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Correlation between inflammatory process and the comorbidity of depression and cardiovascular diseases and therapeutic possibilities

Związek procesu zapalnego ze współwystępowaniem depresji i chorób sercowo-naczyniowych oraz możliwości terapeutyczne

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Abstract

Cardiovascular diseases (CVD) and depression rank among the most common diseases in the general population. Recently, there has been a considerable amount of research on the inflammatory component of these diseases. The causal relationship responsible for such frequent comorbidity between them is not clear. Among the mechanisms associated with the development of depression, identified were the imbalance of the gut-brain axis, impaired microglia activity, increased levels of CRP (C reactive protein), IL-6 (Interleukine 6) and oxidative stress. CVD is associated with activation of the inflammasome NRLP-3 (NOD-like receptor protein 3), increased concentration of hs-CRP (highly sensitive C reactive protein) and interleukins IL-1β, IL-6, IL-18, gut-brain axis dysfunction and oxidative stress. The purpose of this study is to investigate the relationship between CVD and depression in the context of systemic inflammation and to review potential therapeutics, which might reduce or modulate inflammation that could potentially be used clinically to reduce cardiovascular risk among patients with depression.

Keywords: depression, cardiovascular diseases, systemic inflammation

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Introduction

Depression and cardiovascular diseases (CVD) are currently the leading diseases among the global population. In 2019, according to the WHO, CVDs were responsible for 32% of deaths worldwide. Data from the Central Statistical Office (CSO) shows that CVDs were responsible for the deaths of approximately 180,000 Poles and were the leading cause of death in Poland in 2021. According to the WHO, approximately 5% of the global adult population suffers from depression. Data released by the National Health Fund shows that in 2021. 1.5 million Poles purchased reimbursable antidepressants and this is 59% more people than in 2013.

People with depression have a significantly increased risk of developing cardiovascular disease and cardiovascular mortality. It has been shown that there is a 1.44-fold increased risk of cardiovascular mortality in patients with

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depression [1]. It has also been noted that depression is diagnosed more frequently among people with cardiovascular disease than in the general population [2].

The above epidemiological data clearly illustrate the need to investigate the relationship between depression and cardiovascular disease and potential therapeutic solutions that could be used clinically.

The relationship between depression and CVD

It should be noted that the relationship between depression and cardiovascular disease is very complex and multifactorial.

Depression affects risk factors for cardiovascular disease. It has been shown, an association between depression and increased prevalence of central obesity, metabolic syndrome, elevated triglycerides, and lower HDL-C (high-density lipoprotein cholesterol) levels, which are risk factors for CVD [3]. Cardiovascular risk is also influenced by the lifestyle of people with depression — diet, physical activity, quantity and quality of sleep or smoking.

The effect of a genetic predisposition to depression on the risk of myocardial infarction and coronary heart disease has been investigated, with results confirming that a genetic predisposition to depression is causally related to the occurrence of myocardial infarction and coronary heart disease [4].

It has been observed that in both depression and cardiovascular disease, homeostasis is disturbed and the immune system is dysregulated. Due to the frequent co-occurrence of these diseases with each other and the involvement of the inflammatory process in both depression and cardiovascular disease, the search for a potentially common aetiological factor has begun. It is thought that low-grade inflammation may play a key role in the development of these diseases.

Inflammation and depression

Depression is one of the diseases with a multifactorial aetiology. Numerous studies have shown an association between systemic inflammation and elevated inflammatory parameters and the onset of depressive symptoms.

An understanding of the bidirectional action of the gut-microbiota-brain axis seems important in understanding the pathogenesis of depression. The gut microbiota makes up the so-called gut brain. It comprises bacteria, fungi, viruses and protozoa, and through the production of biochemical compounds, for example, short-chain fatty acids, they exert their influence on the function of numerous signalling pathways. The microbiota is a key component regulating the hypothalamic-pituitary-adrenal axis, immune system function, the blood-brain barrier, neurogenesis and myelogenesis, so it has a huge impact on CNS (central nervous system) function [5]. Many factors can affect the composition of the microbiota: mode of delivery, stress, physical activity, type of diet, gastrointestinal infections, use of antibiotics and probiotics. Disturbances in the microbiome can lead to brain disorders, including mental illness. Depressed patients have been shown to have increased permeability of the gastrointestinal tract (so-called leaky gut) to Gram-negative bacteria, which contain lipopolysaccharide (LPS) in their cell membrane. Studies in mice have demonstrated the depressogenic effect of LPS. In in vivo studies, administration of LPS induced inflammation and secondary activation of microglia [6].

Microglia cells are classified as brain-specific macrophages. CNS injury leads to the activation of microglia, which produce numerous cytokines, chemokines and cytotoxic compounds thereby activating the immune response. The production of pro-inflammatory cytokines by microglia is considered one of the main factors leading to the development of depression [7].

Inflammation in depression is usually of low severity. To assess the severity of inflammation, the most commonly studied biomarkers were CRP (C reactive protein) and IL-6 (interleukin 6). Based on a meta-analysis of 30 studies involving 13,541 depressed and 155,728 control subjects, the prevalence of low-grade inflammation with CRP > 3 mg/L in depression was 27% and the prevalence of elevated CRP > 1 mg/L was 58% (which was not associated with other factors such as age, antidepressant treatment, BMI, ethnicity) [8]. In the case of IL-6, it is associated with a reduction in hippocampal volume, which is a characteristic organic brain change in depressed patients [9]. Its action is based on two signalling pathways — classical (IL-6-membrane-receptor) and trans (IL-6-soluble receptor), with most interactions with the brain occurring via the trans pathway. The classical pathway plays an important role in signalling between the immune system and microglia cells [10]. Numerous studies have shown that an increase in IL-6 levels correlates with the onset of depression [11]. A meta-analysis considering 36 studies compared CRP and IL-6 levels in 2679th individuals exhibiting suicidal behaviour with 6839th controls. Suicidal behaviour was associated with higher levels of CRP and IL-6 in the blood compared to the control group and was also higher than in patients with depression alone and in patients with any psychiatric disorder [12]. Despite some association between increases in CRP and IL-6 and depression, there are no studies yet that definitively clarify whether inflammation is a cause of depression or a consequence of depression.

Oxidative stress plays a role in the pathogenesis of depression — an imbalance between levels of reactive oxygen species (ROS) and the body's ability to detoxify ROS with

antioxidants. Unreduced ROS can damage proteins, lipids and DNA and have a pro-inflammatory effect. The brain, on the other hand, is an organ that is extremely vulnerable to reactive oxygen species due to its high metabolism. Increased levels of ROS in the brain are associated with neurodegeneration and with changes in brain structure responsible for the development of depression. Research into the use of antioxidants in the treatment of depression seems warranted [13].

Inflammation a CVD

Inflammation has been studied to play a role in heart failure, myocardial infarction, stroke or atherosclerosis. Immune cells are involved in the induction and regulation of inflammation, including macrophages, monocytes, neutrophils, mast cells, NK cells, T and B lymphocytes, and cytokines, of which the most important pro-inflammatory ones are IL-1β, IL-6, TNFα (tissue necrosis factor α), while IL-10 shows anti-inflammatory properties. One mechanism that plays a role in cardiovascular disease is the activation of the NLRP-3 (NOD-like receptor protein 3) inflammasome, which induces an increase in IL-1β, which causes an increase in IL-6 and IL-18 leading to an increase in hs-CRP (highly sensitive C-reactive protein). HsCRP is a potential biomarker used to determine cardiovascular risk clinically [14, 15].

Endothelial dysfunction is also associated with immune deregulation. The changes that occur in the vascular endothelium in atherosclerosis are associated with abnormal lipid metabolism, haemodynamic changes, activation of inflammatory factors, and oxidative stress. Endothelial cells begin to produce the adhesion molecules ICAM-1 (intercellular adhesion molecule 1), MCP-1 (monocyte chemotactic protein 1), VCAM-1 (vascular cell adhesion molecule 1), P-selectin and E-selectin, which activate neutrophils and monocytes. Monocytes then transform into macrophages and these into foam cells. Other immune cells such as mast cells, B lymphocytes, T lymphocytes and dendritic cells are also involved in plaque formation. The secretion of prothrombotic molecules is increased [16].

In recent years, the influence of the gut microbiota on cardiovascular disease and the immune system has also been studied. Changes in the composition of the gut microbiota have been seen in patients with atherosclerosis or hypertension. One of the metabolites associated with the gut microbiota is trimethylamine N-oxide (TAMO), whose increased plasma concentrations are significantly associated with atherosclerosis, hypertension or elevated CRP levels. Intestinal dysbiosis leads to increased production of TAMO, which affects endothelial dysfunction and increased platelet reactivity, leading to atherosclerosis. It has been noted that TAMO affects foam cell production by impairing cholesterol metabolism in macrophages. Animal studies have shown that increased levels of TAMO may be associated with activation of the NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, leading to the release of the inflammatory cytokines IL-18 and IL-1β thereby contributing to TAMO-induced endothelial dysfunction [17, 18].

Dysbiosis contributes to disruption of the body's homeostasis and changes in the immune system, leading to increased levels of inflammatory cytokines in the body. The effect of an intermitting fasting diet on people with metabolic syndrome has been studied and a reduction in inflammatory cytokine levels, and a positive effect on cardiovascular risk factors has been observed, which has been linked to changes in the composition of the gut microbiota [19].

Numerous studies are underway to modulate immune pathways to reduce cardiovascular risk. The CANTOS trial confirmed the efficacy of anti-inflammatory therapy with canakinumab (a monoclonal antibody against IL-1β) in the secondary prevention of cardiovascular events. Reductions in hs-CRP levels, cardiovascular events and death from cardiovascular events have been observed in patients taking canakinumab daily [20]. The COLCOT and LoDoCo2 clinical trials investigated the effect of colchicine on cardiovascular risk. Colchicine indirectly affects the NLRP-3 inflammasome. Patients treated with colchicine after myocardial infarction had a significantly lower risk of cardiovascular ischaemic events. It has been proven that patients with chronic coronary artery disease taking colchicine had a significantly reduced cardiovascular risk [21, 22].

Studies have confirmed the efficacy of anti-inflammatory treatment in reducing the risk of secondary cardiovascular events. Such therapeutic interventions have limitations; a statistically significant increase in mortality from infection was noted in study participants, probably due to the immunosuppressive effect. Further research, into the immune pathways responsible for inflammation in CVD, may contribute to better therapeutic approaches, reducing adverse effects [23].

Common therapeutic opportunities

Are there compounds that would have a beneficial effect in both adjunctive treatment of depression and cardiovascular risk reduction? The 12-month randomised controlled trial eIMPACT showed that standard treatment of depression internet/telephone-based cognitive behavioural therapy and/or antidepressant treatment with selected medications or treatment of depression with a primary care physician resulted in moderate to major improvements in depression, but no differences in CVD risk biomarkers were observed. Treatment of depression alone did not reduce cardiovascular risk. It seems, therefore, important

Table 1. Comparison of compounds that reduce or modulate inflammation in depression and cardiovascular disease.

Name of the compound tested	Impact on depression	Impact on CVD
Vitamin E (α-tocopherol)	studies have shown that vitamin E intake is inversely associated with the incidence of depression, but further research is needed due to limited evidence [25]	In inconclusive impact, studies to date have not rejected the hypothesis that vitamin E can prevent atherosclerosis and its complications [26]
fFlavonoids	beneficial effects on the course of depression, a meta-analysis of 11 studies showed that depressive symptoms were reduced when the flavonoid dose was 50–100 mg/day or the duration of treatment was ≥ 8 weeks [27]	consumption of flavonoid-rich foods has a beneficial effect in reducing the risk of cardiovascular disease [28]
Coenzyme Q10 (ubiquinone)	shows neuroprotective properties, one study in rats in which a depression-like state was artificially stimulated showed its antidepressant effect (further high-quality clinical studies are needed) [29]	beneficial clinical effects and beneficial effects on cardiovascular risk biomarkers have been demonstrated with coenzyme Q10 supplementation together with selenium (limitation — small number of clinical trials) [30]
Omega 3 polyunsaturated fatty acids (DHA and EPA)	A meta-analysis of 26 studies showed a benefit in mild depression of omega-3s with EPA ≥ 60% at a dose of ≤ 1 g/d, preparations with DHA no benefit [31]	reduction in CRP and IL-1β levels, which have a pathophysiological link to cardiovascular disease [32]
Curcuma (curcumin)	A meta-analysis collecting 9 studies showed a significant effect of curcumin in reducing symptoms of depression and anxiety symptoms, curcumin added to standard antidepressant therapy may help treat depression, but a cautious interpretation of the results was recommended due to the small sample size [33]	Turmeric has a beneficial effect on blood lipid levels and may therefore reduce cardiovascular risk, and can be used as an adjunct to standard therapy, research is needed to establish dosage [34]
Probiotics	numerous studies have confirmed the therapeutic benefits of probiotics in patients with depression through effects on gut-brain axis function [35] (further research is needed to determine the best composition of probiotics, dosage and to determine the duration of therapy)	showed a significant effect of probiotics on lowering blood pressure, total cholesterol, LDL-C, serum glucose, HbA1C and BMI and raising HDL-C levels, no significant changes in triglyceride results were observed, and studies supported the need for a longer treatment period of about 1.5 months [36], subsequent meta-analyses also showed a beneficial effect of probiotics on lipid profile
Infliximab (inhibits TNF-α activity)	patients with baseline hs-CRP levels > 5 mg/L showed a response rate of 62% in the infliximab-treated group compared to 33% among placebo-treated patients, TNF-α antagonism can alleviate depressive symptoms in patients with baseline high hs-CRP [37]	a study evaluating the effect of 12-week infliximab treatment on future cardiovascular risk in patients with bipolar disorder found no significant effect of infliximab treatment on FRS (Framingham risk score), MAP (mean arterial blood pressure) and TC (total cholesterol) [38] (limitation — small number of clinical trials)
Tocilizumab (modulates IL-6 activity)	a low-to-moderate benefit has been demonstrated with the use of an anti-cytokine drug [39]	one study involving 133,449 people published in the Lancet showed that blockade of receptors for IL-6 can prevent ischaemic heart disease, further research is needed in this direction [40]

Explanation of abbreviations: BMI — body mass index; CVD — cardiovascular diseases; CRP — C reactive protein; DHA — Docosahexaenoic acid; EPA — Eicosapentaenoic acid; FRS — Framingham risk score; HbA1c — glycosylated haemoglobin; HDL-C — high-density lipoprotein cholesterol; Il-1β — interleukine 1β; IL-6 — interleukine 6; LDL-C — low-density lipoprotein cholesterol; MAP — mean arterial blood pressure; TNFα — tissue necrosis factor α; TC — total cholesterol

to seek alternative treatments for patients with comorbid depression and CVD [24].

We compared eight compounds that reduce or modulate inflammation — presented in Table 1. The table is not exhaustive of all therapeutic options that modulate inflammation.

As can be seen from the table, many compounds may carry potential benefits for patients with coexisting depression and CVD, so further clinical research into the use of antioxidants, polyphenols, inflammation-modulating compounds or probiotics is extremely important.

Conclusions

A better knowledge of the mechanisms responsible for this frequent co-occurrence of depression and cardiovascular

disease will allow a strategy for the clinical care of patients to be developed. It is advisable to assess the cardiovascular risk in patients suffering from depression and take therapeutic measures to reduce it. It is worthwhile for the treatment of depression to be part of the treatment regimen for cardiovascular disease. Systemic inflammation may be a common therapeutic target in this case, but more research is needed to develop clinical solutions.

Additional information

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The authors declare no conflict of interest

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Streszczenie

Choroby sercowo-naczyniowe (CVD, *cardiovascular diseases*) oraz depresja zajmują czołowe miejsca wśród najczęściej występujących chorób w populacji ogólnej. W ostatnim czasie przeprowadzono wiele badań nad zapalną komponentą tych chorób. Nie jest jasny związek przyczynowo-skutkowy odpowiedzialny za tak częste ich współistnienie. Wśród mechanizmów związanych z rozwojem depresji wyodrębnione zostały między innymi zachwianie osi jelita-mózg, zaburzenia aktywności mikrogleju, zwiększone stężenie CRP (*C reactive protein*), IL-6 (*Interleukine 6*) i stres oksydacyjny. CVD wiążą się z aktywacją inflamosomu NRLP-3 (*NOD-like receptor protein 3*), wzrostem stężenia hsCRP (*highly sensitive C reactive protein*) oraz interleukin: IL-1β, IL-6, IL-18, dysfunkcją osi jelita-mózg i stresem oksydacyjnym. Celem pracy jest ustalenie związku pomiędzy CVD, a depresją w kontekście stanu zapalnego w organizmie (*systemic inflammation*) oraz przegląd związków wpływających na redukcję lub modulację stanu zapalnego, które potencjalnie mogłyby zostać wykorzystane klinicznie w redukcji ryzyka sercowo-naczyniowego wśród pacjentów z depresją.

Słowa kluczowe: depresja, choroby sercowo-naczyniowe, zapalenie

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References

1. Krittanawong C, Maitra NS, Qadeer YK, et al. Association of Depression and Cardiovascular Disease. Am J Med. 2023; 136(9): 881–895, doi: 10.1016/j.amjmed.2023.04.036, indexed in Pubmed: 37247751.
2. Bahall M. Prevalence and associations of depression among patients with cardiac diseases in a public health institute in Trinidad and Tobago. BMC Psychiatry. 2019; 19(1): 4, doi: 10.1186/s12888-018-1977-3, indexed in Pubmed: 30616551.
3. Zhang M, Chen J, Yin Z, et al. The association between depression and metabolic syndrome and its components: a bidirectional two-sample Mendelian randomization study. Transl Psychiatry. 2021; 11(1): 633, doi: 10.1038/s41398-021-01759-z, indexed in Pubmed: 34903730.
4. Li GHY, Cheung CL, Chung AKK, et al. Evaluation of bi-directional causal association between depression and cardiovascular diseases: a Mendelian randomization study. Psychol Med. 2022; 52(9): 1765–1776, doi: 10.1017/S0033291720003566, indexed in Pubmed: 33032663.
5. Carabotti M, Scirocco A, Maselli MA, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015; 28(2): 203–209, indexed in Pubmed: 25830558.
6. Yin R, Zhang K, Li Y, et al. Lipopolysaccharide-induced depression-like model in mice: meta-analysis and systematic evaluation. Front Immunol. 2023; 14, doi: 10.3389/fimmu.2023.1181973, indexed in Pubmed: 37359525.
7. Singhal G, Baune BT. Microglia: an interface between the loss of neuroplasticity and depression. Front Cell Neurosci. 2017; 11: 270, doi: 10.3389/fncel.2017.00270, indexed in Pubmed: 28943841.
8. Osimo EF, Baxter LJ, Lewis G, et al. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med. 2019; 49(12): 1958–1970, doi: 10.1017/S0033291719001454, indexed in Pubmed: 31258105.
9. Kakeda S, Watanabe K, Katsuki A, et al. Relationship between interleukin (IL)-6 and brain morphology in drug-naïve, first-episode major depressive disorder using surface-based morphometry. Sci Rep. 2018; 8(1): 10054, doi: 10.1038/s41598-018-28300-5, indexed in Pubmed: 29968776.
10. Kelly KM, Smith JA, Mezuk B. Depression and interleukin-6 signaling: a mendelian randomization study. Brain Behav Immun. 2021; 95: 106–114, doi: 10.1016/j.bbi.2021.02.019, indexed in Pubmed: 33631287.
11. Köhler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017; 135(5): 373–387, doi: 10.1111/acps.12698, indexed in Pubmed: 28122130.
12. Neupane SP, Daray FM, Ballard ED, et al. Immune-related biomarkers and suicidal behaviors: A meta-analysis. Eur Neuropsychopharmacol. 2023; 75: 15–30, doi: 10.1016/j.euroneuro.2023.05.009, indexed in Pubmed: 37356288.

13. Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. Drug Discov Today. 2020; 25(7): 1270–1276, doi: 10.1016/j.drudis.2020.05.001, indexed in Pubmed: 32404275.
14. Goswami SK, Ranjan P, Dutta RK, et al. Management of inflammation in cardiovascular diseases. Pharmacol Res. 2021; 173: 105912, doi: 10.1016/j.phrs.2021.105912, indexed in Pubmed: 34562603.
15. Kuppa A, Tripathi H, Al-Darraji A, et al. C-Reactive protein levels and risk of cardiovascular diseases: a two-sample bidirectional mendelian randomization study. Int J Mol Sci. 2023; 24(11), doi: 10.3390/ijms24119129, indexed in Pubmed: 37298077.
16. Xu S, Ilyas I, Little PJ, et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. Pharmacol Rev. 2021; 73(3): 924–967, doi: 10.1124/pharmrev.120.000096, indexed in Pubmed: 34088867.
17. Li D, Lu Y, Yuan S, et al. Gut microbiota-derived metabolite trimethylamine-N-oxide and multiple health outcomes: an umbrella review and updated meta-analysis. Am J Clin Nutr. 2022; 116(1): 230–243, doi: 10.1093/ajcn/nqac074, indexed in Pubmed: 35348578.
18. Qian B, Zhang K, Li Y, et al. Update on gut microbiota in cardiovascular diseases. Front Cell Infect Microbiol. 2022; 12, doi: 10.3389/fcimb.2022.1059349, indexed in Pubmed: 36439214.
19. Guo Yi, Luo S, Ye Y, et al. Intermittent fasting improves cardiometabolic risk factors and alters gut microbiota in metabolic syndrome patients. J Clin Endocrinol Metab. 2021; 106(1): 64–79, doi: 10.1210/clinem/dgaa644, indexed in Pubmed: 33017844.
20. Ridker PM, Everett BM, Thuren T, et al. CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017; 377(12): 1119–1131, doi: 10.1056/NEJMoa1707914, indexed in Pubmed: 28845751.
21. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019; 381(26): 2497–2505, doi: 10.1056/NEJMoa1912388, indexed in Pubmed: 31733140.
22. Nidorf SM, Fiolet ATL, Mosterd A, et al. LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020; 383(19): 1838–1847, doi: 10.1056/NEJMoa2021372, indexed in Pubmed: 32865380.
23. Henein MY, Vancheri S, Longo G, et al. The role of inflammation in cardiovascular disease. Int J Mol Sci. 2022; 23(21), doi: 10.3390/ijms232112906, indexed in Pubmed: 36361701.
24. Stewart JC, Patel JS, Polanka BM, et al. Effect of modernized collaborative care for depression on depressive symptoms and cardiovascular disease risk biomarkers: eIMPACT randomized controlled trial. Brain Behav Immun. 2023; 112: 18–28, doi: 10.1016/j.bbi.2023.05.007, indexed in Pubmed: 37209779.
25. Ding J, Zhang Yi. Associations of dietary vitamin C and E intake with depression. A meta-analysis of observational studies. Front Nutr. 2022; 9, doi: 10.3389/fnut.2022.857823, indexed in Pubmed: 35464032.
26. Violi F, Nocella C, Loffredo L, et al. Interventional study with vitamin E in cardiovascular disease and meta-analysis. Free Radic Biol Med. 2022; 178: 26–41, doi: 10.1016/j.freeradbiomed.2021.11.027, indexed in Pubmed: 34838937.
27. Jia S, Hou Y, Wang D, et al. Flavonoids for depression and anxiety: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2023; 63(27): 8839–8849, doi: 10.1080/10408398.2022.2057914, indexed in Pubmed: 35400250.
28. Parmenter BH, Croft KD, Hodgson JM, et al. An overview and update on the epidemiology of flavonoid intake and cardiovascular disease risk. Food Funct. 2020; 11(8): 6777–6806, doi: 10.1039/d0fo01118e, indexed in Pubmed: 32725042.
29. Abuelezz SA, Hendawy N, Magdy Y. Targeting oxidative stress, cytokines and serotonin interactions via indoleamine 2, 3 dioxygenase by coenzyme Q10: role in suppressing depressive like behavior in rats. J Neuroimmune Pharmacol. 2017; 12(2): 277–291, doi: 10.1007/s11481-016-9712-7, indexed in Pubmed: 27730347.
30. Alehagen U, Johansson P, Svensson E, et al. Improved cardiovascular health by supplementation with selenium and coenzyme Q10: applying structural equation modelling (SEM) to clinical outcomes and biomarkers to explore underlying mechanisms in a prospective randomized double-blind placebo-controlled intervention project in Sweden. Eur J Nutr. 2022; 61(6): 3135–3148, doi: 10.1007/s00394-022-02876-1, indexed in Pubmed: 35381849.
31. Liao Y, Xie Bo, Zhang H, et al. Efficacy of omega-3 pufas in depression: a meta-analysis. Transl Psychiatry. 2019; 9(1): 190, doi: 10.1038/s41398-019-0515-5, indexed in Pubmed: 31383846.
32. Bersch-Ferreira ÂC, Sampaio GR, Gehringer MO, et al. Association between polyunsaturated fatty acids and inflammatory markers in patients in secondary prevention of cardiovascular disease. Nutrition. 2017; 37: 30–36, doi: 10.1016/j.nut.2016.12.006, indexed in Pubmed: 28359359.
33. Fusar-Poli L, Vozza L, Gabbiadini A, et al. Curcumin for depression: a meta-analysis. Crit Rev Food Sci Nutr. 2020; 60(15): 2643–2653, doi: 10.1080/10408398.2019.1653260, indexed in Pubmed: 31423805.
34. Zeng L, Yang T, Yang K, et al. Efficacy and safety of curcumin and extract in the treatment of arthritis: a systematic review and meta-analysis of randomized controlled trial. Front Immunol. 2022; 13, doi: 10.3389/fimmu.2022.891822, indexed in Pubmed: 35935936.
35. Ansari F, Pourjafar H, Tabrizi A, et al. The effects of probiotics and prebiotics on mental disorders: a review on depression, anxiety, alzheimer, and autism spectrum disorders. Curr Pharm Biotechnol. 2020; 21(7): 555–565, doi: 10.2174/1389201021666200107113812, indexed in Pubmed: 31914909.
36. Dixon A, Robertson K, Yung A, et al. Efficacy of probiotics in patients of cardiovascular disease risk: a systematic review and meta-analysis. Curr Hypertens Rep. 2020; 22(9): 74, doi: 10.1007/s11906-020-01080-y, indexed in Pubmed: 32860083.
37. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013; 70(1): 31–41, doi: 10.1001/2013.jamapsychiatry.4, indexed in Pubmed: 22945416.
38. Gill H, Rodrigues NB, Mansur RB, et al. The effect of adjunctive infliximab treatment on future cardiovascular disease risk in patients with bipolar disorder. J Affect Disord. 2022; 316: 273–279, doi: 10.1016/j.jad.2022.07.020, indexed in Pubmed: 35878838.
39. Kappelmann N, Lewis G, Dantzer R, et al. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry. 2018; 23(2): 335–343, doi: 10.1038/mp.2016.167, indexed in Pubmed: 27752078.
40. Swerdlow DI, Holmes MV, Kuchenbaecker KB, et al. Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012; 379(9822): 1214–1224, doi: 10.1016/S0140-6736(12)60110-X, indexed in Pubmed: 22421340.