitive function by boosting neuroplasticity, decreasing inflammation, and regulating neurotransmitter systems.

This review primarily aims to explore the combined effects of polyphenol supplementation and exercise on depression and brain health parameters. By examining current research, this review aims to clarify how these interventions help reduce depressive symptoms and improve cognitive and emotional well-being.

Depression and brain health

Understanding depression

Depression is a type of mood disorder, influenced by multiple factors, and marked by persistent feelings of sadness and a lack of interest or pleasure in activities [17]. The term "depression" can describe both a symptom and a medical condition. As a symptom, it encompasses a range of feelings from mild sadness to severe, pathological depression. However, as a syndrome, it requires a specific set of diagnostic criteria to be met [18]. Depression is identified by a range of symptoms including ongoing feelings of hopelessness, cognitive decline, physical discomfort, decreased motivation, impaired thinking, disrupted sleep patterns, and reduced verbal and physical activity. Patients with mild depression often exhibit physical dysfunctions, such as weight loss, sleep disturbances, fatigue, and weakness. In contrast, those with severe depression may experience more extreme symptoms, including suicidal behavior [19]. Given the significant burden of these symptoms, depression is recognized as one of the most common and debilitating mental health conditions worldwide. It affects individuals of all ages and backgrounds, significantly impairing daily functioning and quality of life. The WHO reports that depression impacts around 5% of the global adult population, ranking it among the most prevalent mental health disorders worldwide. According to the same report, depression is more common in women, affecting about 6% of women compared to 4% of men at any given time. Moreover, depression affects approximately 5.7% of adults aged 60 and above, underscoring its widespread occurrence across various age demographics [4]. Depressive disorders vary in presentation and severity. The most common form, Major Depressive Disorder (MDD), affects approximately 51.3% of individuals diagnosed with depression. Other subtypes include melancholic depression, psychotic depression (38% prevalence), and bipolar disorder, which alternates between depressive and manic episodes. Additionally, antenatal and postnatal depression, cyclothymic disorder, and seasonal affective disorder are recognized variations with distinct clinical characteristics [20]. During a bout of depression, a person experiences a prolonged state of low mood marked by feelings of sadness, irritability, or emptiness. This period can also include a significant reduction in interest or enjoyment from activities that previously brought happiness or satisfaction [21]. This condition persists throughout most of the day, almost every day, for a minimum of two weeks, clearly setting it apart from normal fluctuations in mood [22]. In addition to feeling depressed, individuals often display a variety of other symptoms. These can encompass challenges with concentration, heightened feelings of guilt or diminished self-esteem, a pervasive feeling of hopelessness regarding the future, recurring thoughts about death or suicide, disruptions in sleep patterns, alterations in appetite resulting in either weight loss or gain, and a persistent sense of fatigue or lack of energy [23, 24]. Depression significantly impacts various aspects of life, including social interactions, productivity at work or school, and participation in community activities [25]. The severity of a depressive episode is classified as mild, moderate, or severe depending on the number and intensity of symptoms and how they disrupt daily activities [26]. Depressive episodes can present in different patterns. For instance, individuals with a single episode depressive disorder experience their initial and singular episode of depression [27]. On the other hand, those with recurrent depressive disorder have a history of encountering at least two separate episodes of depression, typically alternating with periods of normal mood [28]. Bipolar disorder is characterized by alternating episodes of depression and manic symptoms. During manic phases, individuals typically experience elevated mood, heightened activity levels, rapid speech, inflated self-esteem, reduced need for sleep, distractibility, and impulsivity [29].

Diagnosis and treatment

Diagnosing depression involves a thorough evaluation by a healthcare professional, which typically includes a clinical interview, standardized screening tools, and an assessment of the patient's medical and psychological history. The primary method for diagnosing MDD follows the American Psychiatric Association's DSM-5 criteria, which require at least five specific symptoms (e.g., depressed mood, loss of interest) to be present over a two-week period. While the diagnosis is primarily clinical, physical exams and laboratory tests may be used to exclude underlying medical conditions that mimic depressive symptoms, such as thyroid dysfunction or vitamin deficiencies [30]. Common tools used to assess depression include the Patient Health Questionnaire-9 (PHQ-9) and the Beck Depression Inventory (BDI). These tools help quantify the severity of depression symptoms [31, 32]. In addition, clinicians may use structured interviews like the SCID-5 (Structured Clinical Interview for DSM-5) for a more detailed evaluation [33]. Getting an accurate diagnosis is crucial to differentiate depression from other mental health conditions and to ensure that the patient receives the most effective treatment. Effective treatment options for depression involve

both psychological therapies and medications. Psychological treatments are generally considered the primary approach for managing depression. In cases of moderate to severe depression, these psychological therapies can be supplemented with antidepressant medications [34]. However, for mild depression, medication is usually not necessary. Psychological therapies focus on helping individuals develop new perspectives, coping mechanisms, and interpersonal skills. These approaches typically involve talk therapy sessions with trained professionals or supervised lay therapists, and can take place either face-to-face or through online platforms [35, 36].

Brain health parameters

Cognitive function

Cognitive function encompasses the mental abilities that allow individuals to perform tasks, from the simplest to the most complex. These abilities include memory, attention, language, problem-solving, and decision-making. Maintaining cognitive function is essential for everyday activities and significantly impacts the overall quality of life. As individuals age, a decline in cognitive abilities is often observed, but this process can be influenced by factors such as genetics, lifestyle, and environmental conditions. Studies show that engaging in physical exercise, following a healthy diet, and staying mentally active through activities like reading or solving puzzles can help sustain or even enhance cognitive function [37, 38]. Moreover, progress in neuroimaging technologies such as magnetic resonance imaging (MRI) and positron emission tomography (PET) has offered a more comprehensive understanding of the structural and functional alterations in the brain associated with cognitive decline. These alterations include hippocampal atrophy, reduced gray matter volume in the prefrontal cortex, impaired synaptic density, and disruptions in neural network connectivity. Functionally, cognitive decline is linked to decreased cerebral blood flow, altered neurotransmitter activity, and impaired neurogenesis, which collectively contribute to deficits in memory, attention, and executive functioning [39].

Neuroplasticity

Neuroplasticity refers to the extraordinary capacity of the brain to reshape itself by creating new neural pathways throughout an individual's lifetime. This flexibility is essential for acquiring new skills, consolidating memories, and recovering from brain injuries [40]. Neuroplasticity plays a crucial role in depression recovery, as it allows the brain to adapt to stress and form new neuronal connections. Deficits in neuroplasticity are linked to cognitive decline and mood disorders, making it a critical target for therapeutic interventions. Several factors can enhance neuroplasticity, including enriched environments, physical exercise, and pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs), N-methyl-D-aspartate (NMDA) receptor modulators like ketamine, and neurotrophic agents such as BDNF enhancers. These pharmacological interventions promote synaptic remodeling, enhance neuronal survival, and improve cognitive function in individuals with neuropsychiatric disorders. A critical molecule in this process is BDNF, which supports the survival and growth of neurons [41]. Research indicates that aerobic exercise can increase BDNF levels, which in turn enhances cognitive function and emotional health. This demonstrates the brain's remarkable ability to adapt and recover, even when confronted with damage or disease [42].

Neuroinflammation

Neuroinflammation refers to the activation of the brain's immune response, which can be initiated by infections, toxic substances, or brain injuries. While acute neuroinflammation acts as a natural and protective mechanism, prolonged neuroinflammation is linked to numerous neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [43]. Pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) play a key role in the inflammatory processes and are associated with the advancement of neurodegenerative diseases. To address neuroinflammation, various strategies are employed, including the use of anti-inflammatory drugs and lifestyle modifications like improved diet and consistent physical activity. These approaches have demonstrated potential in lowering inflammation levels and enhancing overall brain health [44].

Neurotransmitter regulation

Neurotransmitters are essential chemicals that facilitate communication between neurons and play a crucial role in regulating mood and cognitive function. Imbalances in neurotransmitter systems—particularly in serotonin, dopamine, and norepinephrine—are strongly implicated in depression. Low serotonin levels are associated with mood dysregulation, while deficits in dopamine contribute to anhedonia and lack of motivation. Additionally, disruptions in the balance between excitatory neurotransmitters like glutamate and inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) can further exacerbate depressive symptoms. Given these complex interactions, targeting neurotransmitter regulation is a primary focus of depression treatment strategies [45]. Serotonin and dopamine play critical roles in regulating mood, and many psychiatric treatments are designed to correct imbalances in these neurotransmitters [46]. Furthermore, maintaining a proper equilibrium

between excitatory neurotransmitters, such as glutamate, and inhibitory neurotransmitters, like GABA, is crucial for ensuring stable neural function. An imbalance in neurotransmitter systems can contribute to various disorders, including anxiety and seizures. Gaining a thorough understanding of these systems is crucial for creating effective treatments and enhancing the overall outcomes for patients [47, 48].

Exercise and mental well-being

Types of exercise

Exercise is fundamental for sustaining and enhancing overall health. Different types of exercise provide unique physiological and psychological benefits, making them important for mental well-being. Aerobic activities, resistance training, and high-intensity interval training (HIIT) each contribute to health improvements in distinct ways, particularly in the context of depression and cognitive function.

Aerobic exercise

Aerobic exercise, often referred to as cardiovascular or endurance training, encompasses activities designed to elevate the heart rate and breathing rate by involving large muscle groups. Examples of aerobic exercise include walking, running, cycling, and swimming. The health advantages of aerobic exercise are widely recognized. Engaging consistently in aerobic activities boosts cardiovascular health, increases lung function, and supports effective weight management [49]. Furthermore, engaging in aerobic exercise has been associated with a lower risk of developing chronic conditions, including type 2 diabetes, high blood pressure, and some types of cancer [50]. The American College of Sports Medicine advises that adults should aim for a minimum of 150 min of moderate-intensity aerobic activity or 75 min of vigorous-intensity exercise each week to gain significant health benefits [51].

Resistance training

Resistance training, also known as strength training, focuses on enhancing muscle strength, endurance, and size through exercises that counteract a force. This type of training can be performed using free weights, resistance bands, various weight machines, or body weight exercises such as calisthenics, pull-ups, push-ups, and squats, which require no external resistance but rely on the individual's own body weight to build strength [52]. Resistance training is notably effective in combating muscle loss associated with aging and enhancing the ability to perform everyday tasks [53]. The American College of Sports Medicine advises incorporating resistance exercises targeting all major muscle groups at least twice a week into a well-rounded fitness regimen [51].

High-intensity interval training (HIIT)

HIIT involves alternating between brief, vigorous exercise and lower-intensity recovery or rest periods. This training method can encompass various activities like sprinting, cycling, body-weight exercises, and circuit training. HIIT has become increasingly popular because it effectively enhances cardiovascular fitness and reduces body fat more quickly than traditional aerobic exercise [54]. Research has demonstrated that HIIT can boost insulin sensitivity, elevate mitochondrial density, and enhance overall physical performance [55]. Importantly, HIIT also exerts significant mental health benefits, including reductions in depressive symptoms and anxiety levels. Studies suggest that short bursts of intense exercise stimulate endorphin release, enhance serotonin production, and improve cognitive flexibility, making HIIT a valuable intervention for mental well-being [56]. However, it may not be appropriate for everyone, especially individuals with specific medical conditions or those new to exercise. Thus, aerobic exercise, resistance training, and HIIT each provide distinct advantages and can collectively form a comprehensive fitness program. The selection of exercise types should be tailored to personal objectives, current fitness levels, and any existing health issues. Including a mix of these exercises can maximize overall health benefits and improve physical performance.

Effects on depression

Reduction of depressive symptoms

Extensive research has investigated the impact of exercise on depression, consistently demonstrating its effectiveness in alleviating depressive symptoms. Engaging in regular physical activity is known to elevate mood, boost energy levels, and enhance overall well-being, making it a beneficial strategy for individuals dealing with depression [57]. Various forms of exercise, including aerobic training, resistance training, and dance-based therapies, have been studied for their role in mental health improvements. Table 1 provides an overview of these exercise modalities and their specific effects on depressive symptoms and cognitive function, illustrating the most effective approaches for different populations. The studies included span various populations, including adolescents, older adults, and individuals with major depressive disorder or mild cognitive impairment. The data highlights that aerobic exercise, resistance training, and dance-based therapies show significant improvements in mood and cognition. Notably, high-intensity and structured exercise programs yield the most substantial benefits, suggesting that tailored exercise interventions could be an effective non-pharmacological strategy for managing depression and cognitive decline.

Exercise alleviates depressive symptoms through several neurochemical pathways. One key mechanism is

Table 1 The effects of different types of exercise on depressive symptoms and cognitive functions

Exercise Type	Intervention	Population	Results	Reference
Aerobic exercise	12 sessions of preferred intensity aerobic exercise alongside treatment as usual	87 adolescents with depression	No immediate effect on depressive symptoms post-intervention, but a significant improvement was observed at 6-month follow-up.	[262]
Aerobic exercise	6-week structured aerobic program	66 low-income Hispanic children (Grade 4)	Significant reduction in depression and increased self-esteem in the aerobic group.	[263]
Supervised exercise therapy	3 one-on-one supervised sessions per week for 8 weeks, followed by a home program	81 obese adolescents (11–16 years)	Significant improvements in self-esteem and depressive symptoms. No significant changes in BMI.	[264]
Combined aerobic and resistance training	22-week aerobic, resistance, and combined training program	304 obese adolescents (14–18 years)	Resistance and combined training showed significant improvements in depressive symptoms, body image, and physical self-perception.	[265]
Aerobic exercise	12 weeks of high-intensity exercise (> 12 kg/kcal/week)	30 adolescents with major depressive disorder	Significant improvement in depressive symptoms (100% response and 86% remission in the exercise group). Sustained remission observed at 26 and 52 weeks.	[266]
Dance Movement Therapy	12 weeks of dance movement therapy (DMT)	40 adolescents with mild depression	Significant improvement in depressive symptoms and stabilization of serotonin and dopamine levels.	[267]
Jogging	8 weeks of jogging, 50-minute sessions, 5 days per week	49 adolescent females with mild-to-moderate depression	Significant reduction in depressive symptoms, urinary cortisol, and epinephrine levels. Improved cardiovascular fitness and stress response.	[267]
Aerobic exercise	13-week aerobic exercise (low dose: 20 min/day, high dose: 40 min/day)	207 overweight children (7–11 years)	Dose-response benefits on depressive symptoms. Improved self-worth in White children, but no significant improvement in global self-worth in Black children.	[268]
Personalized exercise	12-week individualized aerobic or resistance training program, 45–60 min, 3 times/week	86 college students with depressive symptoms	Significant reduction in depressive symptoms and improved physical activity in both aerobic and resistance training groups.	[269]
Square dance	12-week square dance program	136 older women with mild cognitive impairment	Improved cognitive function, quality of life, and reduced depressive symptoms.	[270]
Structured limbs exercise	24-week structured exercise program, 60 min/session, 3 sessions/week	116 older adults with mild cognitive impairment	Improved cognitive function mediated by reduced depressive symptoms and improved sleep quality.	[271]
Ballroom dancing	10 months of ballroom dancing	129 older adults with amnestic mild cognitive impairment	Improved cognitive performance and reduced depressive symptoms in the intervention group.	[272]
Aerobic dance	12 weeks of a specially designed aerobic dance routine	60 patients with mild cognitive impairment	Significant improvement in episodic memory and processing speed.	[273]
Yoga	12 weeks of twice-weekly yoga sessions	37 older adults with mild cognitive impairment	Reduced stress and modest improvement in visuospatial skills.	[274]
Kundalini yoga	12 weeks of Kundalini yoga, 60 min/session	81 adults with mild cognitive impairment	Improved executive functioning and resilience. Reduced depressive symptoms.	[275]
Sport stacking	12 weeks of sport stacking, 30 min/session, 5 days/week	48 older adults with mild cognitive impairment or AD	Improved cognitive function and increased neuroprotective growth factors (BDNF, IGF-1).	[276]
Walking	12 weeks of walking (moderate: 150 min/week, vigorous: 75 min/week)	37 older adults with mild cognitive impairment	Significant improvements in cognitive performance, reduced anxiety severity, and improved cardiorespiratory fitness.	[277]

the release of endorphins, which are natural pain relievers that induce feelings of euphoria, commonly known as the 'runner's high' [58, 59]. Another crucial factor is the enhancement of neurotransmitter activity. Regular physical activity increases serotonin levels, which helps regulate mood, emotions, and sleep, thereby reducing depressive symptoms [57]. Additionally, exercise boosts dopamine production, improving reward processing and motivation—factors often impaired in individuals with depression [60]. These neurochemical changes collectively contribute to the antidepressant effects of physical activity. A meta-analysis by Morres et al. revealed that individuals who consistently participated in regular exercise had considerably lower levels of depressive symptoms compared to their sedentary counterparts. This meta-analysis reviewed research on aerobic exercise programs. The results indicate that while the specific type of exercise may not be the most important factor, maintaining regularity and intensity in physical activity is crucial for reducing depressive symptoms

[61]. Exercise not only induces biochemical alterations but also fosters psychological benefits. Participating in physical activity often leads to a sense of achievement and boosts self-esteem, aspects that are frequently diminished in individuals suffering from depression [62]. Structured exercise routines provide a sense of regularity and purpose, which can be particularly advantageous for individuals dealing with depressive symptoms [63]. Another way exercise alleviates depression is by encouraging behavioral activation, a key psychological intervention for mood improvement. Individuals with depression often withdraw from social interactions, worsening feelings of isolation and sadness [64]. Engaging in structured physical activities, particularly in group settings such as fitness classes or sports teams, provides opportunities for social connection. These interactions not only enhance mood but also reinforce a sense of community and belonging, which are crucial for mental well-being [65]. Participating in group fitness classes, joining sports teams, or being part of walking clubs creates opportunities for social interaction. These activities can significantly enhance mood and contribute positively to overall mental well-being [66]. Moreover, engaging in physical activity can act as a helpful diversion from negative thinking and repetitive worries that often accompany depression. The concentration needed for exercise helps shift focus away from troubling thoughts, offering temporary relief from the mental strains of depression. With regular practice, this shift in focus can lead to a noticeable decrease in the severity of depressive symptoms [67]. Crucially, the positive effects of physical activity on depression extend beyond those already diagnosed with the condition. Studies indicate that regular exercise can also help prevent the development of depression in individuals who are at risk [13]. Research conducted by Harvey et al. revealed that increased physical activity is linked to a decreased likelihood of developing depression over time. This finding underscores the value of exercise as a practical and affordable approach for promoting mental health and preventing depressive disorders [68]. Hence, exercise offers a broad range of benefits for managing and preventing depression. Its positive impact on mood regulation, biochemical processes, psychological well-being, and social interaction highlights its effectiveness as a comprehensive approach to mental health. Consistent engagement in physical activity, no matter the form, can substantially alleviate symptoms of depression and enhance the overall quality of life for those experiencing this condition [69, 70].

Impact on anxiety and stress

Exercise not only helps with depressive symptoms but also significantly influences anxiety and stress. Engaging in physical activity can serve as a natural remedy for anxiety, alleviating both its physical and psychological symptoms. Exercise's impact on anxiety can be attributed, in part, to its influence on the hypothalamic-pituitary-adrenal (HPA) axis, a key regulator of the body's stress response [71]. This system controls the release of cortisol, a hormone crucial for managing stress. When stress becomes chronic, it can lead to persistent activation of the HPA axis, causing consistently high levels of cortisol. This prolonged exposure to elevated cortisol can contribute to increased anxiety and various other health problems [72]. Engaging in consistent physical activity has been demonstrated to lower cortisol levels, which helps stabilize the body's response to stress. Research conducted by Hill et al. revealed that individuals who regularly participated in aerobic exercises exhibited notably reduced cortisol levels when faced with stressors, compared to those who led a sedentary lifestyle. This decrease in cortisol helps counteract the detrimental effects of prolonged stress and contributes to better mental well-being [73]. Additionally, physical activity promotes the release of neurotrophic factors like BDNF, which plays a crucial role in supporting neuronal growth and function. Elevated levels of BDNF have been linked to lower levels of anxiety and enhanced cognitive performance, underscoring the positive impact of exercise on brain health and function [74]. Another significant effect of exercise on anxiety and stress is its positive influence on sleep quality. Anxiety and stress often lead to poor sleep, and physical activity has been demonstrated to improve both the duration and quality of sleep [75]. Brand et al. conducted a study revealing that adolescents engaging in regular physical activity experienced better sleep quality and lower anxiety levels than their less active counterparts. Enhanced sleep quality contributes to improved emotional regulation and reduced anxiety, establishing a beneficial cycle that promotes overall mental well-being [76].

Behavioral mechanisms significantly contribute to the anxiety-reducing effects of physical activity. Engaging in exercise offers a healthy way to release accumulated energy and tension, often experienced by those with anxiety. The rhythmic movements involved in activities like running, cycling, or swimming can induce a meditative state, aiding in calming the mind and alleviating anxiety symptoms [63, 77]. Social engagement is another crucial element. Joining group exercises or team sports can cultivate a sense of community and provide social support, which is vital for handling anxiety and stress [78]. Being socially connected offers emotional backing, diminishes feelings of loneliness, and creates opportunities for positive social interaction. This structured environment can be especially advantageous for individuals dealing with social anxiety, as it facilitates safe and supportive social experiences [79, 80].

Mechanisms of action

Neurotransmitter modulation

Depression and anxiety are closely linked to dysfunctions in neurotransmitter systems, particularly the monoaminergic, neurotrophic, and neuropeptide pathways. Among these, serotonin, dopamine, and noradrenaline are central to mood regulation and are frequently dysregulated in depressive disorders [81]. Additionally, BDNF and neuropeptide Y (NPY) contribute to neurogenesis and neuronal health, playing crucial roles in emotional resilience [82]. Excitatory and inhibitory neurotransmitter systems, such as glutamate and GABA, also influence stress response and cognitive function. Moreover, neuropeptides like orexins regulate sleep-wake cycles and interact with monoaminergic pathways, further implicating their role in depression pathophysiology [83, 84]. Balancing the catecholaminergic, monoaminergic, glutamatergic, and orexinergic systems is crucial for maintaining mental health. Unfortunately, many current antidepressants take a long time to start working and are not always effective, highlighting the need for quicker, more efficient treatments with fewer side effects.

Research indicates that lifestyle choices, such as regular exercise, can positively influence these neurotransmitter systems, providing significant benefits for mental well-being [85]. Various forms of physical activity, including aerobic exercise, resistance training, and HIIT, influence neurotransmitter regulation and neurobiological pathways in distinct ways, leading to different mental health outcomes. These variations are linked to changes in key neurochemical systems, including serotonin, dopamine, endorphins, GABA, and BDNF, which contribute to mood enhancement, cognitive function, and emotional resilience (Table 2).

Serotonin plays a critical role in mood regulation, sleep patterns, and appetite control, and its dysregulation is strongly linked to depression and anxiety [86]. In individuals with depression, serotonin levels are frequently lower than normal, leading to mood disturbances and cognitive impairments. One well-established way to enhance serotonin function is through physical activity, which has been shown to boost serotonin production and release in the brain. This process leads to increased sensitivity of serotonin receptors and stimulation of hippocampal neurogenesis, contributing to long-term improvements in mood and cognitive abilities [87, 88].

The impact of exercise on serotonin regulation in the brain varies depending on exercise type, intensity, and duration. Aerobic training, such as running at 19 m/min for 8 weeks, has been shown to promote hippocampal neurogenesis and counteract serotonin receptor deficits associated with chronic stress-induced depression [89, 90]. Swimming-based exercise models further confirm this effect, with studies showing increased 5-HT2 receptor responsiveness and postsynaptic 5-HT1A receptor function in the brain after four weeks of training [91]. The duration and intensity of exercise influence serotonin metabolism in distinct brain regions: acute swimming (1 h) increases 5-HT and 5-HIAA levels specifically in the brainstem, while prolonged swimming (4 weeks) enhances serotonin turnover in the cerebral cortex, with effects persisting for up to a week post-exercise. However, chronic swimming results in a transient reduction of hippocampal and hypothalamic 5-HT levels, followed by a rebound effect after a week of rest [92].

Beyond direct serotonin modulation, exercise influences stress-related biochemical pathways. In models of chronic stress-induced depression, swimming has been shown to reduce serum corticosterone (CORT) levels and proinflammatory cytokines (IFN-γ, TNF-α), while simultaneously increasing serotonin levels in the prefrontal cortex, reinforcing its antidepressant effects [93]. Additionally, exercise contributes to better sleep quality by modulating striatal serotonin and norepinephrine levels in sleep-deprived mice, potentially alleviating symptoms such as fatigue, mood instability, and impaired cognitive function [94]. These findings highlight the multifaceted role of exercise in serotonin regulation, suggesting that its benefits extend beyond serotonin alone and involve broader neurobiological mechanisms.

Endorphins, a different set of neurotransmitters, are released during vigorous exercise, excitement, and in response to pain, functioning as natural analgesics and mood boosters [95]. These neuropeptides, which include β-endorphin, enkephalins, and dynorphins, play a crucial role in enhancing mood, lowering anxiety levels, and promoting a general sense of well-being [6]. Notably, β-endorphin has been found to exert substantial antidepressant effects by influencing dopamine neurons involved in motivation and pleasure [96]. The influence of exercise on depressive symptoms varies based on exercise modality and intensity. In elderly individuals, a six-week structured aerobic regimen was associated with significant reductions in Beck Depression Inventory (BDI) scores, particularly in somatic symptoms, suggesting that physical activity contributes to emotional well-being and mood stabilization [67]. Similarly, research suggests that resistance training may induce a more pronounced increase in β-endorphins compared to aerobic exercise, pointing to distinct neurochemical responses across exercise types [97]. Furthermore, HIIT has been demonstrated to trigger the acute release of plasma β-endorphins, supporting both stress reduction and mood enhancement. While peripheral β-endorphins are often linked to analgesia and mood regulation, their direct influence on central nervous system activity remains debated. This effect is particularly notable in HIIT due to the rapid energy demands and metabolic

Table 2 Effects of different exercise modalities on neurotransmitter regulation and depressive symptoms in animal and human studies

Exercise Type	Intervention	Population	Neurobiological Effects	Results	Reference
Animal studies					
Aerobic exercise	1-hour swimming daily for 4 weeks	Male rats	Increased hippocampal neuropeptide Y (NPY) content; attenuated depressive symptoms.	Exercise reduced immobility in the tail suspension test and increased hippocampal NPY levels.	[139]
Aerobic treadmill	30 min/day for 2 weeks	Postpartum depression (PPD) rat model	Increased serotonin (5-HT) and tryptophan hydroxylase (TPH) expression in the dorsal raphe.	Improved depressive behaviors in PPD rats; treadmill running enhanced serotonergic activity.	[150]
Swimming exercise	Chronic swimming regimen	Chronically stressed rats	Decreased corticosterone, inflammatory cytokines (IFN-γ, TNF-α), and IDO activity; increased 5-HT levels.	Ameliorated depression-like behavior induced by chronic stress through inhibition of inflammation and IDO activity.	[93]
High-intensity running	Voluntary wheel running for 5 weeks	Flinders Sensitive Line (FSL) rats	Increased hippocampal cell proliferation; no significant change in brain-derived neurotrophic factor (BDNF).	Antidepressant effects of running associated with increased hippocampal neurogenesis.	[100]
Treadmill exercise	4 weeks of treadmill running	Rats with chemically induced seizures	Upregulated GABAA receptor α1 and GAD65 in the hippocampus; neuroprotective effects.	Reduced seizure severity and increased neural viability via enhanced GABAergic signaling.	[278]
Aerobic exercise	Treadmill exercise (30 min, 5 days/week for 4 weeks)	Alzheimer's disease mouse model	Decreased hippocampal amyloid-β, glutamate, and pro-inflammatory cytokines; increased BDNF levels.	Improved cognitive and depressive behaviors; reduced hippocampal inflammation.	[125]
High-intensity running	Voluntary wheel running for 3 weeks	Rats	Increased dopamine (DA) in the medial prefrontal cortex (mPFC); decreased corticosterone response to stress.	Exercise-induced antidepressant effects were mediated by CORT-GR-DA-D2R pathways in the mPFC.	[107]
Resistance training	8-week resistance training (3 sessions/week)	Rats	Increased hippocampal BDNF and decreased pro-inflammatory cytokines.	Improved depressive symptoms and reduced inflammation through BDNF-mediated mechanisms.	[149]
Swimming exercise	30 min/day, 5 days/week for 3 weeks	Rats treated with monosodium glutamate (MSG)	Decreased cortical spreading depression (CSD) velocity; increased microglial reaction.	Swimming reduced cortical excitability despite MSG treatment, suggesting neuroprotective effects.	[128]
Anaerobic exercise	6-week resistance training	Depression-resistant mouse model	Enhanced hippocampal noradrenaline and neurogenesis; no change in 5-HT.	Prevented chronic stress-induced depression-like behavior independent of serotonergic pathways.	[152]
Aerobic	Voluntary wheel running for 6 weeks	Male F344 rats	Increased striatal dopamine (DA), reduced stress-evoked serotonin (5-HT)	Reduced stress-induced depressive behaviors	[279]
Aerobic	Wheel running for 4 weeks	Rats	Altered GABAA receptor subunits, increased GAD67 expression in the hippocampus	Improved stress coping and emotionality	[115]
Aerobic	Running	Rats	Increased dynorphin mRNA in the medial caudate putamen, similar to effects of cocaine	Running induced molecular adaptations associated with addiction-like behaviors	[101]
Aerobic	running at 19 m/min, 5 days/week for 8 weeks	Mice with tricyclic antidepressant treatment-resistant depression	Increased hippocampal neurogenesis and serotonin levels	Exercise-induced antidepressant effects mediated by 5-HT3 receptors	[89]
Aerobic	1-hour swimming daily for 4 weeks	Male rats	Increased 5HT and its metabolites in brainstem and cortex	Sustained antidepressant effects mediated by enhanced serotonin metabolism	[92]
Aerobic	8-week treadmill exercise	Sleep-deprived mice	Increased serotonin, reduced norepinephrine, decreased serotonin turnover	Prevented depressive behavior and reduced striatal neurotransmitter alterations	[94]
Aerobic	12-week treadmill running	C57BL/6 mice with repeated stress	Reduced hypocretin/orexin and MCH in basolateral amygdala	Counteracted stress-induced depression via suppression of neural systems	[280]
Aerobic	15 min cycle ergometer at 75 W	Healthy males	Increased plasma orexin A and physiological parameters (HR, GSR)	Exercise-induced physiological adaptations involving orexin A	[281]

Table 2 (continued)

Exercise Type	Intervention	Population	Neurobiological Effects	Results	Reference
High-Intensity	6-week high-intensity exercise program	Moderately depressed males	β-Endorphin release, improved mood	Significant reduction in depressive symptoms	[97]
Prolonged swimming	25 km swim competition	16 male long-distance swimmers	Increased plasma neuropeptide Y (NPY) and decreased leptin levels.	Compensatory regulation of energy balance via the NPY-leptin axis.	[140]
Moderate-intensity yoga	12-week yoga program, 60 min/session, 3 sessions/week	Healthy adults	Increased thalamic GABA levels correlated with mood and anxiety improvements.	Improved mood and reduced anxiety; associated with increased GABAergic activity.	[118]
Aerobic exercise	12-week exercise program	Humans with metabolic syndrome (MetS)	Increased plasma orexin A; decreased triglycerides, BMI, and resting heart rate.	Improved metabolic parameters and sympathetic activation linked to orexin A.	[137]
Aerobic (Treadmill)	45-minute treadmill exercise with Acipimox (Aci) administration	Bulimia nervosa patients and healthy women	Increased plasma NPY and GH levels, improved glycerol turnover	Exercise and Aci improved neuropeptidergic responses in bulimia nervosa patients	[141]
Aerobic exercise	12-week cycling program	33 trained athletes	Increased kynurenine and kynurenic acid levels; decreased tryptophan levels.	Modulated tryptophan-kynurenine pathway linked to immune activation and cognitive function.	[146]
Mixed exercise	Yoga (12-week program) vs. walking (metabolically matched)	Healthy adults	Yoga increased thalamic GABA levels; no such effect with walking.	Yoga improved mood and reduced anxiety more effectively than walking.	[118]

stress, leading to both immediate and long-term psychological benefits. Importantly, the interaction between endorphins and other neurotransmitter systems, such as dopamine and serotonin, suggests a broader, integrated mechanism by which exercise supports mental well-being. This highlights the synergistic effects of exercise-induced neurotransmitter modulation, reinforcing the role of physical activity as an effective non-pharmacological intervention for depression and anxiety [98].

Intense exercise has been shown to increase plasma β-endorphin and leu-enkephalin levels, which may contribute to mood stabilization and relaxation. While plasma β-endorphin levels correlate with stress resilience, central β-endorphin release in the brain remains a subject of ongoing investigation [95]. Unlike β-endorphins and enkephalins, dynorphins act on kappa opioid receptors (KORs) and are often released in response to stress. While dynorphins have been associated with anxiety and depressive symptoms in certain contexts, some studies indicate that they can enhance serotonin levels, providing potential antidepressant effects [99]. Exercise-induced dynorphin release is linked to increased BDNF expression, which supports neuroplasticity and may contribute to antidepressant effects [100]. In animal models, voluntary exercise has been shown to upregulate dynorphin mRNA, further suggesting a potential therapeutic role for physical activity in depression management [101].

Dopamine is a vital neurotransmitter that plays a key role in reward, mood regulation, and attention. Physical activity stimulates the mesolimbic dopamine pathway, increasing dopamine levels and receptor sensitivity, which are essential for both mood stabilization and cognitive function [102]. Importantly, dopamine does not act in isolation but interacts with serotonin, BDNF, and other neurochemical systems to regulate emotional resilience. Exercise enhances dopaminergic transmission by activating D1 and D2 receptors, leading to improved synaptic plasticity and neurogenesis [103]. These mechanisms collectively contribute to the antidepressant effects of exercise. Dopamine receptor activation facilitates cyclic AMP (cAMP) signaling and the activation of protein kinase A (PKA), which in turn enhances the expression of brain-derived neurotrophic factor (BDNF)—a key regulator of neurogenesis and cognitive enhancement. Additionally, dopamine modulates hippocampal neurogenesis by promoting the proliferation of neural progenitor cells in the dentate gyrus, a process essential for learning and memory [104]. The activation of dopamine pathways by exercise has also been shown to improve working memory and executive function by strengthening prefrontal cortex activity, which plays a crucial role in cognitive flexibility and emotional regulation [105].

Treadmill running (10 m/min, 5 days/week for 6 weeks) increases dopamine D2 receptor-like binding in the dorsomedial caudate putamen, ventrolateral caudate putamen, ventromedial caudate putamen, and olfactory tubercle, supporting its potential antidepressant effects [106]. Voluntary exercise enhances dopamine release, but blocking D2 receptors eliminates these benefits, indicating its key role in mood regulation [107]. Exercise also

restores dopamine receptor function in addiction models, highlighting its therapeutic potential [108]. A combination of aerobic and resistance training increases dopamine levels more effectively than aerobic exercise alone. Studies show that mixed training improves mental health and dopamine production, reducing depression symptoms [109]. Exercise stimulates dopamine release via BDNF, enhancing neuroplasticity and cognitive function. Voluntary running boosts BDNF and dopamine levels in the striatum, with sustained effects even after a week of rest [110].

GABA is an inhibitory neurotransmitter essential for reducing neuronal excitability and promoting relaxation [111]. Physical activity enhances GABAergic transmission by increasing receptor expression and synthesis, with different exercise modalities influencing this system in distinct ways [112, 113]. For instance, aerobic exercise significantly increases GABA receptor subunit expression (α2, α5, γ2) in the prefrontal cortex and hippocampus, contributing to improved mood regulation [114]. Long-term voluntary running also elevated GAD67 enzyme expression in the forebrain, facilitating greater GABA production and modulating the GABAergic system to counteract depression [115]. Meanwhile, anaerobic and high-intensity circuit training induce acute GABAergic responses through lactate metabolism, which serves as a precursor for GABA synthesis in the sensorimotor cortex [116]. These differences underscore the importance of tailoring exercise interventions for optimal mental health benefits.

Yoga has been found to significantly boost plasma GABA levels, with some studies suggesting parallel increases in brain GABA concentrations by 27%. Moreover, a positive correlation exists between reduced anxiety levels and increased GABAergic activity in the thalamus, suggesting that yoga could serve as an effective intervention for anxiety and depression [117, 118]. These findings highlight the different types of exercise that influence GABA regulation in distinct ways and the importance of tailoring exercise interventions for optimizing mental health benefits and suggest that a combination of aerobic, anaerobic, and mind-body exercises may provide the most effective outcomes.

Glutamate, the primary excitatory neurotransmitter, plays a crucial role in synaptic plasticity and neurogenesis [119]. Engaging in physical activity transforms the brain's pro-inflammatory state into an anti-inflammatory one, enhancing glutamate function and alleviating depressive symptoms. The exercise-induced boost in neurotransmitters and blood flow in the hippocampus and prefrontal cortex amplifies these positive effects [120, 121]. Moreover, physical activity influences glutamatergic neurotransmission, which is vital in mitigating the neurotoxic effects linked to elevated levels of quinolinic acid. By regulating the balance between excitatory and inhibitory neurotransmitters, exercise helps prevent neuronal damage and supports overall brain health [122]. Moreover, physical activity influences glutamatergic neurotransmission, which is vital in mitigating the neurotoxic effects linked to elevated levels of quinolinic acid. Quinolinic acid, a downstream metabolite of the kynurenine pathway, acts as an N-methyl-D-aspartate (NMDA) receptor agonist, leading to excessive excitotoxicity, oxidative stress, and neuronal damage, which have been implicated in neurodegenerative diseases and psychiatric disorders, including depression and anxiety [123]. Exercise regulates glutamatergic signaling, promoting synaptic balance and protecting against excitotoxic damage. Notably, the kynurenine pathway is a key mediator of exercise-induced glutamate modulation. Regular physical activity enhances the conversion of kynurenine into kynurenic acid, a neuroprotective metabolite that mitigates the toxic effects of quinolinic acid, reducing neuroinflammation and excitotoxicity [124].

Aerobic training has been shown to reduce excessive glutamate levels in neurodegenerative conditions such as Alzheimer's disease by increasing receptor sensitivity rather than merely lowering glutamate concentration, contributing to improved mood and cognitive function [125]. High-intensity training (above 80% of maximum heart rate) elicits an immediate increase in brain glutamate and its precursor glutamine in the visual cortex and anterior cingulate cortex, regions involved in cognitive processing and mood regulation [126, 127]. This transient glutamate may contribute to the antidepressant effects of exercise, enhancing neuroplasticity and counteracting neuroinflammatory pathways that contribute to depression and schizophrenia [121]. While aerobic and high-intensity training primarily influence acute glutamate dynamics, resistance exercise may contribute to long-term glutamate balance by promoting BDNF-mediated neuroprotection. Strength training has been associated with improved glutamatergic signaling, reducing neuroinflammation and oxidative stress, key contributors to depression and cognitive decline [128]. Different exercise modalities influence glutamate regulation through distinct mechanisms. Understanding these differential effects could help optimize exercise-based interventions for neuropsychiatric disorders, including depression and neurodegeneration.

Irisin, a hormone produced by muscles during physical activity, creates a direct link between the muscles and the brain. It significantly boosts levels of BDNF and IGF-1, which encourages neurogenesis and provides antidepressant benefits [129]. Irisin also plays a role in reducing oxidative stress and inflammation, thereby improving overall brain health. By regulating energy metabolism and offering neuroprotection, this hormone becomes essential in

the fight against depression and anxiety [130]. Swimming for four weeks has been found to alleviate hypothyroidism-related depression by stimulating irisin-mediated pathways that enhance serotonin activity and reduce oxidative stress. The long-term benefits of aerobic training include improved metabolic health, increased resistance to neuroinflammation, and enhanced mitochondrial function, all contributing to reduced depressive symptoms [131, 132].

Orexins, produced in the hypothalamus, play a key role in regulating wakefulness, motivation, and mood. Physical activity boosts orexin levels, which in turn enhance neurogenesis and hippocampal function. This improvement leads to better cognition and mood, helping to alleviate depressive symptoms [133, 134]. Additionally, orexin's influence on increasing physical activity and energy expenditure further reinforces its antidepressant effects [135]. Aerobic exercise significantly elevates plasma orexin-A levels, enhancing hippocampal neurogenesis and cognitive function. Human studies show that moderate-intensity aerobic exercise (e.g., 30 min of cycling or walking at 4.5 km/h, three times per week) leads to a notable increase in orexin secretion, contributing to improved mood and reduced depressive symptoms. Additionally, engaging in aerobic activity with a heart rate of 120–140 bpm for 45 min stimulates orexin release, reinforcing its role in energy regulation and emotional resilience. While orexin generally supports mood regulation and cognitive enhancement, its effects vary across brain regions. In the amygdala, an upregulation of orexin expression has been associated with depression, while exercise-induced suppression of orexin in this region exerts antidepressant effects [136, 137].

Neuropeptide Y (NPY) plays a crucial role in regulating mood, managing stress responses, and maintaining energy balance. Physical activity elevates NPY levels, which possess antidepressant qualities and promotes the proliferation of hippocampal cells. NPY influences stress and depressive symptoms by affecting neuroplasticity and maintaining energy balance. Its ability to regulate mood and lessen negative emotional experiences underscores its significance in mental health [138, 139].

Aerobic endurance exercise has been shown to significantly increase NPY expression in both animal and human models. In a rat model, a 6-week swimming exercise protocol (60 min/day) increased hippocampal NPY levels and mitigated depressive behaviors. However, these effects were attenuated when exercise was combined with nandrolone decanoate administration, suggesting an interaction between anabolic steroid exposure and exercise-induced neuropeptide regulation [139]. Similarly, in humans, endurance activities like a 25 km swimming competition significantly increased plasma NPY levels, which correlated with metabolic adjustments related to energy homeostasis and leptin regulation [140]. A 45-minute aerobic exercise session (cycling at 2 W/kg lean body mass) significantly elevated plasma NPY levels in individuals with bulimia nervosa, particularly when combined with the anti-lipolytic drug acipimox. This response, which was more pronounced in BN patients, highlights the role of NPY in appetite regulation and metabolic adaptation to energy expenditure. However, the modulation of plasma NPY by different exercise modalities, including resistance training and prolonged high-intensity exercise, requires further investigation [141].

NPY's antidepressant potential has been demonstrated in forced swim test (FST) studies. In rats, intracerebroventricular (i.c.v.) injections of NPY over 24 h increased swimming and reduced immobility in a dose-dependent manner, mimicking serotonergic antidepressants. This suggests that NPY modulates stress-related behaviors and may contribute to exercise-induced antidepressant effects by enhancing neuroplasticity and stress resilience. These findings highlight the need to explore how different exercise types, durations, and intensities regulate NPY signaling to optimize mental health benefits [142]. Central administration of NPY in the brain via intracerebroventricular (i.c.v.) injections has been shown to exert antidepressant-like effects in forced swim test (FST) studies. In rats, i.c.v. injections of NPY into the lateral ventricle at 0, 8, and 23 h post-preswim increased swimming and reduced immobility in a dose-dependent manner, mimicking the effects of serotonergic antidepressants [143].

Tryptophan, a precursor to serotonin, is essential for regulating mood and emotional stability. Physical activity increases tryptophan availability, enhancing serotonin synthesis and neurotransmission [144, 145]. Exercise helps regulate tryptophan metabolism, thereby alleviating depressive symptoms and supporting mental health. These benefits are observed in both central and peripheral tryptophan levels, underscoring the antidepressant effects of regular physical activity [87]. Aerobic exercise at moderate intensity (cycling at 60 rpm) decreases plasma tryptophan by 12%, increases kynurenine by 6%, and correlates with neopterin, an immune activation marker. This suggests exercise-mediated depression relief through immune pathways [146]. In elderly individuals, 60 min of treadmill running increased the plasma tryptophan-to-BCAA ratio by 78%, which is associated with enhanced brain tryptophan availability and potentially improved mood [147]. In rats, chronic treadmill running (30 min/day, 28 days) increased serotonin receptor (5-HT1A) and tryptophan hydroxylase (TPH) levels, reducing forced swim test immobility, confirming its antidepressant effects [148, 149].

Postpartum depression, linked to serotonergic dysfunction, improves with treadmill running (30 min/day, 2 weeks), leading to increased serotonin and TPH expression and enhanced exploratory behavior in postpartum rats [150]. Additionally, exercise reduces maternal separation-induced depression by promoting hippocampal neurogenesis [151]. While aerobic exercise primarily enhances serotonin metabolism, anaerobic and HIIT exercise may modulate mood through noradrenergic and neurogenesis-related pathways. In rats, moderate to vigorous-intensity exercise (3 days/week) increased hippocampal neurogenesis and noradrenaline while preventing serotonin and tryptophan depletion-related memory impairments. While serotonin plays a critical role in mood regulation, emerging evidence suggests that exercise exerts antidepressant effects through multiple interconnected mechanisms, including neurotransmitter modulation, neurogenesis, and inflammatory response reduction [152].

Cholinergic receptors, which include nicotinic and muscarinic receptors, play key roles in neurotransmission and mood regulation [153]. Physical activity enhances acetylcholine levels and receptor activity, leading to improved cognitive function and better mood. Nicotinic receptors, specifically, are considered potential therapeutic targets for treating depression. The modulation of cholinergic transmission through exercise mimics the antidepressant effects of nicotine, thereby alleviating depressive symptoms [154, 155].

Thus, exercise provides a multi-faceted antidepressant effect by modulating serotonin, dopamine, endorphins, GABA, glutamate, and neuropeptides such as irisin, orexins, and NPY. These neurochemical adaptations enhance neurogenesis, synaptic plasticity, and emotional resilience, reinforcing the role of exercise as a non-pharmacological intervention for depression and anxiety. Future research should further explore the differential effects of exercise modalities on neurotransmitter regulation to optimize clinical applications in mental health treatment.

Neurogenesis

Regular physical activity has been demonstrated to boost adult neurogenesis, especially in the hippocampus, a region vital for learning and memory [156]. Studies in both humans and animals indicate that consistent exercise is associated with enhanced cognitive abilities and a decrease in depressive symptoms [128, 157–159]. Research shows that individuals who participate in moderate exercise demonstrate superior memory retention and learning abilities compared to those who lead a sedentary lifestyle [160, 161]. This positive impact is also observed in animals, where physical activity promotes the growth and longevity of new neurons in the hippocampus, a key region involved in memory and mood regulation [162, 163]. The antidepressant effects of exercise are similar to those obtained from pharmacological treatments, with the benefits continuing for months even after stopping the exercise regimen. This indicates that exercise has a long-lasting positive impact on brain health [164, 165]. These benefits are primarily driven by an increase in neurotrophic factors like BDNF, IGF-1, and VEGF, which are crucial for neurogenesis and brain plasticity [166]. Exercise stimulates the proliferation of neural progenitor cells, especially type 2 progenitor cells, which eventually mature and become integrated into the hippocampal network. This process is supported by both the proliferation and survival phases of neurogenesis, with exercise having a stronger effect on the survival of new neurons [167]. The benefits of exercise-induced neurogenesis are not confined to young animals; older animals also experience increased neuron production, suggesting that physical activity can help counteract age-related declines in neurogenesis [168]. Beyond encouraging cell proliferation, exercise also triggers structural changes in the hippocampus. These changes include modifications in dendritic structure and an increase in synaptic density, especially in the dentate gyrus and CA1 regions. These alterations are essential for synaptic plasticity, a key factor in learning and memory [169, 170]. IGF-1 plays a significant role in this process, not only by promoting cell proliferation but also by increasing dendritic spine density and enhancing overall neuronal connectivity [171]. Inhibiting IGF-1 signaling can counteract these benefits, emphasizing its critical importance in the neurogenic and neuroplastic effects of exercise [172]. The connection between stress and hippocampal plasticity highlights the advantages of exercise. Chronic stress is known to decrease neurogenesis and cause dendritic atrophy, especially in the CA3 region of the hippocampus. This structural degradation is linked to impaired cognitive function and a heightened risk of depression [173]. Conversely, exercise helps counteract these stress-related alterations by fostering resilience and improving hippocampal function [174]. This indicates that physical activity not only boosts neurogenesis but also shields the brain from structural and functional harm caused by chronic stress [174].

Overall, the enhancement of neurogenesis and structural plasticity in the hippocampus due to exercise is driven by a complex interaction of growth factors and neurotrophic signals. The increase in BDNF and IGF-1 levels in response to physical activity is especially important, as these factors help new neurons survive and integrate into existing networks, boost synaptic plasticity, and lead to better cognitive function and mood. These findings highlight the promise of physical activity as a non-drug approach to enhancing mental health,

especially in addressing depression and cognitive decline associated with aging.

Anti-inflammatory effects

Engaging in physical exercise has gained recognition as an effective approach to managing depression and anxiety, largely due to its impact on neuro-inflammation. The beneficial mechanisms are diverse and intricate, primarily centered around the reduction of pro-inflammatory activities within the body [175]. Research has shown that engaging in physical activity can reduce the levels of circulating (plasma) pro-inflammatory cytokines, including IL-1β, TNF-α, IL-6, IL-8, and IL-10. These cytokines are commonly elevated in individuals with chronic illnesses and depression [176, 177]. Engaging in moderate-intensity physical activity has been found to lower blood concentrations of pro-inflammatory cytokines, which is associated with reductions in stress and depressive symptoms. This decrease in inflammatory markers, particularly IL-1β, has been associated with reductions in stress and depressive symptoms. Notably, IL-1β is also implicated in sleep regulation, suggesting that exercise-induced reductions in this cytokine may contribute to improved sleep quality, which is often disrupted in depression [178].

Exercise influences the regulation of the HPA axis and glucocorticoid levels, which are frequently imbalanced in depression. Since prolonged glucocorticoid activation contributes to oxidative stress and mitochondrial dysfunction, exercise plays a crucial role in restoring homeostasis. By enhancing mitochondrial function in the hippocampus, exercise counteracts glucocorticoid-induced neurotoxicity and reduces systemic inflammation, thereby improving mental health outcomes [179–182].

Exercise has shown promising therapeutic benefits, especially for individuals with treatment-resistant depression (TRD), a condition often characterized by elevated pro-inflammatory cytokines. Accordingly, studies have found that increased circulating levels of TNF-α correlate positively with the antidepressant effects observed after a 12-week aerobic exercise regimen. Moreover, the reduction in IL-1β levels correlates with a decrease in depressive symptoms, indicating that exercise may help alleviate the severe chronic inflammation frequently associated with TRD. This reduction in inflammation is crucial, as it is often a contributing factor to the poor overall health observed in individuals with TRD [183].

The anti-inflammatory effects of exercise are partly attributed to a decrease in visceral fat, a known source of pro-inflammatory cytokines such as TNF-α and IL-6. A key factor in this inflammatory modulation is IL-6, which exhibits dual roles depending on its source. While IL-6 secreted from adipose tissue is linked to chronic low-grade inflammation, exercise-induced IL-6 functions as a myokine with predominantly anti-inflammatory effects [184]. This exercise-induced IL-6 promotes the secretion of IL-10, an anti-inflammatory cytokine, and suppresses TNF-α production, thereby contributing to the resolution of inflammation [185–188]. This dual role of IL-6 highlights the nuanced relationship between physical exercise and immune modulation, reinforcing the importance of regular physical activity in managing inflammation-related disorders such as depression.

The anti-inflammatory effects of exercise extend beyond cytokine modulation, involving pathways that regulate mitochondrial function and neuroinflammation. A central regulator of this process is peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), which promotes mitochondrial biogenesis and reduces inflammatory signaling. Furthermore, PGC-1α plays a key role in the kynurenine metabolic pathway, facilitating the conversion of neurotoxic kynurenine into kynurenic acid, a metabolite that protects against neuroinflammation. This conversion is crucial in reducing the harmful effects of quinolinic acid, a metabolite that worsens neuroinflammation and can lead to neuronal damage [189–191]. In depressive disorders, the regulation of these neurotransmitters is often disrupted, and physical activity helps to rebalance their levels, thereby reducing depressive symptoms. Collectively, these anti-inflammatory mechanisms—including cytokine regulation, mitochondrial support, and kynurenine metabolism—highlight the integral role of exercise in modulating neuroimmune interactions. Through these pathways, exercise exerts antidepressant and anxiolytic effects, reinforcing its importance as a non-pharmacological strategy for improving mental well-being (Fig. 1).

Polyphenols and mental well-being

Introduction to polyphenols

In recent years, consumer interest in polyphenol-rich foods has increased significantly due to their diverse health benefits. Polyphenols are a diverse class of secondary metabolites characterized by multiple hydroxyl groups attached to aromatic rings, contributing to their strong antioxidant, anti-inflammatory, and neuroprotective properties [186, 192–194]. Historically referred to as "vegetable tannins" due to their role in leather tanning, polyphenols are now classified based on their chemical structure and biological function [195]. The primary categories include flavonoids, phenolic acids, lignans, tannins, and stilbenes, each exhibiting distinct physiological effects [196].

Flavonoids, the most abundant subgroup, include flavonols (e.g., quercetin), flavones (e.g., apigenin), and anthocyanins (e.g., cyanidin), known for their antioxidant and anti-inflammatory properties. Phenolic acids,

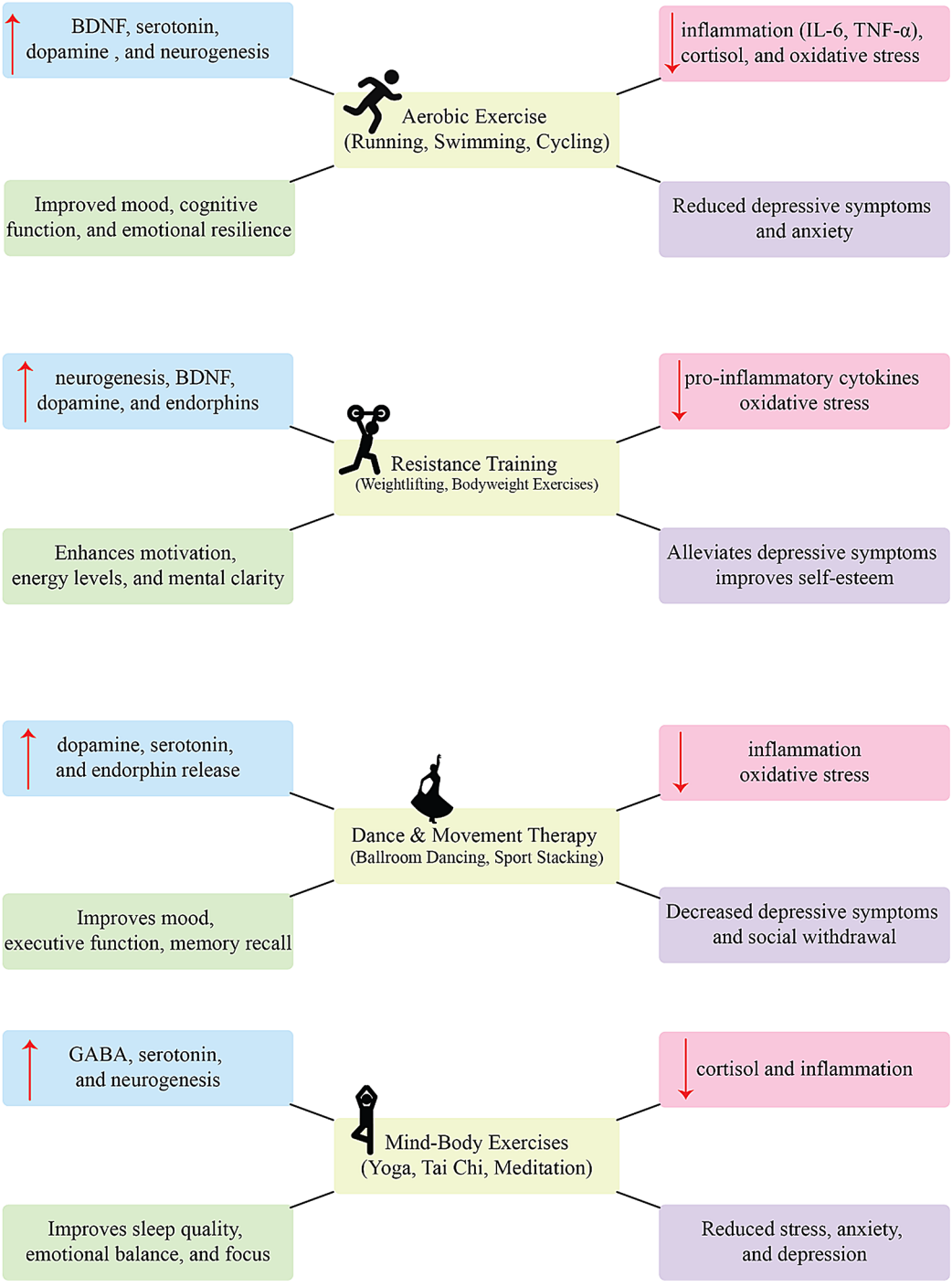

Fig. 1 Exercise modalities and their effects on mental health

derived from benzoic and cinnamic acids, are prevalent in plant-based foods and contribute to oxidative stress modulation. Other key subgroups, such as lignans (found in flaxseeds) and stilbenes (e.g., resveratrol in red wine), have been linked to neuroprotection and cardiovascular benefits [197–199].

Tannins, a distinct polyphenol subclass, are divided into hydrolyzable and condensed tannins. Hydrolyzable tannins, found in foods like pomegranates and tea, degrade into bioactive phenolic acids (gallic and ellagic acid), which exhibit antimicrobial, antioxidant, and cardioprotective effects [200]. Condensed tannins, or proanthocyanidins, are polymers of flavan-3-ols (e.g., catechin, epicatechin) that resist enzymatic hydrolysis, instead undergoing microbial metabolism to produce bioactive

compounds that support metabolic and cardiovascular health [201].

The functional differences between these tannin types influence their physiological effects—hydrolyzable tannins provide rapid benefits through hydrolysis-derived phenolic acids, while condensed tannins exert sustained effects via gut microbiota interactions. Both classes contribute to food preservation, nutraceuticals, and therapeutic applications, underscoring their relevance in modern health sciences [195, 202].

Hence, polyphenols constitute a highly complex and diverse category of compounds known for their substantial health advantages, largely attributed to their antioxidant capabilities. Beyond their general health benefits, emerging research highlights their neuroprotective and antidepressant properties, which stem from their ability to modulate oxidative stress, neuroinflammation, and key neurotransmitter pathways. These mechanisms position polyphenols as promising candidates for supporting mental health and mitigating depressive symptoms.

Antidepressant properties

Polyphenols, a diverse set of naturally occurring compounds, have attracted considerable attention for their potential antidepressant effects. This interest largely arises from their capability to influence various biochemical pathways that are crucial for regulating mood (Fig. 2) [203]. Table 3 provides an overview of the effects of different polyphenols, including crocin, curcumin, and quercetin, on depressive symptoms and cognitive functions. These polyphenols exert neuroprotective effects by modulating neuroinflammation, neurotransmitter function, and oxidative stress pathways.

One of the most extensively researched mechanisms is the inhibition of serotonin reuptake. Serotonin, a critical neurotransmitter that plays a major role in regulating mood, is frequently observed at lower levels in people suffering from depression. By preventing the reuptake of serotonin, polyphenols boost its presence in the synaptic cleft, thus enhancing serotonergic communication and potentially lifting mood [204, 205]. Polyphenols inhibit serotonin reuptake through multiple mechanisms, primarily by interacting with the serotonin transporter (SERT), reducing its efficiency, and increasing extracellular serotonin levels in the brain [206, 207]. Additionally, they suppress monoamine oxidase-A (MAO-A), the enzyme responsible for serotonin degradation, thereby prolonging serotonin's availability [208]. Some polyphenols, like curcumin and crocin, also enhance serotonin biosynthesis by upregulating TPH, the key enzyme in serotonin production [209, 210]. Beyond direct effects on serotonin metabolism, polyphenols regulate SERT expression through their anti-inflammatory and antioxidant properties further supporting serotonin homeostasis by mitigating stress-induced increases in SERT activity [211, 212]. Beyond their direct influence on serotonin metabolism, polyphenols exert additional antidepressant effects by modulating neurotrophic factors. Notably, their ability to enhance BDNF supports serotonergic signaling, neuronal plasticity, and long-term synaptic adaptations that contribute to mood stabilization [213].

Through these combined actions—direct inhibition of SERT, suppression of MAO-A, increased serotonin synthesis, and modulation of inflammation and epigenetics—polyphenols effectively enhance serotonergic neurotransmission. This mechanism resembles the action of selective SSRIs, a widely used class of antidepressants [210, 214]. Additionally, polyphenols interact with other neurotransmitter systems, including dopamine and noradrenaline, which play crucial roles in motivation, pleasure, and cognitive function [215, 216]. Animal studies have demonstrated that compounds such as curcumin (from turmeric), resveratrol (from grapes), and baicalin (from Scutellaria baicalensis) significantly reduce depressive-like behaviors in models using the Forced Swim Test (FST) and Tail Suspension Test (TST) [217–222]. Polyphenols typically decrease immobility and enhance sucrose preference, indicating their potential to counteract both despair and anhedonia [210, 223].

Another essential pathway affected by polyphenols is the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's response to stress. Chronic stress can lead to excessive cortisol production, negatively impacting brain regions such as the hippocampus, which is critical for mood regulation. Polyphenols have been suggested to modulate the HPA axis by reducing cortisol levels, thereby alleviating stress-induced depressive symptoms [224–226].

Additionally, polyphenols are known for their potent antioxidant capabilities, which play a crucial role in reducing oxidative stress-a state where there is an overabundance of free radicals in the body. This condition is associated with the development of depression, as it can lead to brain cell damage and promote neuroinflammation. By neutralizing free radicals and decreasing oxidative stress, polyphenols help safeguard neural tissues from harm. This protective effect can help maintain cognitive function and potentially ease symptoms of depression [227–230]. In addition to reducing oxidative stress, polyphenols possess anti-inflammatory properties. Chronic inflammation has been increasingly linked to depression, as pro-inflammatory cytokines such as IL-6 and TNF-α can interfere with neurotransmitter synthesis and disrupt neural pathways. Polyphenols mitigate these effects by lowering the levels of pro-inflammatory cytokines and promoting anti-inflammatory signaling, thereby restoring normal brain function [8, 231].

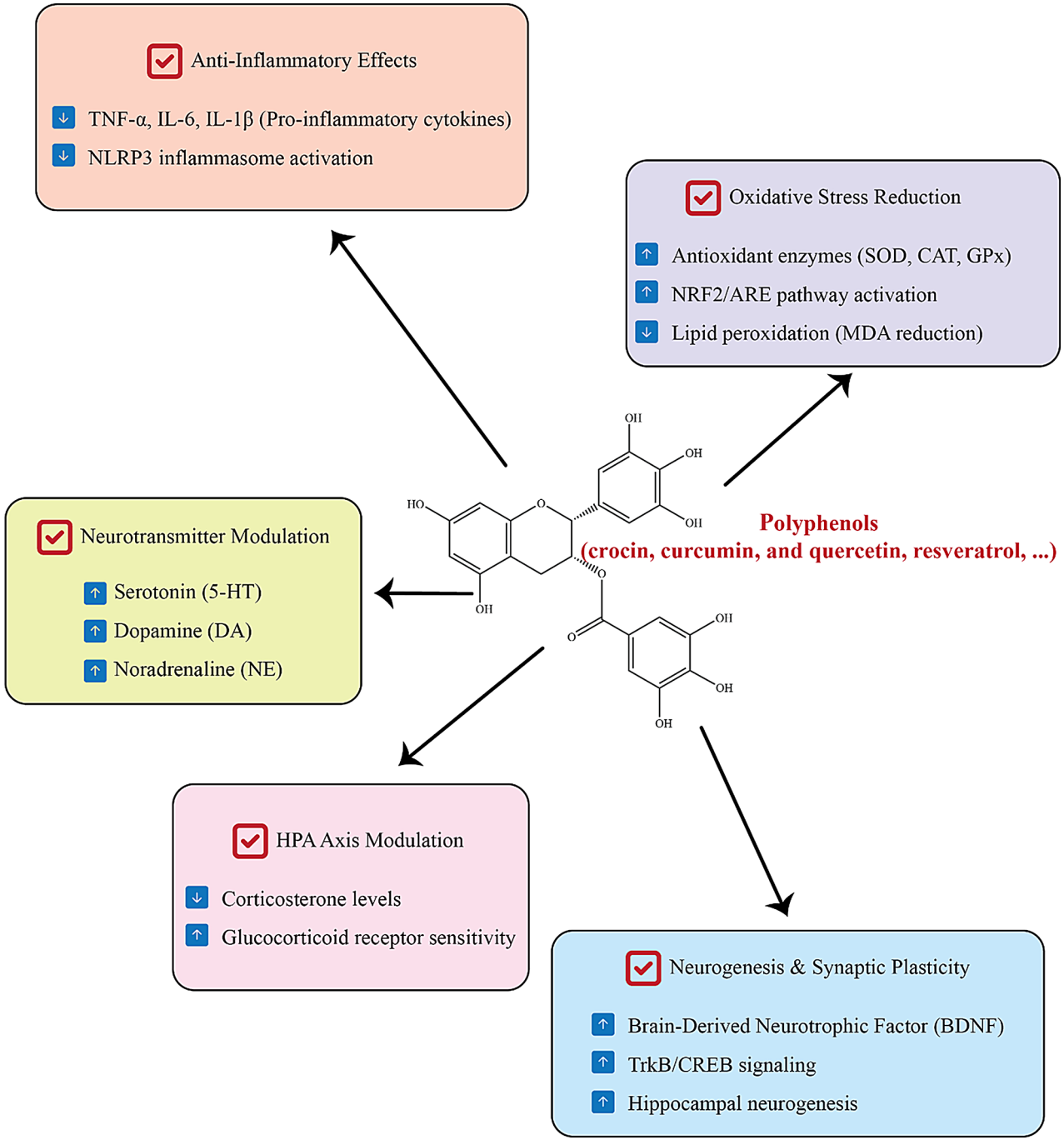

Fig. 2 Effects of polyphenols on depression and cognitive functions

Polyphenols also influence the gut-brain axis by modulating the composition of gut microbiota. They promote the growth of beneficial bacteria while suppressing harmful ones, leading to the production of neuroactive compounds that positively affect mood and cognition. Some polyphenols also enhance the synthesis of short-chain fatty acids, which possess anti-inflammatory and neuroprotective properties [232, 233].

Together, these mechanisms highlight the promising role of polyphenols in mental health. By influencing neurotransmitter systems, reducing oxidative stress and inflammation, regulating the HPA axis, and promoting neurogenesis, polyphenols offer a multifaceted approach to depression management. While much of the existing evidence is derived from preclinical studies, these findings underscore the need for further human clinical trials to validate their efficacy and long-term safety.

Table 3 The effects of polyphenols on depressive symptoms and cognitive functions

Polyphenol	Intervention	Population	Results	Reference
Epicatechin	Oral gavage, twice daily for 5 weeks during chronic mild stress	Male mice	Reduced anhedonia, anxiogenic behavior; modulated aminotransferase KAT	[282]
Apigenin	20-day treatment at 10 and 20 mg/kg in a PTZ-kindled mouse model	Kindled mice	Reversed behavioral and cognitive impairments via CREB-BDNF upregulation in the hippocampus	[283]
Apigenin	20 mg/kg treatment in STZ-induced depression model	Rats	Improved antioxidant markers, reduced inflammation, regulated AMPK expression, and improved behavioral deficits	[284]
Arctigenin	Repeated administration (10 and 30 mg/kg) in CMS model	CMS-induced mice	Improved depressive and anxiety-like behaviors, increased serum VEGF, ANG, and TPO	[285]
Astilbin	Administered in LPS-induced postnatal immune activation (PIA) model	PIA mice	Improved depressive-like behavior; inhibited astrocyte activation and neuroinflammation	[286]
Naringin	10, 20, 40 mg/kg post intracerebroventricular collagenase-induced intracerebral hemorrhage	Rats	Reduced oxidative stress, improved memory and depression symptoms, restored TNF-α and antioxidants	[287]
Luteolin	10 mg/kg daily for 8 days in LPS-induced depression model	Mice	Increased BDNF, dopamine, and noradrenaline levels; reduced inflammation and depressive-like behavior	[288]
Luteolin	Administered in Alzheimer's disease mouse model	AD model mice	Reduced ER stress and microglial activation; improved depression-like behaviors	[289]
Rutin	21-day CUS model in mice, oral dosing	Chronic stress-induced mice	Reduced depression and anxiety-like behaviors, improved cognition and locomotor abilities, and protected against hippocampal neuronal loss in the CA3 region.	[290]
Naringenin	10–50 mg/kg, i.p., daily for 14 days	Hypoxic stress-induced mice	Ameliorated depressive and anxiety-like behaviors, reduced oxidative stress and inflammation (TNF-α, IL-1β), and increased BDNF and antioxidant levels in the hippocampus.	[291]
Naringenin	25–100 mg/kg, oral dosing for 14 days	OBX-induced depression in mice	Improved depressive behavior, restored serotonin and kynurenine balance, reduced neuroinflammation and oxidative stress, and increased BDNF levels.	[292]
Ellagic Acid	20–100 mg/kg, oral dosing in a CUMS model	CUMS-induced depression in mice	Reduced depressive behaviors (FST, TST), increased BDNF and serotonin levels, suppressed hippocampal inflammation, and restored metabolic balance (lipid, amino acid, and purine metabolism).	[293]
Ferulic Acid	5 mg/kg, oral dosing for 7 days	Male ICR mice (TST model)	Reduced immobility time, increased dopamine and noradrenaline levels, enhanced energy metabolism (ATP levels), and promoted cell survival and proliferation.	[294]
Fisetin	Oral dosing, duration not specified	Spatial restraint and Ahi1-KO mice	Reduced immobility in FST and TST, activated the TrkB signaling pathway, and increased phosphorylated TrkB levels, indicating antidepressant effects.	[295]
Gallic Acid	30–60 mg/kg, oral dosing	TST and MFST mouse models	Reduced immobility time, increased serotonin and catecholamine levels, and modulated serotonergic and dopaminergic receptor activity (5-HT2A, D1, D2).	[296]
Hesperidin	100–200 mg/kg, oral dosing in a CUMS model	CUMS-induced depression in mice	Reduced depressive behaviors (SPT, FST), decreased neuroinflammation (IL-1β, IL-6, TNF-α), and activated the BDNF/TrkB pathway, providing neuroprotection.	[218]
Hesperidin	50 mg/kg, oral dosing for 28 days	6-OHDA-induced Parkinson's model in mice	Reduced depressive and anxiety behaviors, attenuated proinflammatory cytokines, increased neurotrophic factors (BDNF, NT-3), and restored striatal dopaminergic neurons.	[215]
Crocin	10–30 mg/kg, oral gavage for 4 weeks	UCMS-induced anxiety and depression in rats	Reduced anxiety and depression (OF, EPM, FS tests), decreased corticosterone levels, oxidative stress (MDA, TNF-α, IL-6), increased IL-10, SOD, CAT, and thiol levels, and improved BDNF levels in cortical tissues.	[297]

Table 3 (continued)

Polyphenol	Intervention	Population	Results	Reference
Crocin	40 mg/kg, oral dosing for 6 weeks	CRS-induced depression in mice	Improved depressive behaviors (behavioral tests), reduced hippocampal TNF-α, IL-6, and LPS levels, increased BDNF, and restored gut microbiota (increased Lactobacillus spp., SCFAs, and intestinal barrier proteins Occludin and Claudin-1).	[298]
Crocin	30 mg/kg, i.p., in LPS-induced depression in mice	LPS-induced neuroinflammation in mice	Reduced depressive-like behaviors (FST, TST), decreased inflammatory markers (NO, TNF-α, IL-1β), inhibited NF-κB/NLRP3 inflammasome activation, and promoted M1-to-M2 phenotypic conversion of microglia.	[299]
Crocin	50 mg/kg, daily i.p. injections	COPD-induced depression in mice	Reversed depressive markers (sucrose preference, body weight, TST, FST), reduced inflammatory cytokines in BAL fluid and hippocampus, and suppressed NF-κB activation via PI3K/Akt pathways.	[300]
Crocin	30 mg/kg, oral dosing in a CUMS model	CUMS-induced depression in rats	Improved depressive behaviors (OF, FST, TST), increased BDNF, P-mTOR, and P-ERK levels, and enhanced cellular synaptic growth. Inhibition of the antidepressant effects was observed with rapamycin pretreatment, implicating mTOR signaling.	[301]
Quercetin	40 mg/kg, orally	LPS-induced depression in rats	Reduced immobility time (FST), increased saccharin preference, improved hippocampal BDNF, Copine 6, TrkB, and TREM1/2 balance; alleviated depression-like behavior and cognitive impairment.	[302]
Quercetin	30 mg/kg, orally for 30 days	Glyphosate-based herbicide (GBH)-exposed mice	Reduced oxidative stress markers, restored GSH levels, alleviated depressive-like behaviors (FST, EPM), and reversed GBH-induced hippocampal toxicity.	[303]
Quercetin	40 mg/kg, orally for 21 days	CUMS-induced depression in mice	Improved depressive-like behaviors (SPT, FST), restored hippocampal PI3K/Akt/Nrf2/HO-1 pathway, increased SOD and GST, reduced MDA and inflammatory markers (iNOS, NO).	[304]
Quercetin	10 mg/kg, single dose	LPS-induced depression in mice	Reduced immobility time (FST), decreased hippocampal inflammatory factors (IL-10, IL-1β, TNF-α), restored BDNF/CREB/PSD95/Synapsin1 expression, suppressed PI3K/AKT/NF-κB signaling, and improved neuroplasticity.	[305]
Quercetin	25, 50, 100 mg/kg, i.p. for 14 days	Social defeat stress (SDS) model in mice	Reversed anxiety, depression, and cognitive impairment; restored serotonin, dopamine, and BDNF levels; reduced neuroinflammation (TNF-α, IL-6) and oxidative stress; inhibited caspase-3 activity in the hippocampus and prefrontal cortex.	[306]
Quercetin	20 mg/kg	Early-life stress (maternal separation) in rats	Prevented anxiety and depression-like behaviors; improved microbiota diversity, BDNF levels, and gut-brain axis signaling; partially restored corticosterone levels and neurochemical balance.	[307]
Quercetin	100 mg/kg, orally	Depression in ERα-deficient female mice	Reduced immobility time (TST, FST), decreased systolic blood pressure, improved hippocampal and cardiac BDNF-AKT/ERK1/2 signaling; provided antidepressant and cardioprotective effects.	[308]
Quercetin	50 mg/kg, i.p. during predator stress exposure	Predator stress-induced innate fear in mice	Reduced anxiety-like and depressive-like behaviors; alleviated oxidative stress and innate fear without affecting cognitive function.	[309]
Quercetin	40 mg/kg, orally	CUMS-induced depression in mice	Improved hippocampal FoxG1/CREB/BDNF signaling, increased neurogenesis markers (DCX, BrdU/NeuN), reduced immobility time (FST), and improved locomotion and sucrose preference.	[310]
Resveratrol	40 or 80 mg/kg/day for 4 weeks	CUMS-induced depressed rats	Alleviated depressive-like behaviors, reduced hippocampal apoptosis, normalized proinflammatory cytokines (TNF-α, IL-6, IL-1β), and increased Akt/GSK3β signaling.	[220]
Resveratrol	20, 40, or 80 mg/kg for 7 days	Physical and psychological stress mice	Reduced depressive-like behaviors in physical stress; reduced immobility time in TST; moderate effects in psychological stress; no significant effect on amygdala CRF mRNA expression.	[311]
Resveratrol	10, 20, or 30 mg/kg for 21 days	Social isolation & stress-induced depression in mice	Improved depressive behaviors (FST, TST, sucrose consumption), increased dopamine, serotonin, and BDNF levels in the prefrontal cortex; enhanced NPY protein expression.	[248]
Resveratrol	0–80 mg/kg for 8 weeks	CUMS-induced depressed male rats	Improved depressive-like symptoms, increased serum testosterone levels, normalized testicular expression of StAR, β-catenin, and GSK-3β, and reduced oxidative stress and inflammation in the testis.	[312]
Resveratrol	0–80 mg/kg for 8 weeks	CUMS-induced depressed male rats	Improved depressive-like behavior, reduced corticosterone levels, normalized β-catenin, BDNF, and serotonin levels, and mitigated oxidative stress and inflammation in the hippocampus.	[313]

Table 3 (continued)

Polyphenol	Intervention	Population	Results	Reference
Resveratrol	10–30 mg/kg/day	Stress-induced cytokine release rats	Reduced proinflammatory cytokines (IL-1β, TNF-α) in the locus coeruleus; prevented stress-induced anhedonia; improved depressive symptoms only in passive coping rats.	[314]
Resveratrol	0–10 mg/kg/day, 22 days	CACS-induced depression rats	Normalized depressive-like behaviors, improved 5-HT signaling in the brain-gut axis, and regulated PKA/CREB/BDNF pathway in the hippocampus and gut.	[315]
Resveratrol	20 mg/kg/day for 8 weeks	CUMS-exposed male rats	Reversed depressive-like behaviors, normalized testosterone and nNOS/eNOS expression, and mitigated inflammation in the penile tissue.	[316]
Resveratrol	0-0.8 mg/kg/day	LPS-induced depressive mice	Prevented mitochondrial oxidative stress, restored hippocampal ATP production, reduced apoptosis, and alleviated depressive-like behaviors.	[317]
Resveratrol	0–80 mg/kg/day	CUMS-induced depressed rats	Restored behavioral and hepatic antioxidant levels, normalized MAPK/ERK/JNK pathway signaling, and reduced inflammation and apoptosis in the liver.	[318]
Resveratrol	0-100 mg/kg/day	Aluminum-induced depression in mice	Restored intestinal barrier function, reduced inflammatory cytokines, and normalized tight junction protein expression via SIRT1 activation.	[319]
Resveratrol	0–10 mg/kg/day	Corticosterone-induced cell injury in vitro and in vivo	Improved neuroprotection via PDE4D inhibition, increased cAMP signaling, and restored PKA/CREB/BDNF pathway, leading to antidepressant- and anxiolytic-like effects.	[320]
Curcumin	100 mg/kg orally daily for 1 month	Ovariectomized rats	Improved depression-like behavior by modulating serotonin levels, increasing BDNF and ERK1/2, and reducing MAO expression in the limbic system. Comparable effects to fluoxetine and estradiol.	[210]
Curcumin	40 mg/kg pre-treatment in LPS-induced depression	LPS-induced depression in rats	Reduced oxidative stress, neuronal apoptosis, and synaptic loss in the hippocampal CA1 region. Neuroprotective effects mediated via miR-146a-5p/ERK signaling pathway.	[321]
Curcumin-coated iron oxide nanoparticles (Cur-IONPs)	0–5 mg/kg/day, 2-week treatment after reserpine-induced depression	Reserpine-induced depressed rats	Increased serotonin, norepinephrine, dopamine levels, reduced oxidative stress, and restored monoamine neurotransmitter levels. Attenuated depressive behavior in forced swim tests.	[322]
Curcumin nanoparticles	20 mg/kg for 7–15 days in reserpine-induced depression	Reserpine-induced depressed rats	Restored cortical and hippocampal levels of serotonin, norepinephrine, and dopamine; improved depression-related behaviors and normalized electrocorticogram patterns.	[247]
Curcumin-loaded nanocapsules	10 mg/kg for 12 days in Aβ25-35-induced Alzheimer's model	Alzheimer's-induced depression mice	Reversed depressive-like behavior; reduced oxidative stress and improved superoxide dismutase and CAT activities. Curcumin nanocapsules were more effective than free curcumin.	[323]
Curcumin	50 mg/kg for 15 days in gentamicin and sodium salicylate-treated rats	Neurotoxicity model rats	Mitigated neurobehavioral deficits (memory and depressive behaviors), reduced oxidative stress and apoptosis markers, and improved histopathology of hippocampal tissues.	[324]
Curcumin-loaded nanostructured lipid carriers	Nanocarriers tested in LPS-induced depression and anxiety model	LPS-induced depression rats	Reduced depressive and anxiety behaviors, suppressed TNF-α and COX-2 expression in the brain, and enhanced histological neuroprotection.	[325]
Curcumin	200 mg/kg in CRS-induced depression	CRS-induced depressed rats	Restored corticosterone levels, BDNF, serotonin, dopamine, and acetylcholine levels in the hippocampus; improved pseudodementia and depression-related behaviors.	[326]
Curcumin	40 mg/kg daily for 5 weeks	CUMS-induced depressed rats	Alleviated neuronal apoptosis, reduced IL-1β, IL-6, and TNF-α in the medial prefrontal cortex, and improved depression-like behaviors.	[327]
Curcumin	150–300 ppm in HgCl2-induced depression in offspring	Mice exposed to HgCl2	Reduced depressive and anxiety-like behaviors in offspring; improved locomotor activity and mitigated depression-like effects due to HgCl2 exposure during gestation and lactation.	[328]
Curcumin	0–80 mg/kg in CUMS model	CUMS-induced depressed rats	Restored BDNF, CREB, and synaptic proteins (PSD-95, synaptophysin) and activated Nrf2-ARE signaling; reduced oxidative stress and depressive behaviors.	[329]
Curcumin-loaded hydrogel	Nasal delivery system tested in mice depression model	Depression-induced mice	Reduced immobility in forced swim tests and tail suspension tests; increased norepinephrine, dopamine, and serotonin levels in the hippocampus and striatum.	[330]

Table 3 (continued)

Polyphenol	Intervention	Population	Results	Reference
Baicalin	60 mg/kg in chronic unpredictable mild stress (CUMS) mice model	CUMS mice	Reduced depressive-like symptoms via inhibition of TLR4 expression through the PI3K/AKT/FoxO1 pathway	[331]
Baicalin	25 and 50 mg/kg in CUMS mice	CUMS mice	Ameliorated depressive behavior by inhibiting HMGB1/TLR4/NF-κB pathways, reducing inflammatory cytokines (IL-1β, IL-6, TNF-α)	[332]
Baicalin	50 and 100 mg/kg orally for 21 days in CUMS-induced depression model	CUMS mice	Promoted hippocampal neurogenesis via Wnt/β-catenin signaling pathway, alleviated depressive behavior	[333]
Baicalin	20 and 40 mg/kg in olfactory bulbectomy-induced depression rats	Olfactory bulbectomy rats	Reversed depressive behavior, reduced corticosterone levels, and downregulated SIRT1-NF-κB pathway	[334]
Baicalin	25 and 50 mg/kg in CUMS mice	CUMS mice	Increased BDNF, ERK, CREB expression in the hippocampus, improved cognitive functions, and reduced depressive symptoms	[222]
Baicalin	0–50 mg/kg in inflammatory pain-induced depressive mice	Mice with inflammatory pain	Promoted adult hippocampal neurogenesis via Akt signaling, reduced depressive symptoms and pain	[335]
Baicalin	0–60 mg/kg/day	CORT-induced depressed mice	Normalized HPA axis by regulating GR nuclear translocation and phosphorylation, reduced immobility time in behavioral tests	[336]
Baicalin	0–40 mg/kg/day	CUMS rats	Reduced NLRP3 inflammasome activation, decreased pro-inflammatory cytokines, and improved depressive-like behavior in the prefrontal cortex	[337]
Baicalin	0–40 mg/kg/day	Depression model rats	Inhibited GSK3β/NF-κB/NLRP3 signaling, reduced inflammation, promoted neuronal survival, and alleviated depressive symptoms	[338]
Baicalin	0-100 mg/kg/day in CUMS-induced mice	CUMS mice	Activated the Rac1-cofilin pathway, increased synaptic plasticity markers (SYP, PSD95, BDNF), and reduced depressive behavior	[339]
Baicalin	0-6.7 mg/kg//day	CORT-induced depressed mice	Modulated APPL2/GR signaling, promoted neurogenesis in SVZ and hippocampus, improved depressive and anxiety-like behaviors	[340]

Combined effects of exercise and polyphenols on depression and mental health

The integration of regular physical exercise and polyphenol supplementation presents a promising strategy for enhancing mental well-being. Both interventions independently exert antidepressant effects through distinct but complementary mechanisms, including neurotransmitter modulation, neurogenesis stimulation, oxidative stress reduction, and inflammation control [234, 235]. Emerging research suggests that their combination may have synergistic benefits in mitigating depression, anxiety, and cognitive decline [236, 237].

Synergistic effects on neurotransmitter regulation

Several studies indicate that combining polyphenols with exercise influences key neurotransmitter systems, including serotonin, dopamine, and noradrenaline. Ghalandari-Shamami, Nourizade [234] investigated the combined antidepressant effects of crocin (a polyphenol in saffron) and voluntary exercise in adolescent rats subjected to chronic stress. Their findings revealed that the combination of crocin and exercise significantly improved behavioral outcomes and structural changes in the prefrontal cortex. These improvements were linked to increased serotonin and dopamine levels and reduced corticosterone concentrations, which are commonly elevated in stress-related disorders [234].

The ability of polyphenols and exercise to influence neurotransmitter balance extends beyond depression models. For instance, Azarian, Farsi [236] investigated endurance training and crocin supplementation in a rodent model of Alzheimer's disease, revealing improvements in anxiety-like behaviors and aerobic capacity. These findings suggest that the neuromodulatory effects of polyphenols and exercise may also be relevant for neurodegenerative conditions, broadening their therapeutic potential [236].

Effects on neuroinflammation and oxidative stress

Chronic inflammation and oxidative stress contribute significantly to the pathophysiology of depression. Research indicates that polyphenols and exercise independently reduce circulating (plasma) pro-inflammatory cytokines such as IL-1β and TNF-α while also modulating brain-derived neuroinflammatory markers (e.g., microglial activation and astrocytic response in hippocampal tissue), contributing to improved cognitive and mood-related outcomes [238, 239]. In an experimental model of methamphetamine-induced neurotoxicity, Nourolapour, Abbassi Daloii [239] demonstrated that aerobic exercise

and crocin supplementation significantly upregulated hippocampal neuroprotective gene expression, including BDNF and TrkB, which are critical for neuronal survival and plasticity. Notably, the greatest enhancement was observed in the group that received both interventions, supporting the hypothesis that polyphenols amplify the neuroprotective effects of exercise [239].

Amoei, Meshkati [238] examined the combined impact of aerobic exercise and curcumin supplementation on anxiety behaviors and locomotor activity in mice exposed to lead nitrate, a neurotoxic agent. The intervention modulated hippocampal oxidative stress markers (e.g., SOD and MDA levels) and reduced plasma corticosterone, a key indicator of HPA axis activity [238].

Noruzi, Meshkati [237] explored the combined impact of HIIT and curcumin supplementation on cognitive function and oxidative stress markers in male BALB/c mice exposed to lead. The results showed significant cognitive improvements and reductions in oxidative damage in groups that received either HIIT or curcumin alone, but the greatest neuroprotection was observed in the combined intervention group. These findings suggest that curcumin enhances the antioxidant and anti-inflammatory properties of HIIT, which may be particularly beneficial in stress-induced cognitive impairment [237].

Cognitive and behavioral benefits

The cognitive-enhancing effects of polyphenols and exercise have been well-documented, particularly in stress-induced and neurodegenerative conditions [235, 240]. In a study on rats with lipopolysaccharide (LPS)-induced depression, Abdallah, El-Gohary [235] found that quercetin supplementation combined with treadmill exercise significantly reduced oxidative stress, inflammation, and apoptosis, while increasing serotonin and BDNF levels. This suggests that exercise and polyphenols interact through mitochondrial regulation to support cognitive function and mental health.

Osali and Rostami [240] conducted a clinical trial investigating the effects of aerobic exercise and nanocurcumin supplementation in women aged 60–65 with metabolic syndrome. The results indicated that the combination of exercise and nanocurcumin significantly reduced plasma IL-1β and nitric oxide (NO) levels, correlating with improvements in depression scores [240]. Both polyphenols and exercise have demonstrated cognitive-enhancing effects, particularly in stress-induced and neurodegenerative conditions. Moghadam, Bagheri [241] investigated the impact of resistance training in combination with saffron supplementation on mood and peripheral neurochemical markers in young men. Their findings indicated that this dual intervention led to increased plasma serotonin, dopamine, and β-endorphins, which are associated with improved mood and stress resilience [241].

In a randomized controlled trial, Johnston [242] assessed the impact of HIIT combined with curcumin supplementation on mental health and exercise performance. While no significant differences in anxiety and depression scores were observed between groups, the study emphasized the need for further research with larger sample sizes and optimized supplementation protocols [242].

Mechanistic insights into the synergistic effects of exercise and polyphenols on brain function

The combination of exercise and polyphenol supplementation presents a promising strategy for enhancing brain function and mitigating depression through overlapping and complementary mechanisms. Both interventions influence neurotrophic signaling, neurotransmitter regulation, neuroinflammation, oxidative stress, mitochondrial function, and synaptic plasticity. These pathways converge to promote neurogenesis, synaptic integrity, and cognitive resilience, while counteracting neurodegeneration and mood disorders. The synergistic interaction between exercise and polyphenols amplifies these benefits beyond what either intervention achieves alone, making this combined approach a compelling avenue for mental health improvement.

A central mechanism through which exercise and polyphenols exert their beneficial effects is the upregulation of BDNF, a key regulator of synaptic plasticity, neuronal survival, and mood stabilization (Tables 2 and 3). Exercise stimulates BDNF expression through activation of PGC-1α and the cyclic AMP response element-binding protein (CREB) pathway, which enhances synaptic remodeling and neurogenesis, particularly in the hippocampus and prefrontal cortex [129]. Polyphenols such as curcumin, quercetin, and resveratrol complement this effect by increasing histone acetylation and DNA methylation, epigenetic modifications that promote BDNF transcription. Through these pathways, the combined action of exercise and polyphenols enhances cognitive function and confers resilience against stress-induced neuronal damage [243, 244] **(**Fig. 3**).**

The impact of exercise and polyphenols on neurotransmitter regulation further highlights their synergistic potential in combating depression. Exercise increases plasma tryptophan availability, facilitating its transport into the brain, where it is converted into serotonin and increasing the activity of TPH, the rate-limiting enzyme in serotonin synthesis [245]. Simultaneously, polyphenols inhibit monoamine oxidase (MAO), an enzyme responsible for serotonin degradation, thereby prolonging serotonin's availability in the synaptic cleft [210]. This dual modulation of serotonin metabolism results in sustained

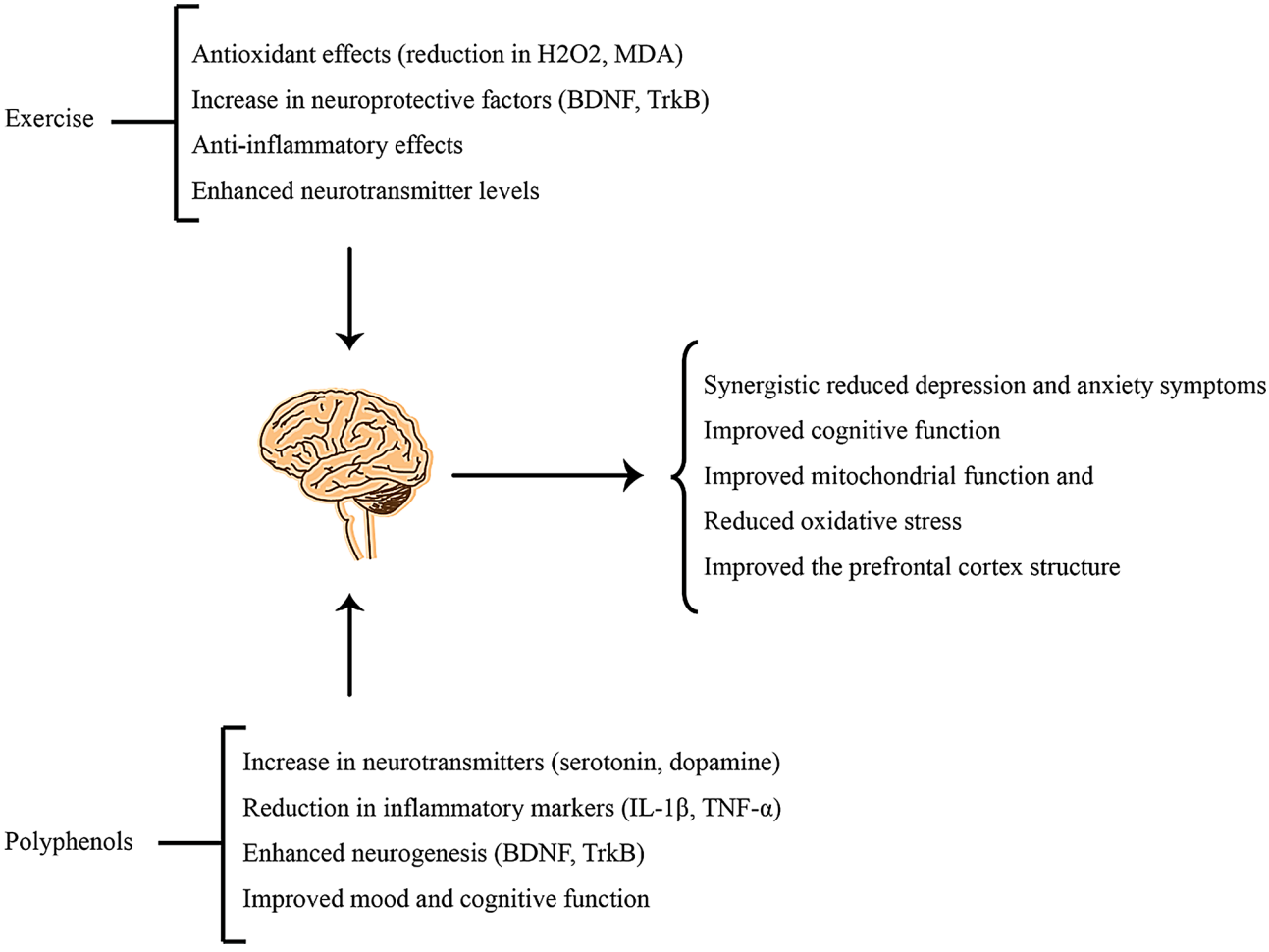

Fig. 3 Synergistic effects of exercise and polyphenols on depression and brain health

improvements in mood and emotional resilience. Similarly, dopamine and norepinephrine levels are elevated through exercise-induced activation of the mesolimbic reward pathway, which enhances motivation, focus, and stress resilience [246]. Polyphenols contribute to the stabilization of dopaminergic neurons by reducing oxidative stress and inflammatory damage, thereby preventing dopaminergic deficits that are commonly associated with mood disorders [247, 248]. Additionally, both interventions modulate GABA and glutamate levels, restoring the balance between inhibitory and excitatory neurotransmission, which is often disrupted in depression and cognitive dysfunction.

A key contributor to mood disorders and neurodegeneration is chronic neuroinflammation, which is mitigated by both exercise and polyphenols through distinct but complementary pathways. Exercise exerts anti-inflammatory effects by suppressing the activation of NF-κB and reducing levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [249]. Polyphenols enhance these effects by inhibiting microglial activation and downregulating inflammatory cascades driven by oxidative stress [249]. The ability of polyphenols to cross the blood-brain barrier enables them to directly modulate neuroinflammation, reinforcing the neuroprotective effects of exercise [250]. This combined regulation of neuroimmune signaling fosters a protective brain environment, reducing the risk of neuropsychiatric disorders.

Another major factor in cognitive decline and mood disorders is oxidative stress, which is markedly attenuated through the synergistic action of exercise and polyphenols. Exercise enhances the endogenous antioxidant defense system by increasing the expression of SOD, CAT, and glutathione peroxidase (GPx), enzymes that neutralize reactive oxygen species (ROS) and prevent oxidative damage [251]. Polyphenols further reinforce these antioxidant defenses by scavenging free radicals and activating nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of oxidative stress response genes [252]. The combined effect of exercise-induced and polyphenol-mediated antioxidant activity reduces

neuronal apoptosis, maintains mitochondrial integrity, and preserves overall brain function.

The regulation of mitochondrial function is another crucial pathway through which exercise and polyphenols synergistically enhance brain health. Mitochondrial dysfunction is a hallmark of neurodegenerative and mood disorders, often resulting in impaired ATP production and increased oxidative stress. Exercise stimulates mitochondrial biogenesis through PGC-1α, nuclear respiratory factors (Nrf1 and Nrf2), and mitochondrial transcription factor A (TFAM), leading to enhanced energy metabolism and improved neuronal survival [253, 254]. Polyphenols contribute to mitochondrial protection by preventing mitochondrial fragmentation, supporting efficient electron transport chain function, and reducing the accumulation of damaged mitochondria [255]. This synergy between exercise and polyphenols ensures optimal energy production, thereby sustaining neuronal activity and cognitive performance.

The kynurenine pathway, a metabolic route that diverts tryptophan from serotonin synthesis to neurotoxic metabolites, is also modulated by exercise and polyphenols. Under conditions of chronic stress and inflammation, tryptophan is preferentially converted into quinolinic acid, a neurotoxin that overactivates N-methyl-D-aspartate (NMDA) receptors, leading to excitotoxicity and neuronal death [256]. Exercise counteracts this process by promoting the conversion of kynurenine into kynurenic acid, a neuroprotective metabolite, thereby shifting the pathway away from neurotoxicity [257, 258]. Polyphenols further reinforce this protective mechanism by inhibiting indoleamine 2,3-dioxygenase (IDO), the enzyme responsible for initiating tryptophan degradation, thus preserving serotonin availability and reducing the harmful effects of excessive glutamatergic activity [259–261].

Beyond molecular mechanisms, behavioral outcomes associated with exercise and polyphenols substantiate their combined benefits. Both interventions have been shown to reduce anxiety-like and depression-like behaviors in preclinical and clinical studies, with measurable improvements in emotional regulation and cognitive flexibility. The engagement of the prefrontal cortex and hippocampus, key regions for executive function and memory, is enhanced through the structural and functional modifications induced by both exercise and polyphenol consumption. By maintaining neural circuit integrity, reinforcing neuroplasticity, and mitigating stress-induced impairments, the combination of exercise and polyphenols provides a robust defense against cognitive decline and mood disorders.

Thus, the synergistic effects of exercise and polyphenol supplementation on brain function are mediated through the modulation of neurotrophic signaling, neurotransmitter balance, inflammatory responses, oxidative stress, mitochondrial function, and kynurenine metabolism. These mechanisms collectively enhance neurogenesis, synaptic plasticity, and cognitive performance while offering protection against mood disorders and neurodegeneration. By integrating regular physical activity with polyphenol-rich diets, individuals can target multiple mechanistic pathways, including neurotransmitter modulation, neurotrophic support, inflammation control, and mitochondrial protection. This combined approach offers a promising strategy for enhancing cognitive resilience, reducing depressive symptoms, and mitigating neurodegenerative risks. Further research should aim to optimize the type, duration, and intensity of exercise, as well as the specific polyphenol compounds and dosages, to maximize these synergistic effects in clinical settings.

Practical guidelines for exercise and polyphenol supplementation in depression management and brain health

To enhance the practical relevance and applicability of our findings, we propose specific guidelines for the application of exercise and polyphenol supplementation in the management of depression and the enhancement of brain function.

To optimize mental health benefits, a dual-intervention approach combining structured exercise with targeted polyphenol supplementation is recommended. Each component contributes uniquely to neuroprotection, mood stabilization, and cognitive resilience, making their combined application particularly effective. A well-structured exercise regimen should include a combination of aerobic and resistance training to maximize the neuroprotective and antidepressant effects. Aerobic exercise, such as brisk walking, jogging, cycling, or swimming, should be performed at moderate to vigorous intensity, maintaining 60–80% of maximum heart rate. A minimum of 150 min per week of moderate-intensity exercise or 75 min per week of vigorous-intensity exercise is recommended, aligning with guidelines from the American College of Sports Medicine. Sessions should ideally be spread across at least three to five days per week to ensure consistent neurobiological benefits. Resistance training, involving weightlifting, bodyweight exercises, or resistance bands, should be incorporated at least twice a week, targeting major muscle groups to enhance neurotrophic factor expression and neurotransmitter balance. HIIT can also be beneficial, particularly in individuals with lower adherence to longer-duration aerobic programs, as it provides substantial cognitive and emotional benefits in shorter timeframes.

Polyphenol supplementation should be tailored to optimize its synergistic effects with exercise. The selection

of polyphenols should focus on those with well-documented neuroprotective and antidepressant properties, including crocin, curcumin, quercetin, resveratrol, and flavonoids from green tea and citrus fruits. Dosage recommendations vary depending on the polyphenol; for instance, crocin supplementation at 30 mg/day has been shown to alleviate depressive symptoms, while curcumin at 100–200 mg/day enhances neurotransmitter balance and reduces inflammation. Quercetin supplementation at 500–1000 mg/day has demonstrated efficacy in modulating oxidative stress and neuroinflammation, while resveratrol at 100–500 mg/day supports mitochondrial function and neuroplasticity. These polyphenols can be consumed in either dietary form, through foods such as saffron, turmeric, onions, berries, and red wine, or as standardized supplements to ensure bioavailability. To maximize absorption and efficacy, polyphenols should be consumed with healthy fats, such as those from olive oil or avocados, or in formulations that enhance bioavailability, such as curcumin with piperine.

To achieve optimal results, exercise and polyphenol supplementation should be consistently integrated into daily routines. Morning exercise sessions may be preferable for enhancing dopamine and serotonin levels throughout the day, while polyphenol intake should be distributed across meals to maintain steady plasma concentrations. The long-term adherence to this combined intervention is crucial for sustained improvements in mood, cognitive function, and overall brain health. The personalized adjustment of exercise intensity and polyphenol dosage, based on individual metabolic responses and mental health status, can further enhance outcomes. While these practical recommendations provide a framework for integrating exercise and polyphenol supplementation into mental health interventions, several research gaps remain. To ensure widespread applicability, future studies must refine dosing strategies, optimize intervention protocols, and establish long-term efficacy.

Critical analysis, research gaps, and future directions

The existing body of research highlights the potential of both exercise and polyphenol supplementation in alleviating depressive symptoms and enhancing cognitive function. However, despite promising results, there remain substantial gaps in understanding the precise mechanisms, dose-response relationships, and long-term effectiveness of these interventions in human populations. While numerous studies have demonstrated the antidepressant and neuroprotective effects of exercise and polyphenols individually, their combined effects remain underexplored, particularly in clinical populations. The existing evidence is primarily derived from preclinical models or short-term human trials, which limits the generalizability of findings to diverse populations with varying degrees of depression severity. Furthermore, while several studies indicate a synergistic effect between exercise and polyphenols, the biological pathways underlying this interaction require further elucidation.

A significant limitation in current research is the lack of standardization in the methodologies used to assess depressive symptoms, cognitive improvements, and biological markers. Variability in exercise protocols (e.g., type, intensity, and duration) and polyphenol dosages, along with inconsistencies in study populations (e.g., age, sex, health status), complicates direct comparisons across studies. A major limitation in translating polyphenol research into clinical practice is their poor bioavailability. Many polyphenols, including curcumin and quercetin, undergo rapid metabolism, reducing their therapeutic efficacy. Future research should focus on optimizing formulations (e.g., nano-encapsulation, co-administration with bioavailability enhancers like piperine) to enhance absorption and prolong systemic circulation.

Another critical aspect that warrants further investigation is the role of individual differences in response to exercise and polyphenol supplementation. Genetic and metabolic variability significantly influence individual responses to exercise and polyphenol supplementation. Variations in neurotransmitter-related genes (e.g., COMT, BDNF Val66Met, SERT polymorphisms) may alter the efficacy of these interventions. Additionally, baseline inflammatory profiles and metabolic differences impact polyphenol metabolism, necessitating a precision medicine approach in future research to tailor interventions based on individual biological profiles. Additionally, while much of the existing literature has focused on aerobic exercise, less attention has been given to the differential effects of resistance training, HIIT, and mind-body exercises like yoga or tai chi on depression and cognitive function. More comparative studies are needed to determine the most effective exercise modalities in combination with polyphenol supplementation.

Beyond mechanistic and methodological gaps, there is also a need for long-term clinical trials to evaluate the sustainability of these interventions. Despite strong evidence supporting the short-term benefits of exercise and polyphenol supplementation, long-term studies remain scarce. Future trials should prioritize longitudinal designs with extended follow-ups to assess whether these interventions provide sustained neuroprotection and reduce depression recurrence. Additionally, the potential interactions between polyphenols and commonly prescribed antidepressants have not been sufficiently explored. Understanding whether polyphenols can serve as adjuncts to conventional pharmacotherapy without

adverse interactions is crucial for integrating these natural compounds into mainstream clinical practice.

Furthermore, the role of lifestyle factors, such as diet quality, sleep patterns, and stress levels, in mediating the effects of exercise and polyphenol supplementation should be examined in more detail. Given that mental health is influenced by multiple interconnected biological and behavioral factors, future research should adopt a multi-dimensional approach that integrates diet, exercise, and psychological interventions to maximize therapeutic outcomes.

Thus, while the current literature provides compelling evidence supporting the use of exercise and polyphenols for mental health, more rigorous, well-controlled human studies are needed to refine dosing strategies, optimize intervention protocols, and establish long-term efficacy. Future research should prioritize standardized methodologies, personalized treatment approaches, and real-world applicability to bridge the gap between experimental findings and clinical implementation. By addressing these research gaps, future studies can refine clinical guidelines, develop precision-targeted interventions, and establish standardized methodologies that maximize the therapeutic benefits of exercise and polyphenol supplementation for depression and cognitive resilience.

Conclusions

The combined effects of exercise and polyphenol supplementation offer a promising, non-pharmacological approach for managing depression and enhancing brain function. Both interventions modulate key biological pathways, including neurotransmitter regulation, neurogenesis, oxidative stress reduction, and inflammation control, contributing to improved mood, cognitive function, and overall mental well-being. Evidence suggests that polyphenols such as crocin, curcumin, and quercetin, when paired with structured physical activity, may yield synergistic benefits beyond their individual effects. However, further clinical studies are needed to optimize dosage, duration, and exercise modalities, ensuring the most effective implementation in depression management. Future research should also explore long-term effects and potential interactions with conventional therapies to establish their broader clinical relevance.

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