

KREŽEL, Maciej, KREŽEL, Olga, RYBIŃSKA, Marcelina and SZAFRANIEC, Artur. The pleiotropic effects of adaptogens in depression: A Systematic Review. *Journal of Education, Health and Sport*. 2026;87:67771. eISSN 2391-8306.
<https://doi.org/10.12775/JEHS.2026.87.67771>
<https://apcz.umk.pl/JEHS/article/view/67771>

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2026; This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Toruń, Poland
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.12.2025. Revised: 19.01.2026. Accepted: 19.01.2026. Published: 19.01.2026.

The pleiotropic effects of adaptogens in depression: A Systematic Review

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Abstract

Depression is a condition that affects increasingly larger groups of people. It involves, among other things, disturbances in neurotransmitter function and nervous system metabolism. The reason for this condition is often an excessive amount of stimuli, according to which the brain must adapt the body to survive in changing conditions. The differences in age, race, gender, and social status that would typically identify groups at higher or lower risk of developing depression are becoming blurred. Today, depressive disorders pose a danger to the entire population. They affect people in various ways. They can result from pathological changes and processes in different systems of the body. Adaptogens, which have strong pleiotropic effects, can be used to improve the patient's condition, well-being, and clinical status across various disorders of the entire body. These are plant-based substances that do not have as well-developed a legislative process as typical drugs on the pharmacological market. However, they play a significant role in supporting the treatment of various organ diseases throughout the body. At the same time, they alleviate neurological aberrations in the course of depressive disorders. In addition, both their antidepressant and health-promoting effects on other systems are mutually beneficial. Therefore, the use of adaptogens can benefit patients and significantly improve their quality of life during illness.

Keywords: adaptogens, depression, pleiotropic mechanisms, treatment, psychiatry

The aim of the work: This review aims to analyze the effects of adaptogens with pleiotropic mechanisms of action in the treatment of depression, based on a comprehensive evaluation of the available evidence on the most frequently studied and utilized compounds.

Materials and Methods:

This article presents a narrative review of the scientific literature addressing the pleiotropic effects of adaptogens in depression, with particular emphasis on their interactions with the nervous, neuroendocrine, immune, cardiovascular, and metabolic systems. The objective of this work was to collect and analyze current scientific evidence regarding the mechanisms of action of adaptogenic plants and their potential role as adjunctive interventions in the management of depressive disorders. The literature search focused on the most extensively studied adaptogens, including *Withania somnifera*, *Rhodiola rosea*, *Panax ginseng*,

Eleutherococcus senticosus, and Schisandra chinensis, in relation to their antidepressant, neuroprotective, anti-inflammatory, antioxidative, and immunomodulatory properties. Scientific articles were retrieved from electronic databases, including PubMed and Google Scholar, as well as from publicly available websites dedicated to the dissemination of reliable medical and scientific information. Publications written in English, Polish, and Spanish were considered. The analysis included preclinical studies, clinical trials, systematic reviews, and meta-analyses. The literature review and article selection process were conducted in December 2025.

Introduction

Depression has been recognized as the mental health disorder with the most tremendous impact on mental health, but also with a higher risk of various diseases of a completely different nature than psychological ones. (Herrman et al., 2019). The definition of depression varies significantly due to its diverse effects on the human body. It is a condition in which a person's allopsychic and autopsychic orientation becomes disturbed by experiencing reality only in a negative and pessimistic way. The impact of this way of perceiving the world is not limited to the realm of thought, but can also affect a person's social life (Bartra et al., 2016). The word itself originates from the Latin *deprimere*, meaning "to bring down," and was used in English literature as early as the 17th and 18th centuries (Gold et al., 2020; Shorey et al., 2022; Horwitz et al., 2016). It is also worth noting that the incidence of depression has increased by almost 50% over the last three decades, which translates into more than 264 million people today (Liu et al., 2020). An additional factor intensifying the problem of depression is its tendency to recur. After the first depressive episode, the likelihood of recurrence can reach 75-90% of cases (Solomon et al., 2000). However, according to other sources, a single episode of the disease is reported in at least half of first-time cases (Monroe et al., 2011).

Definition

The human organism, tasked with surviving in changing environmental conditions, incurs an energy cost defined as allostatic load (Bobba-Alves et al., 2022). The process of adapting to a situation to ensure survival is called allostasis. It is a mechanism by which the brain predicts events that affect the body (Sterling et al., 2012). This prediction triggers a series of events and processes, among other things, thanks to neurotransmitter activity. According to medical literature, neurotransmitter disorders occur during depressive illness and other

conditions such as migraine (Dindo et al., 2017). This is due to one of serotonin's functions: inhibiting pain conduction (Supornsilpchai et al., 2006).

The pathogenesis of depression

From a genetic perspective, some scientists have attributed the selectivity of the depressive process to the polymorphism of the serotonin transporter gene, which in its various forms can increase or decrease an individual's susceptibility to depressive disorders (Dresler et al., 2019). The underlying pathophysiological cause of this condition is metabolic and energy aberration. It is thought to be caused by excessive central nervous system stimulation due to changes in external factors. This overstimulation is both the result and the cause of deepening interoceptive dysregulation, which in turn leads to cortical inhibition (Sennesh et al., 2022). The monoamine theory is also evident in research. It is based on reduced monoamine levels, such as dopamine and norepinephrine, in the limbic system (Brigitta et al., 2022; Fasipe et al., 2019). Furthermore, the monoamine system is influenced by multiple chemical substances, including vasopressin, corticotropin-releasing hormone, meteorological factors, and proinflammatory cytokines (Ogłodek et al., 2014). It is therefore a condition with multifactorial pathogenesis that manifests itself in many ways in the human body.

The link between depression and diabetes

Disorders in the nervous system in the area of depression affect the human body's metabolic system. Studies have shown that there is a causal relationship between depression and various types of incidental diabetes (Cosgrove et al. 2008). The development of depression is associated with insulin resistance and metabolic syndrome. The risk of depression increases fourfold, and life expectancy is reduced by 14 years. Furthermore, the co-occurrence of both disorders increases mortality by 54% (Fanelli et al., 2022). Epidemiological evidence indicates that the co-occurrence of type 2 diabetes and depression is twice as common as the occurrence of each disease separately (Anderson et al. 2001). The risk of depression increases by 29% in people with type 2 diabetes, and in patients with type 2 diabetes who are treated with insulin, it increases by as much as 53% (Li et al., 2008). Additionally, it is worth noting that insulin can cross the blood-brain barrier and stimulate neuroprotective processes that improve neurotransmission and synaptic plasticity (Hamer et al., 2019). As indicated in this study, depression is closely linked to disturbances in stimulus perception, specifically the perception

and processing of often excessive amounts of stimuli. The brain has high metabolic demands to predict behaviors that are adaptive to the environment and situation, enabling the organism to survive. Diabetes-related diseases affect neuronal connections within the brain and prolong stimulus processing, as part of changes in the brain's immunoinflammatory response (Fanelli et al., 2022).

The link between depression and obesity

Researchers point to the link between obesity and depression. It has been observed that people with active depression are much more likely to suffer from obesity (De Wit et al., 2010). Interestingly, this correlation was more common among women than men in the study cited (Luppino et al., 2010). However, it is worth noting that in clinical practice, an increased risk of suicide has been observed in men than in women who are simultaneously struggling with obesity. However, the situation is different for teenage patients. According to research, it is adolescent obesity in girls that increases the risk of severe depression almost fourfold. In teenage boys, however, the risk was found to be insignificant (Anderson et al., 2007). The relationship between depression and obesity is reciprocal. Obese people have a 55% higher risk of depression. At the same time, people with depression have a 58% higher risk of obesity (Luppino et al., 2010). Other studies also indicate an increased risk of suicidal behavior and early onset of depression in people with a high body mass index due to obesity (Kraus et al., 2023). In addition, patients with a high BMI respond much less effectively to antidepressants than patients with a lower obesity index (Kloiber et al., 2007). Ethnicity also plays a role in the correlation between obesity and depression. Researchers found that obesity was a significant depressive factor among young African Americans (Merikangas et al., 2012). Importantly, recent studies confirm the view that treating these two disorders with therapy targeted at one of them, when they occur simultaneously, has a significant impact on the progression of both conditions and is evidence of a bidirectional relationship between obesity and depression (Gerardo et al., 2025).

The link between depression and autoimmune diseases

Depression can induce several autoimmune disorders. Studies have shown that depressed patients face autoimmune diseases significantly more often (Andersson et al., 2015). Several studies indicate a strong correlation between depression and autoimmune disorders.

People who have experienced depression at least once in their lives are 1.25 times more likely to develop diseases related to their own immune system than people who have never suffered from depression (Andersson et al., 2015). The mechanism responsible for linking these types of diseases with depression is the long duration of these diseases. The patient's body is exposed to prolonged stress, which significantly increases the brain's metabolic demand and can easily lead to overload and depressive disorders (Bialek et al., 2019). Examples of diseases that significantly increase the risk of depressive disorders include rheumatoid arthritis, inflammatory bowel disease, and ankylosing spondylitis (Drosselmeyer et al., 2017; Choi et al., 2019; Park et al., 2019). On the other hand, the mechanism causing autoimmune disorders in patients with depression is a significant deterioration in quality of life caused by long-term treatment during the course of the disease. (Malhi et al., 2018). Ultimately, both autoimmune and depressive disorders share an everyday etiological basis - environmental and genetic factors. In turn, their progression is stimulated by ongoing inflammation. (Hodes et al., 2014). For this reason, their occurrence is bidirectional in most patients.

The link between depression and cardiovascular disease

Aberrations in neurotransmitters and metabolism in the central nervous system can also lead to a range of cardiovascular diseases over time. Furthermore, according to research, there is a close relationship not only between the occurrence of depression itself and cardiovascular disease, but also between the worsening of depression and the deterioration of heart disease symptoms (Patten et al., 2008). Among the most common cardiovascular disorders associated with depressive disorders are myocardial infarction and stroke. As a consequence of these clinical events, an increased risk of mortality is observed in people suffering from depression (Hare et al., 2014; Schulz et al., 2000; Penninx et al., 2001; Meng et al., 2020; Rajan et al., 2020). Factors contributing to this type of situation include failure to follow cardiologic recommendations, resulting in behavioral disorders during depression. Several proposals have been put forward in the literature regarding physiological disorders of the body's mechanisms. These include elevated inflammatory markers, reduced levels of brain-derived neurotrophic factor, changes in blood platelet and intestinal bacteria function, and abnormalities in the autonomic nervous system (Carney et al., 2005; Fioranelli et al., 2023). Furthermore, among patients suffering from depression, women are at a higher risk of developing coronary artery disease than men in the same state of health. The same relationship applies in the opposite direction. Women with coronary artery disease are also more likely to suffer from depression

than men. However, smoking remains the most significant and most indisputable factor in both groups of patients (Kim et al., 2020; Melin et al., 2019; Finnell et al., 2016). Researchers often emphasize in their work that cortisol is the link between cardiovascular and depressive disorders. Its concentration in the blood is elevated during depression. (Du et al., 2015). Ultimately, scientists agree on the indisputable fact that the incidence of depression in cardiac patients is 20-40% (Dickens et al., 2015). In addition to standard cardiological procedures, treatment for such patients often involves psychotherapy (Chen et al., 2022). Pharmacological treatment of depression with serotonin reuptake inhibitors also has a beneficial effect on symptoms associated with cardiovascular disease (Zambrano et al., 2020).

Definition of adaptogens and their mode of action

Adaptogens are substances with a vast spectrum of action. They are substances of plant origin. Their main task is to normalize the body's functions (Committee et al., 2008). An example of an adaptogen with broad and well-studied effects is *Withania somnifera*, known as ashwagandha. Generalized tissue sensitivity to *Withania somnifera* and its health-promoting effects on tissues have been discovered (Balasubramani et al., 2011). It is worth noting that it does not operate through a single, specific pharmacological mechanism. Its action is based on a complex physiological process that can be strengthened or activated by prior inhibition caused by the disease (Panossian et al., 2021). Other examples of adaptogens include *Schisandra chinensis*, *Rhodiola rosea*, and *Eleutherococcus senticosus*. Many components that are very valuable for the body's homeostasis have been isolated from the underground parts and fruits of these plants. These include salidroside, rosavin, tyrosol, and schizandrin B. These substances significantly increase stress tolerance. The mechanism that reduces interoception in response to stress involves balancing energy metabolism and the neuroendocrine-immune system (Panossian et al., 2013). This changes the brain's perception of stress, reduces anxiety levels, and improves memory (Todorova et al., 2021).

Negative effects of adaptogenic therapy

Despite the pleiotropy of adaptogens' positive effects, researchers have described an equally wide range of adverse effects, which, due to the broad tissue sensitivity to adaptogens, can manifest across many areas of the body. It should be noted that substances isolated during specialized studies, such as those originating from *Withania somnifera*, are bioactive. Scientists

have isolated 12 alkaloids and 40 withanolides, which may act pharmacologically independently (Mirjalili et al., 2009). Therefore, adaptogens should be used with awareness of their bioactive composition, both in terms of their health-promoting properties and the risk of adverse effects (Woron et al., 2018). An essential fact about adaptogens is that within the European Union, the name used in this article is not recognized as a proper pharmacological term. This is due to the pharmaceutical market's insufficient verification of the plant substance's positive and negative effects. Ultimately, plant origin and health-promoting factors should not be sufficient to classify a given substance as an adaptogen.

Adaptogens in the treatment of diabetes

Due to the broad impact of depressive disorders on the overall condition of the human body, as outlined in this paper, it is worth emphasizing the health-promoting effect of adaptogens on areas affected by pathologies coexisting with depression or being its consequence or indirect cause. A plant substance such as the aforementioned *Withania somnifera*, commonly known as ashwagandha, has been shown to have anti-diabetic properties (Mandlik et al., 2021). The action mechanism of *Withania somnifera* water extract is to normalize hyperglycemia by increasing insulin sensitivity in cells. In addition, this adaptogen improves glucose tolerance (Anwer et al., 2008). It is essential to note the cause-and-effect relationship of the drug's action. By bringing the body closer to homeostasis during illness by reducing the effects of diabetes, plant substances improve brain metabolism, which, when not exposed to stressors, can restore healthy functioning and reduce the impact of depression. Another health-promoting effect in the treatment of diabetes is the reduction of inflammation and the improvement of beta-cell function. Subsequent studies have revealed additional positive mechanisms of adaptogens and have confirmed previous findings indicating increased cellular sensitivity to insulin and improved glucose tolerance (Alhasani et al., 2025). Therefore, the therapeutic effect of selected adaptogens on diabetes should be emphasized. Thanks to the improvement in the metabolism of these substances, depressed patients, who are often also diabetic patients of diabetologists in the course of this disease, experience significant improvement (Makhlof et al., 2024).

Adaptogens in the treatment of obesity

Nowadays, obesity is increasingly recognized as a separate disease entity. However, its significance as a disease is still not recognized by many doctors and patients. As previously

demonstrated, depression can manifest itself in obesity and be exacerbated by it. Therefore, the therapeutic effect of selected herbal remedies is significant in the fight against both obesity and depression. An example is Rhodiola rosea, which inhibits preadipocyte differentiation into adipocytes at the cellular level. In addition, it reduces triglyceride accumulation, which could contribute to adipose tissue formation. Ultimately, the substance increases lipolysis, thereby reducing adipose tissue growth and body weight (Pomari et al., 2015). In addition, the plant substance mentioned above may increase the expression of thermogenic genes, which underlie the greater conversion of fat into energy in the form of heat. Furthermore, they increase the number of mitochondrial proteins involved in fat-burning processes. (Zhu et al., 2023). Therefore, the indirect sensitivity of adipose tissue to adaptogens through the stimulation of catabolic processes may reduce the symptoms of obesity and thus improve the quality of life of patients with depression. It is through the pleiotropic action of plant substances that the effects of depression in obesity and obesity in depression can be inhibited.

Adaptogens in the treatment of autoimmune diseases

Autoimmune diseases are not easy to treat with medication. At the same time, there is growing evidence that medicinal adaptogens can significantly improve the health of patients with this disease (Mikulska et al., 2023). The therapeutic process involves alleviating inflammation, which in autoimmune diseases is directed against the body's own tissues. Therefore, the anti-inflammatory effect of *Withania somnifera*, for example, is key in treating and alleviating the symptoms of such diseases (Rasool et al., 2006). Studies show that Ashwagandha's anti-inflammatory properties can also help treat skin conditions caused by inflammation (Sikandan et al., 2018). Both autoimmune diseases and, even more so, skin diseases are significant factors contributing to depression, and therefore, combating their effects can significantly improve the well-being of patients suffering from depression. In addition, several immunosuppressive mechanisms have been demonstrated, including those stimulated by adaptogens such as Rhodiola rosea, which can directly enhance the therapeutic effects in many autoimmune diseases (Gatica et al., 2011). Plant-based medicinal substances inhibit COX-2 and certain phospholipases, thereby stabilizing cell membranes and reducing swelling. This mechanism is therefore considered to be the most likely cause of the anti-inflammatory effects of specific adaptogens (Pooja et al., 2009). In summary, although still in its early stages, research into the impact of adaptogens on inflammation caused by the body's own immune

response already provides some grounds for recognizing this effect as inhibiting inflammation and stabilizing cellular functions. (Jaganjac et al., 2022).

Adaptogens in the treatment of cardiovascular diseases

In studies on adaptogens such as Panax ginseng, several dozen chemical compounds, such as polysaccharides, peptides, alkaloids, and others, have been analyzed. Thanks to such a diverse range of compounds, the therapeutic effect of Panax ginseng, for example, in cardiovascular diseases has been confirmed (Kim et al., 2018; Irfan et al., 2020; Lee et al., 2014). The mechanism by which adaptogens act as pharmaceuticals in vascular diseases is based on their antihypertensive effect. Vascular endothelial cells are stimulated to convert L-arginine to L-citrulline for the synthesis of nitric oxide. The nitrogen compound triggers the production of cyclic guanosine 3',5'-monophosphate (cGMP), which mediates vasodilation. Vasodilation lowers blood pressure and thus reduces the symptoms of hypertension (Kang et al., 1995; Kim et al., 1994; Tousoulis et al., 2012). In addition, Panax ginseng has many benefits in minimizing the side effects associated with antiplatelet drugs. These include, among others, prolonged bleeding time or thrombocytopenia (Barrett et al., 2008; Mackman et al., 2008). This adaptogen prevents prolonged bleeding when aspirin is used, thereby protecting the patient from excessive blood loss despite its inhibition of platelet activation (Irfan et al., 2019; Endale et al., 2012). In addition, plant-based substances have therapeutic effects on the patient's lipid profile, increasing HDL cholesterol levels and lowering LDL cholesterol levels (Yamamoto et al., 1983; Hwang et al., 2008; Saba et al., 2016). This makes the blood less viscous and improves vascular flow. Therefore, adaptogens have a positive effect on cardiovascular disease treatment. At the same time, by improving the vascular system and its function, plant substances reduce the depressive impact of diseases of this system. This is another example of the key role of adaptogens in combating the symptoms of depression in the human body, and thus indirectly depression itself.

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