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REVIEW ARTICLE

FOLIC ACID – IMPORTANCE FOR HUMAN HEALTH AND ITS ROLE IN COVID-19 THERAPY

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ABSTRACT

Folic acid (folacin, B_9) is a vitamin that performs many very important functions in the human body, and its inadequate level - deficiency as well as excess, may contribute to an increased risk of developing many disease processes. The aim of this study was to analyze the available scientific literature on folic acid and its impact on human health. A systematic review of the studies, published until November 2022, was made on the basis of searching bibliographic databases such as: PubMed, Elsevier and Google Scholar. The following keywords and combinations were used: folic acid, folate, folic acid supplementation, folate deficiency. Folic acid, thanks to its high biological activity, has a direct and indirect effect on the metabolism of the human body cells. It plays a very important role, among others in the prevention of neural tube defects and megaloblastic anemia, the proper functioning of the nervous system, as well as reducing the risk of developing certain cancers. Currently, the important role of folic acid in maintaining the proper functioning of the immune system is also emphasized, which is of particular importance both in the prevention and in the situation of SARS-CoV-2 (COVID-19) infection.

The effects of deficiency and excess of vitamin B_9 may turn out to be dangerous to health and even life. There is a need for nutritional and health education of the society regarding the importance of folic acid for human health, due to the presence of large deficiencies in the population, which is particularly important for some social groups, such as, for example, women of procreation age, pregnant or breastfeeding, people with a nutrient malabsorption, and people who smoke or abuse alcohol.

Key words: *folic acid, folate, deficiency, supplementation, health*

STRESZCZENIE

Kwas foliowy (folacyna, B_9) to witamina, która pełni wiele bardzo ważnych funkcji w organizmie człowieka, a jej nieodpowiedni poziom – niedobór jak i nadmiar, może przyczynić się do zwiększonego ryzyka rozwoju wielu procesów chorobowych. Celem niniejszej pracy była analiza dostępnej literatury naukowej dotyczącej kwasu foliowego i jego wpływu na zdrowie człowieka.

Systematycznego przeglądu badań, opublikowanych do listopada 2022 r., dokonano na podstawie przeszukiwania bibliograficznych baz danych takich jak: PubMed, Elsevier oraz Google Scholar. Użyto następujących słów kluczowych i ich kombinacji: kwas foliowy, foliany, suplementacja kwasem foliowym, niedobór kwasu foliowego. Kwas foliowy, dzięki swojej wysokiej aktywności biologicznej ma wpływ bezpośredni, jak i pośredni na metabolizm komórek organizmu człowieka. Pełni bardzo ważną rolę m.in. w zapobieganiu powstawania wad cewy nerwowej, niedokrwistości megaloblastycznej, prawidłowym funkcjonowaniu układu nerwowego, jak również redukcji ryzyka rozwoju niektórych nowotworów. Obecnie, podkreśla się również istotną rolę kwasu foliowego w utrzymaniu prawidłowego funkcjonowania układu immunologicznego, co ma szczególne znaczenie zarówno w profilaktyce jak i w sytuacji zakażenia wirusem SARS-CoV-2. Skutki niedoboru, jak i nadmiaru witaminy B_9 mogą okazać się niebezpieczne dla zdrowia, a nawet życia. Istnieje potrzeba edukacji żywieniowo – zdrowotnej społeczeństwa w zakresie znaczenia kwasu foliowego dla zdrowia człowieka, ze względu na występowanie dużych niedoborów w populacji, co jest szczególnie ważne, dla niektórych grup społecznych takich jak np. kobiety w wieku prokreacyjnym, w ciąży czy też karmiące piersią, osoby z upośledzeniem wchłaniania składników odżywczych oraz osoby palące papierosy lub nadużywające alkohol.

Słowa kluczowe: *kwas foliowy, foliany, niedobór, suplementacja, zdrowie*

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INTRODUCTION

A well-balanced diet is a key factor for maintaining good health. One of vitamin that performs many very important functions in the human body is folic acid (folacin, vitamin B_9, pteroylmonoglutamic acid). Inadequate levels of this vitamin in the body - deficiency as well as excess - can contribute to an increased risk of developing many disease processes [18, 28].

In terms of chemical structure, folic acid consists of p-aminobenzoic acid, pteridine base, and glutamic acid (Figure 1). The biologically active form of folic acid is levomepholic acid, or L-5-methyl-tetrahydrofolate (5-MTHF) [18].

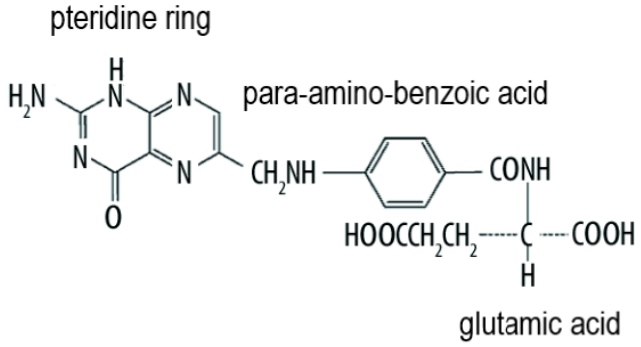

Figure 1. The structural formula of folic acid [1].

Folic acid, naturally occurs in food in the form of folates (salts of folic acid) - a group of compounds that differ in the number of glutamic acid residues and the oxidation state of the pteridine ring, which also includes folic acid derivatives such as dihydrofolate (DHF), tetrahydrofolate (THF) or methylfolate. It is worth noting that folic acid has the highest stability and bioavailability among the above-mentioned group of compounds [16, 32, 68].

It should be mentioned that the human body is not capable of synthesizing this vitamin, except in trace amounts, which are formed with the participation of the intestinal microbiota, mainly intestinal microorganisms of the genus *Bifidobacterium* (especially *B. asoledcentis* and *B. pseudocatenulatum*), *Lactobacillus, Bacterioidetes, Fusobacteria, Proteobacteria* and *Actinobacteria* [6]. Therefore, this vitamin should be supplied from exogenous sources, i.e. with food or appropriate supplementation [18, 23, 32, 39].

Sources of folate in the diet are both products of plant and animal origin. High in their content, among products of plant origin, are characterized by short-cooked and raw green leafy vegetables (Brussels sprouts, lettuce, broccoli, cabbage, spinach, asparagus, parsley leaf and root), legumes (peas, soybeans, beans), whole grain products, citrus fruits or nuts. Among products of animal origin high content of vitamin B_9 are: eggs, offal (mainly liver), soft ripened cheeses (brie, camembert) and some species of fish (e.g. salmon, tuna) [16, 51, 53, 41].

Folic acid, due to its high biological activity, has a direct and indirect effect on the metabolism of cells in the human body. It plays a very important role in, among other things, preventing neural tube defects [9, 50], reducing the risk of megaloblastic anemia [33, 41], proper functioning of the nervous system [9, 15, 41] and reducing the risk of developing certain cancers [6, 13, 63].

The purpose of this study was to review the current literature on the analysis of the impact of folic acid deficiency on the risk of fetal developmental disorders, megaloblastic anemia, neurodegenerative diseases, cancer, as well as to assess the importance of folic acid in maintaining the proper functioning of the immune system, especially in terms of prevention as well as in the situation of SARS-CoV-2 infection.

A systematic review of studies published up to November 2022 was done by searching bibliographic databases such as PubMed, Elsevier and Google Scholar. The following keywords and their combinations were used: folic acid, folate, folic acid supplementation, folic acid deficiency.

CAUSES AND EFFECTS OF FOLIC ACID DEFICIENCY IN THE ORGANISM

An important cause of folate deficiency in the human body is the dietary mistakes made, especially the insufficient intake of vegetables and fruits and whole grain cereal products each day - they are a valuable source of this vitamin [41, 78]. Low dietary folate content may also be due to high losses of folate during food processing and storage [17, 41]. Impaired utilization, absorption, and storage of folacin in the body's body cells can also be caused by drinking large amounts of tea or coffee [17], alcohol abuse [41], and smoking [17].

The concentration in the body of such vitamins and minerals as vitamin B_{12}, ascorbic acid, zinc, iron, among others, as well as proper levels of methionine, can have a significant impact on the human body's utilization of folate. Insufficient vitamin B_{12} in the body results in decreased folate retention in cells. Ascorbic acid deficiency, in turn, contributes to impairing the body's ability to maintain folate in a reduced, or metabolically active, state. Impaired folate absorption can also be caused by structural and functional disorders of the small intestine and a deficiency of conjugases that break down polyglutamine compounds [16].

Painkillers such as aspirin or ibuprofen, antiepileptic drugs, antibiotics, cortisone, sulfamides, as well as folic acid antagonists (e.g., trimethopim, methotrexate) also have a lowering effect on folate.

In addition, those at risk of folate deficiency include cigarette smokers, women who use oral contraceptives and alcohol abusers [55].

Folic acid deficiency in the human body leads to an increased risk of developing a number of disease processes, including megaloblastic anemia, which is characterized by: impaired concentration, tachycardia, chronic fatigue, headaches and dizziness, or pallor of the skin and mucous membranes (although there may also be foci of hyperpigmentation, especially of the dorsal surfaces of the fingers). Folic acid deficiency is also the cause of non-specific gastrointestinal complaints, manifested by: diarrhea or constipation, loss of appetite, burning tongue - the so-called "buffalo" tongue, which is characterized by a dark red color and smoothness. Symptoms of psychiatric disorders such as depression, cognitive function abnormalities, mood swings, delusions and dementia syndrome, thrombosis are attributed to hyperhomocysteinemia, which in turn is the result of folate inactivity [41, 58]. In the context of reproduction, folic acid deficiency significantly correlates with a higher incidence of neural tube defects. Deficiencies of this compound in the diet of pregnant women may increase the risk of cleft lip and palate in the child and the incidence of Down syndrome [64].

There is also scientific evidence that indicates that folic acid deficiencies may increase the risk of certain cancers, i.e. uterine cancer, ovarian cancer, breast cancer, colorectal cancer, lung cancer. What's more, there are also emerging scientific studies that confirm that not only deficiencies, but also excessive folate intake can contribute to accelerating the development of cancers such as prostate cancer and laryngeal cancer. However, the role and importance of folic acid in the process of cancer formation requires further research [60, 41].

Based on available scientific findings, it is indicated that with folic acid deficiency, neuropsychiatric symptoms may occur, including irritability, insomnia cognitive decline, fatigue, depression and psychosis [29, 41].

Folate deficiency can also affect genetic stability, as it is involved in the synthesis of purines and thymines. A reduction in the thymine pool needed for polymerization and DNA (deoxyribonucleic acid) repair is a consequence of folate deficiency. This can be followed by the misattachment of uracil in place of thiamine. The appearance of uracil, and on the opposite side of adenine, can lead to the conversion of base pairs during replication from a GC pair to an AT pair in the newly formed molecule. There is a high risk that such a disruption will have significant mutagenic consequences. When there is too little folate (which is also thymidine nucleotides) in the subsequent repair processes, complete genetic destabilization can occur, which is associated with chromosomal aberrations and DNA strand breakage [38]. Research indicates that the amount of defectively attached uracil to lymphocyte DNA decreases in women of childbearing age, which is related to the supply of 400 μg of folic acid per day, and this in turn confirms the need for folic acid supplementation during the procreative period. The genetic stability of the cell is also influenced by the level of methylation of the genome, where this compound is known to play an important role [26]. Thus, dietary folic acid deficiency contributes to the disruption of many very important metabolic processes, and can result in impaired cell growth and development. Among the best known functions of folic acid is the prevention of the development of neural tube defects and complications of pregnancy. Prevention of cardiovascular disease, neurodegenerative diseases, cancer and megaloblastic anemia are also cited [7, 16, 41].

FOLIC ACID AND FETAL DEVELOPMENT DISORDERS

Pregnant women are among those with a special need for folic acid. Deficiency of this component can cause many negative consequences. Folic acid is very important for the growth of cells of the developing fetus. The baby's spinal cord and brain grow from the neural tube - so the timing of its formation is very important. Statistics show that defects of the central nervous system (CNS) are one of the leading causes of neonatal deaths [9, 24, 50].

During pregnancy, folic acid deficiency leads to birth defects and complications such as miscarriage, fetal demise, premature placental separation, placenta previa, prematurity, low birth weight, and megaloblastic anemia [41, 50].

During pregnancy, the need for folate increases and can be met only partially through the supply of appropriate foods that are sources of these nutrients. It is estimated that the diet allows 50% of the daily requirement for these nutrients. For this reason, supplementation is recommended and plays a special role during the planning period of pregnancy and in its early stages. During pregnancy, the daily requirement for folic acid is 600 μg. The recommendations emphasize that all women of childbearing age should include folate-rich products in their diets, as well as fortified foods [71]. Women planning pregnancy should additionally supplement folic acid for at least 12 weeks before conception at 400 μg/day. During the first trimester of pregnancy - until the 12th week - folic acid should be supplemented at 400-800 μg/day. After the 12th week of pregnancy, women without additional risk factors should take folic acid supplementation at a dose of 600-800 μg/day [75]. Adequate intake of folic

acid prevents the development of neural tube defects. These are congenital disorders that arise in embryonic life and are very severe, affecting the child's nervous system. Neural tube defects manifest themselves as: brainlessness, microcephaly, spina bifida or hernias of the nervous system, causing, among other things, paralysis of the legs, rectal and bladder dysfunction, hydrocephalus, mental retardation, epilepsy, and in extreme cases can contribute to death. The neural tube is an organ that forms early in the pregnancy, during the embryonic period, roughly around its 4th week. Unfortunately, at this time very many women are unaware that conception has occurred. Folate deficiency during this period will adversely affect the formation of the baby's nervous system and the closure of the neural tube [22]. Based on the study, it was shown that women who gave birth to children with CNS defects had low plasma folate and elevated homocysteine levels [64].

All clinicians should remember that failure to educate pregnant women about the importance of folic acid can result in a medical malpractice lawsuit if the baby is born with a neural tube defect [41].

It should be mentioned, however, that scientific data suggest caution in the case of, for example, the presence of megaloblastic anemia, where the supply of folic acid may conceal the true cause of this condition, which may be vitamin B_{12} deficiency, and in the case of reduced metabolism of folic acid in the liver, where it is then recommended to supplement 5-MTHF instead of folic acid, since this compound does not require activation and is immediately available to the mother and fetus, not accumulating in the blood [24, 52].

A number of epidemiological studies have shown that folic acid supplementation of the mother's diet before pregnancy, as well as during the first weeks of pregnancy, can be an important element in the primary prevention of congenital vascular and cardiac defects in the child. Interpretations on selected types of these defects have proven that taking folacin supplements significantly reduces the risk of cardiac septal defects (primarily ventricular septal defect), but also cone defects, as well as vascular trunk defects (especially Fallot Syndrome and transposition of the great vessels) [78]. Women with obesity were found to have twice the risk of fetal neural tube defects, compared to women of normal weight. In addition, it was observed that folic acid supplementation reduced the risk of neural tube defects, which was particularly evident in women with a BMI >25 kg/m^2 compared to women whose BMI was <25 kg/m^2 [10]. In addition, it was found that nervous system defects in the fetus, significantly more often affect women who have type 1 or type 2 diabetes. An analysis by *Parker* et al. [57] found a lower rate of nervous system defects among a group of women with diabetes who supplemented with folic acid at a dose of more than 400 μg/day.

FOLIC ACID AND MEGALOBLASTIC ANEMIA

Megaloblastic anemia (MBA), otherwise known as macrocytic anemia, is a type of anemia characterized by both reduced numbers and the presence of unusually large and underdeveloped erythrocytes (megaloblasts) and their mature forms (macrocytes and megalocytes) [2, 69]. The underlying pathophysiology of this condition includes abnormalities in DNA synthesis and induction of apoptosis in pre-erythroblasts, which ultimately leads to pancytopenia [21, 41]. As indicated by the results of the study, the induction of apoptosis in cells, is associated with increased expression of the transcription factor - p53 protein, which may be due to low levels of vitamin B_{12}, as well as B_9, and high plasma homocysteine levels [33, 65]. In a study by *Yadav* et al. [79, 80], based on immunohistochemical analysis, p53 protein expression levels were found to be significantly higher in megaloblastic anemia patients who also showed very low levels of vitamin B_{12} and B_9, compared to controls.

According to research results, anemia associated with micronutrient deficiencies, including folic acid deficiency, is very common among pregnant women [30].

In infants as well as young children, megaloblastic anemia can also be caused by folic acid deficiency. Factors that cause this condition can be: increased need for folic acid (increased hemolysis of red blood cells, infections, rapid weight gain, prematurity); inadequate supply in food (severe malnutrition, use of goat's milk, exclusively milk feeding); interference with absorption from the gastrointestinal tract (cystic fibrosis, celiac disease); increased loss of folic acid (liver damage or abnormal tubular reabsorption in the neonatal period); inborn abnormal metabolism of folic acid; others (presence of parasites in the gastrointestinal tract, taking anticonvulsant drugs) [70].

Treatment of megaloblastic anemia caused by folic acid deficiency includes the use of a properly balanced diet, including the supply of foods rich in the folic acid component, and/or the use of folic acid in the form of oral, intravenous or subcutaneous preparations, usually in a dose of 1 to 5 mg/day [19, 48]. This dose exceeds the recommended daily supply of folic acid, which is 400 μg, thus allowing adequate supplementation of the deficiency of this component, even in the case of malabsorption syndrome. Treatment continues through the period of hematological recovery or until the cause of the deficiency is eliminated. For patients with malabsorption syndrome, treatment continues

indefinitely [69]. As the results of the study indicate, some foods, especially those intended for children, are fortified with folic acid, making folic acid deficiency extremely rare in children. In contrast, people who consume foods without folic acid fortification and with negligible amounts of vitamin B_9 have a higher risk of megaloblastic anemia [2].

FOLIC ACID AND THE DEVELOPMENT OF NEURODEGENERATIVE DISEASES

Folic acid plays an important role in the functioning of the nervous system, by, among other things, participating in the synthesis of neurotransmitters, i.e. epinephrine, norepinephrine and dopamine. Its deficiency in the body, can contribute to delayed development of the nervous system, increased risk of demyelination of the brain and peripheral nerves, deterioration of motor and behavioral abilities, as well as neurocognitive disorders [9, 15, 35, 42].

It should be mentioned that the occurrence of the above-mentioned dysfunctions concerning the nervous system, is primarily associated with high plasma levels of homocysteine, which, under conditions of folic acid deficiency, is not properly metabolized to methionine. According to research findings, homocysteine is an independent risk factor for both the development of cardiovascular [34] and cerebrovascular diseases, including *Alzheimer's* disease, *Parkinson's* disease and vascular dementia [40, 49, 59].

C*heng* et al. [14] conducted a study to analyze the effects of oral supplementation with folic acid, vitamin B_6 and B_{12} on cognitive function and plasma homocysteine levels, among the elderly. For this purpose, study participants were divided into two groups - an intervention group that received oral supplementation with 800 μg of folic acid, 10 mg of vitamin B_6 and 25 μg of vitamin B_{12}, for a period of 14 weeks, and a control group receiving a placebo. Patients' cognitive functions were assessed using the Basic Cognitive Aptitude Tests (BCAT). Based on the data obtained, an improvement in cognitive function was observed, as well as a significant reduction in homocysteine levels, with a concomitant increase in serum levels of folic acid, vitamin B_6 and B_{12} in subjects taking supplementation with the aforementioned vitamins.

Interesting results were also presented by *Ma* et al. [46], who analyzed the effects of 6 months of oral supplementation with folic acid (800 μg/day) or vitamin B_{12} (25 μg/day), or folic acid (800 μg/day) combined with vitamin B_{12} (25 μg/day), on cognitive function in people 65 years of age and older. Based on the data obtained, greater improvements in cognitive function, as assessed by the Wechsler Adult Intelligence Scale - Revised by China (WAIS-RC), were observed with a combination of folic acid and vitamin B_{12} supplementation than with oral supplementation with folic acid or vitamin B_{12} alone. Identical results were obtained for the improvement of pro-inflammatory cytokines, i.e. IL-6, TNF-α and MCP-1.

Folate deficiency not only contributes to an increase in plasma homocysteine levels, but also leads to inhibition of the synthesis of S-Adenosylmethionine (SAM), which plays an important role in both the synthesis and catabolism of catecholamines in the brain, resulting in a disruption of neurotransmission, symptoms of which can include cognitive decline and mood changes. Reduced levels of S-Adenosylmethionine (SAM) have been found both in depressed individuals and among those with *Alzheimer's* disease [18].

Alzheimer's disease, referred to as "senile" dementia, is the most common factor in dementia disorders in the elderly. It is a degenerative disease of the central nervous system that is characterized by progressive deficits in cognitive functions, especially memory, and behavioral disorders, such as apathy, agitation or psychotic symptoms. The presence of neurofibrillary degeneration and extracellular amyloid deposits in the form of amyloid plaques are neuropathological features of *Alzheimer's* disease [27].

A meta-analysis of studies conducted by *Wang* et al. [74] to evaluate the association between plasma homocysteine and folic acid levels and the risk of vascular dementia or *Alzheimer's* disease observed that a 5 μmol/L increase in plasma homocysteine levels was associated with a 9% increase in the risk of vascular dementia and a 12% increase in the risk of developing *Alzheimer's* disease.

A different conclusion was reached by *Ford* et al. [25], who in their study found no improvement in cognitive function, as assessed by the *Alzheimer's* Disease Assessment Scale - Cognitive Subscale (ADAS - Cog), between a group of subjects who took folic acid, vitamin B_6 and vitamin B_{12} supplementation (at doses of 2 mg, 25 mg, 400 μg per day, respectively) and a control group. Based on the results of a study by *Bae* et al. [8], it was concluded that not only hyperhomocysteinemia, but also hypohomocysteinemia can significantly increase the risk of dementia and *Alzheimer's* disease in the elderly. During a follow-up period of 5.5 years, both study participants with high serum homocysteine levels ≥10.6 μmol/L and low levels ≤8.9 μmol/L had a 4-5 times higher risk of developing dementia and *Alzheimer's* disease than those with serum homocysteine levels between 9.0 and 10.5 μmol/L. The study's authors suggest that the risk of dementia from overuse or misuse of vitamin preparations, including those containing folic acid, should be taken into account.

As already mentioned, too low levels of folic acid, as well as vitamin B_{12}, can result in increased homocysteine levels [41], in effect contributing to accelerated dopaminergic degeneration, a factor in cognitive impairment in *Parkinson's* disease. Patients with *Parkinson's* disease, with symptoms of cognitive decline, and who are being treated with levodopa should have their homocysteine levels measured annually, and should consider folic acid supplementation to lower their homocysteine levels if they reach levels higher than 10 μmol/L [31, 62].

A*namnart* and *Kitjarak* [3], analyzing the effect of folic acid and vitamin B_{12} supplementation on plasma homocysteine levels in *Parkinson's* disease patients treated with levodopa, showed that supplementation with the aforementioned vitamins was associated with a significant decrease in plasma homocysteine in the subjects.

Similar results were obtained by *Dong* and *Wu* [20], who, in a meta-analysis of 26 clinical-control studies, observed that patients with *Parkinson's* disease, were characterized by higher plasma homocysteine levels, with low levels of folic acid, as well as vitamin B_{12}, compared to control subjects. The results obtained by the above-mentioned authors, testify to the significant role of proper folic acid concentration in the body of people with *Parkinson's* disease.

FOLIC ACID AND CANCER RISK

Folate, plays an important role in the prevention of cancer, by influencing the proper course of DNA synthesis, transcription and repair. Deficiency of the aforementioned nutrient, can promote an increased risk of damage to genetic material, as well as hypomethylation, which can consequently initiate the process of carcinogenesis. Moreover, the results of the study indicate that folic acid deficiency, indirectly contributes to increased activity of protooncogenes, thus promoting the process of tumorigenesis [56, 82].

A meta-analysis of 16 prospective studies and 26 case-control studies examining the association between folic acid intake and breast cancer risk, conducted by *Chen* et al. [13], found that a dietary supply of folic acid at 153-400 μg per day was associated with a significantly lower risk of breast cancer among study participants than a dietary supply of less than 153 μg per day.

Folate has also been shown to have a preventive role in the early stages of colorectal carcinogenesis; however, concerns have been raised over its excessive consumption, which would in turn be a potential pro-cancer factor [47]. *Wang* et al. [73] conducted a study to analyze the association between increased folate intake and colorectal cancer risk among 86,320 women. Based on the data obtained, it was concluded that a high intake of folic acid, expressed as dietary folate equivalents, was not associated with an increased risk of colorectal cancer among the study population of women. The same results were also obtained by Australian researchers *van der Pols* et al. [71]. In contrast, a 2022 meta-analysis of studies, including randomized controlled trials, which aimed to evaluate the effect of folic acid supplementation on atrophic gastritis, intestinal metaplasia and endothelial neoplasia, which are referred to as gastric precancerous conditions (GPC), showed that a folic acid supplementation dose of 20-30 mg/day for 6 months was associated with a reduction and even a reversal of the progression of gastric precancerous conditions, which may have potential clinical application in the treatment of the above-mentioned abnormalities [44].

An interesting study was also conducted by *Yan* et al. (2022), who showed that maternal supplementation with folic acid and/or multivitamins, during pregnancy, was associated with a statistically lower risk of childhood and adolescent nasopharyngeal carcinoma in the offspring compared to the control group [81].

Depending on the type of cancer, various factors are distinguished that increase the risk of the disease. Increasing attention is being paid to disorders of the oxidation-antioxidation balance of the body. Oxidative stress is an important factor in the pathogenesis of many diseases including cardiovascular, pulmonary, neurodegenerative diseases, but also cancer. ROS (reactive oxygen species) significantly contribute to the acceleration of aging processes, the accumulation of oxidative damage products, which play an important role in the processes of carcinogenesis [36].

A systematic review and meta-analysis of studies aimed at evaluating the effects of folic acid supplementation on markers of oxidative stress showed that folic acid supplementation at a dose of 0.4-10 mg/day (mean 5.1 mg/day), applied over a period of 8 to 25 weeks, can significantly improve markers within the antioxidant defense system by increasing serum glutathione and total antioxidant capacity, and by reducing serum malondialdehyde (MDA) levels, which exhibit cytotoxic, mutagenic and carcinogenic properties [6]. In addition, as shown in a study by *Asbaghi* et al. [5], supplementation at doses ranging from 0.8-10 mg/day promoted a reduction in C-reactive protein (CRP) levels. Although the study did not show any side effects of high doses of folic acid supplementation, the authors of the study suggested caution when supplementing this nutrient at doses above 1 mg/day [5]. *Li* et al., in a recently published study in an animal model, found that a high-folate diet can significantly promote the development of hepatocellular carcinoma [45].

IMPORTANCE OF FOLIC ACID IN THE PREVENTION AND TREATMENT OF COVID-19

The processes affecting the body's effective immune response to infectious agents, such as respiratory viruses, among others, are extremely complex and still not entirely clear. However, it is known that the rate of innate immune responses, regulatory processes that prevent damage to the body's tissues, and the development of acquired adaptive responses are influenced by both environmental and lifestyle factors. Among lifestyle-related factors, the important role of dietary factors is particularly emphasized [11, 54].

Voelkle et al. [72] conducted a study in which they analyzed the prevalence of vitamin and mineral deficiencies, such as vitamin A, B_{12}, D, E, zinc, selenium, copper and folic acid, among 57 hospitalized patients with COVID-19, and analyzed the impact of deficiencies in the aforementioned components on the severity of the disease course. Based on the data obtained, it was found that higher serum levels of vitamin A, zinc, and folic acid were associated with a lower risk of severe progression of COVID-19 disease among the subjects.

Based on two, independent studies, conducted using computer simulations, it has been shown that folic acid can limit the replication of SARS-CoV-2. In one of these studies, *Sheybani* et al. [67], showed that folic acid can contribute to the inactivation of the furin endoprotease, which facilitates virus entry into the host cell, while in the second study, *Serseg* et al. [66], observed that folic acid inactivates the 3CLpro protease, which in turn has been shown to be essential in the replication of all coronavirus strains. *Acosta-Elias* et al. [1], summarizing the two aforementioned studies in their paper, however, believe that it is unlikely that folic acid can simultaneously inhibit two different proteases; nevertheless, they do not rule out a potential effect of folic acid on the inactivation of SARS-CoV-2, especially in pregnant women, who are mandatorily recommended to supplement the nutrient discussed in this paper. An increased supply of folic acid, the researchers noted, may have an impact on the lower rate of hospitalization of pregnant women for COVID-19 infections.

The results of another study to analyze the impact of nutraceutical compounds to achieve therapeutic targets against SARS-CoV-2, conducted by molecular docking, showed that folic acid alone or in combination with derivatives, i.e. tetrahydrofolic acid and 5-methylhydrofolic acid may be potential molecules against COVID-19 infection. This study, conducted by *Kumar* et al. [43], however, indicates a strong need to investigate the effects of folic acid and its derivatives against SARS-CoV-2 in *in vitro* and *in vivo* assays.

A complication of severe pneumonia is pulmonary hypertension, which studies have reported can also be a complication of severe pneumonia in COVID-19 infection. The primary mechanism underlying pulmonary hypertension is impaired function of the enzyme endothelial nitric oxide synthase (eNOS), thereby reducing local nitric oxide (NO) production [37]. It should be mentioned that folate supplementation has a direct effect on vascular endothelial function, eNOS (by increasing the availability of the tetrahydrobiopterin cofactor BH4), as well as increasing NO bioavailability. Based on available data, significantly lower serum folic acid levels have been reported among patients with severe COVID-19, which may significantly affect the increased risk of complications [12, 77].

The above-mentioned studies suggest that folic acid may be a potential prophylactic factor as well as an adjunct to the treatment of COVID-19 infection, as well as its complications, i.e. pulmonary hypertension. However, as this is a new issue, it requires further research to clarify the exact mechanism of the effect of folic acid and/or its derivatives on the reduced risk of SARS-CoV-2 infection [4].

CONCLUSION

In conclusion, based on the collected data, it can be said that folic acid has multidirectional biological effects and is an essential compound for maintaining the proper functioning of the body [68]. Both deficiency and excess of folic acid in the diet, is a factor that can promote an increased risk of cardiovascular disease, diseases of the central nervous system or certain cancers, among others [7, 9, 15, 16]. In order to reduce the risk of the aforementioned diseases, one should follow a well-balanced diet that includes foods that are rich sources of folic acid, such as green leafy vegetables, legumes, whole grains, citrus fruits and nuts, among others. If it is not possible to ensure a sufficient supply of folic acid with the diet, one should consider supplementation of the nutrient discussed in this paper [51].

According to the results of the study, folate supplementation, in particular, is recommended for people with megaloblastic anemia, neurodegenerative diseases, women in the preconception period, pregnant and breastfeeding women, people with elevated plasma homocysteine levels, as well as those taking certain medications (e.g. oral contraceptives, methotrexate). It should be emphasized that there is a need for further research to clarify both the optimal dose and length of supplementation that will provide measurable benefits [61].

Undoubtedly, there is a need for nutrition and health education of the public on the importance

of folic acid for human health, which would bring significant benefits not only for individuals, but also for the general public, contributing to improving public health.

Authors' contributions

K.K., M.K. analyzed the data, performed data interpretation and drafted the manuscript. K.A. designed and reviewed the manuscript. All authors revised and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest

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