



Physiological effect and role of dietary folic acid in regenerative medicine: Review

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Abstract

Globally, there are several chronic and risk diseases like Alzheimer's, Parkinson's, coronary heart disease, high blood pressure, and congenital anomalies. Generally, the treatment of these diseases is very costly. However, many researchers

recognize the ways of their treatment by less cost with low potential toxicity. Researchers have been looked to the dietary sources and find the complex link between the food, especially the essential vitamins and the diseases. Folic acid or pteroylglutamic acid is active than a synthetic drug. Folic acid is one of the eight a water-soluble vitamins B. It is tremendously necessary for several activities in the body such as DNA synthesis, normal erythropoiesis with red blood cell maturation, inhibition of neural tube defects, depressing high homocysteine levels, nutritional regulation of the methionine cycle, reduce hematological indications, neurological, cancer diseases, and physiological condition of nutritional stress. Folate, vitamin B12, and vitamin B6 are working as a substrate in the methylation cycle. Using folic acid (folacin) supplement daily at a standard dose is essential to reduce the level of serum homocysteine. It is chiefly governing blood pressure, blood sugar, obesity, and control body weight. This review aims to study the applications of folic acid supplementation and its benefit to the body. Additionally, to recognize the improvements in lifestyles with using these supplements.

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Introduction

The structure of folic acid was not an active pattern. It can be converted to active form such as dihydrofolic and (reduced form) of tetrahydrofolic in the target liver organ (Bailey & Ayling, 2009). Folic acid is the oxidized form. It can be taken through diet since 1941. Folic acid belongs to the Latin term "foila," and it had been prepared synthetically from leaves of spinach plant (Beck, 2012). The chemical name of folic acid is a pteroyl-glutamic acid. It is included in pteridine, para-aminobenzoic, and

glutamic acid (Hazra & Tripathi, 2001). Folate is played a part in the transfer of a 1-carbon unit (methyl, methylene, and formyl unite) to the vital substrates, which comprises the synthesis of DNA, RNA, and proteins (Brocardo *et al.*, 2008). It is revealed a well-identified vitamin of the B-complex that soluble in water. Additionally, it plays a chief role in all mammals' actions (Choi & Mason, 2000). Moreover, folate has a great job at the therapeutic intervention level, with regenerative medicine plus neural engineering (Al-Mashhadane *et al.*, 2018). The leafy greens (Brussels sprouts), potatoes, broccoli, legumes, bread, white cereal products, dried beans, peas, and citrus fruits are the sources of folic acid in food (Dunlap *et al.*, 2011). The folic acid form is more bioavailable and stable than other shapes of folate (Ohrvik & Witthoft, 2011). In the methionine cycle, folate has precisely responsible for the conversion of homocysteine to methionine and production of the universal methyl donor S-adenosylmethionine (SAM) (Ganji & Kafai, 2006). Moreover, essential biochemical reactions are provided precursors for the synthesis of amino acids, purines, pyrimidines, methylation of DNA, and regular erythropoiesis (Zhao *et al.*, 2014). The collective supplements of folic acid and other vitamins have effected through pregnancy by given enough energy of metabolism and preventing child defects (Graulet *et al.*, 2007). Folate had a major effect in cows that had been amplified lactation performance and ruminal production (Lia *et al.*, 2016). In the first year of age, the serum folate levels were 60 % than at birth (Hay *et al.*, 2008). During pregnancy and lactation, the female body is needed a higher amount of folate that reached to a half (Erinç, 2018). Folate has a vital role in the central nervous system (CNS) (Reynold, 2006; Tettamanti *et al.*, 2006) with the enhancement of the nervous system and brain tasks of different ages (Schmidt *et al.*, 2012). Also, it might be acted as a preventive anti-teratogenic (Wentzel *et al.*, 2005). It could be a novel choice for patients, which suffered from a high average of homocysteine as a risk aspect for cardiovascular illnesses (Ansari *et al.*, 2009). Folate has been lowered the risk of cancers in certain tissues, the most notable in the colorectum (Choi & Mason, 2000), with a hepatoprotective agent (Woo *et al.*, 2006). Vitamins B groups are essentially working as a cofactor on the metabolism of homocysteine to methionine via the remethylation-process (Dominguezly *et al.*, 2010; Soares *et al.*, 2007). Folic acid also revealed an important action in angiogenesis and vasculogenesis that occurred during the physiological process such as pregnancy (Williams *et al.*, 2011). Folic acid supplementation is recommended by physicians for patients with chronic kidney disease, especially for those under the hemodialysis, to prevent nutritional deficiency and to facilitate hematopoiesis (Bravo-Soto *et al.*, 2016). Taking a special amount of folic acid might be prevented several malformations involving problems in craniofacial clefts, heart, limbs, and others (Cieřlik & Cieřlik, 2018).

Folate deficiency

Nutritional folate deficiency is one of the most significant dietary health problems worldwide (Ganji *et al.*, 2006). It leads to an imbalance and impairs DNA replication with damage in chromosomes due to incorrect access of DNA uracil that uses in cell division and tissues such as bone marrow (Duthie1999; Kawakita *et al.*, 2018). The low level of folate is the cause of different abnormalities in the newly born like neural tube defects, megaloblastic anemia, abruption placentae, spontaneous abortion, and congenital heart defects (WHO, 2015). It is also responsible for impair fertility (Laanpere *et al.*, 2010) and slowed tumor growth in rat mammary compared with other

animals (Sie *et al.*, 2009). Studies showed that the diminished folate had been alternated with choline and acetylcholine metabolism in young rats. It has a larger effect on the peripheral nervous system than on the brain that leads to abnormalities of synaptic function in model animals (Crivello *et al.*, 2010; Shea & Chan, 2008; Serra *et al.*, 2008). The effects of folic acid supplementation on central nervous system growth processes are not restricted only to the embryonic period. However, it can also be useful for enhancing growth and repair in the later phases of pregnancy and during lactation (Iskandar *et al.*, 2004). Elevated homocysteine levels due to folate deficiencies were associated with cell death and DNA damage. Also, the defects of hemoglobin include sickle cell anemia and Thalassemia that could be explaining in these cases (Rabaneda *et al.*, 2008; Sati'Abbas *et al.*, 2011). In some conditions, the correction of folate deficiency or additional supplementation may be beneficial, while in other conditions, it may be unfavorable (Branda *et al.*, 1998).

Megaloblastic anemia can be due to folate or vitamin B12 deficiency. Because the two vitamins share a metabolic pathway, treating a vitamin B12 deficient patient with folic acid will resolve the megaloblastic anemia but not resolve neurological damage due to vitamin B12 deficiency. It is the basis for the concern over 'masking' vitamin B12 lowering (Crider *et al.*, 2011). Folic acid increases the risk of cancer in cell and animal tissues (Krokan *et al.*, 2017). It has an excellent antioxidant property (Quang, 2018) as well as, other researchers were showed a high level of the weights of animals like ewes and lambs who were dealing with folic acid (Suhdoon *et al.*, 2009). It is highly sensitive to several environmental factors such as heat, UV light, and oxygen and related to hazard dropping folic acid in the blood (Thomas *et al.*, 2002). The folic acid is the active form of vitamin B9 with top choice is absorbed without needing any bio alteration (Patel & Bhaumik, 2019). Also, it acts as a first -carbon carrier, and vitamin B12 acts as co-factor for the enzyme methionine synthase (Mahajan *et al.*, 2019). Methotrexate and pemetrexed are done most prescribed anti-folates, and these are mainly treated with acute myeloid leukemia, osteosarcoma, and lung cancers (Samodelov *et al.*, 2019).

Increased of folic acid

In early reports were observed, the increase of folic acid intake might delay the diagnosis of vitamin B-12 deficiency. However, the higher folate intake may be decreased the risk of Alzheimer's disease independent of other risk factors, mainly vitamins B6 and B12 (Luchsinger *et al.*, 2007). The higher doses of folate are the possible masking of cobalamin deficiency in pernicious anemia (Sahay & Hen., 2007). As well as neurogenesis by neurological mask signs (Kadziela *et al.*, 2003) also profoundly damage of prostate cancer (Tester, 2014).

Dosage of folic acid

Folic acid is recommended at 400 micrograms, for healthcare and avoidance from genetic malformations (neural tube defects) for three months before conception and during the first trimester of female pregnancy (Hashmi *et al.*, 2018).

Using folic acid supplement 0.4 mg daily is essential to reduce the level of serum homocysteine, especially in hypertensive, diabetic patients, to decrease the risk of cardiovascular events and to controlling blood pressure, blood sugar, and obesity (El-Maghraby *et al.*, 2016). Continuously used vitamin B supplementation did not decrease

the danger of emerging type II diabetes (Song *et al.*, 2009). Folate availability is important acted during the first few weeks of pregnancy, and that reduces the risk of newborn defects (Niculescu & Zeisel, 2002). The super dose of folic acid was initiated by acute kidney damage (Bravo-Soto & Madrid, 2016). Daily folate intake of 200–320 µg appeared to be associated with a lower risk of breast cancer (Zhang *et al.*, 2014). Obeid & Herrmann, (2012) found that dose, 5mg of folic acid supplementation lead to high weight mass in animals fed a high-fat diet.

Folic acid effective

Aghamohammadi *et al.*, (2011) has been determined the pharmacological doses of folate. They found that folate supplementation lowered plasma homocysteine in patients with type II diabetes mellitus. Depression is associated with elevated cortisol levels (Stetler & Miller, 2011). On the other hand, Folates were operated as an antidepressant without a co-current pharmacological mediator (Brocardo *et al.*, 2008). The combination treatment between betaine and folic acid was more effective in lowering serum homocysteine than treatment by either alone (Kamel, 2010). When vitamin B-12 status was normal, however, high serum folate was associated with protection against cognitive impairment (Morris *et al.*, 2007.)

Diminished phagocytosis process and bactericidal of neutrophils are caused by folate deficiency (Stanger, 2002). Folic acid had become biofunctional in carcinogenesis (Rashedi *et al.*, 2018). At the same time, it is considered as an anti-oxidants agent in along of life (Rathor *et al.*, 2015). Dietary supplements of folic acid did not affect reproduction variables such as ovulation rate, fertility, and mortality rate (Méthot *et al.*, 2008).

Folate is absorbed in about 50% efficiency, while folic acid is absorbed in 85%-95% efficiency (Bailey, 2004). The molecule of folic acid effect by different types of solutions like Dimethylsulphoxid, Acetic Acid, Ethanol, and others (Attaf & Hasan, 2019). An anti-folate drug is called Pemetrexed (MTA) that use for lung cancer treatment (Yang *et al.*, 2013). The folates were more sensitive to technologic processes, mainly UV, ions (copper, iron), and chiefly heating exposure in a long period, all these factors reduce the quantity of this vitamin (Kapka *et al.*, 2012). The anemia and other diseases of blood might be resulted by deficiencies of zinc, vitamin B12, and folate (Guralnik *et al.*, 2004). Therefore vitamins B 12 are the most effective factor in preventing oxidative reactions (Lee *et al.*, 2015).

Folic acid relationship with Homocysteine

Homocysteine is a midway structure of methionine degradation; it is usually methylated to methionine. However, the process of catalyzed by the methionine synthase needs a metabolite of folate as a methyl donor and a metabolite of vitamin B12 as a substrate (Rezvani& Rosenblatt, 2008). Homocysteine is metabolized by remethylation or transsulfuration (De la Calle *et al.*, 2003). Hyperhomocysteinemia results from genetic defects in the enzymes or nutritional deficiencies in vitamin cofactors (Zhang *et al.*, 2004). Folic acid is absorbed into the bloodstream by the intestines, then converted to other forms of folate by the liver. However, there is no evidence of harmful effects of metabolized folic acid in the blood of infants (Kawakita *et al.*, 2018). All the results were revealed that rat liver folate metabolism represents a typical case of the modular

organization of cellular metabolism with several separate metabolic systems (Mitra *et al.*, 2013). Metabolites of the 5-MTHF and folic acid metabolic cycle -contribute to the formation of purine rings and the conversion of uracil to thymidine for DNA creation (Scott *et al.*, 2000). High cortisol levels were negatively associated with serum folate levels and positively associated with serum homocysteine levels (Casalheira *et al.*, 2008).

Conclusion

This review showed that folate-targeted liposomes that can promote enhanced drug uptake by the diseased cells, also profoundly reduce the collateral normal tissue toxicity like in cancer and inflammatory diseases. Moreover, folic acid has doubled actions in carcinogenesis depended on the dose and biological conditions of folic acid. Therefore, more studies were founded as the main place on the surface of cells as folate receptors. Also, folic acid can be used for diagnosis and treatment of cancer in non- invasive diagnosis methods. More studies found a poor association between dietary folate and lung cancer. Likewise, High dietary folate intake was associated with pointedly decreased damage to breast cancer. Cancer cells are more needed of this vitamin than other cells, It is prevented the progression of pre-existing tumors. Folate plays a dual role in cancers. It protects against the initiation of cancer but also aids in the growth and progression of pre-neoplasms and subclinical cancers. More studies found there was no association between total folate and many types of tumors like lung, gastric, oesophageal, breast, prostate and ovarian cancer if presented there is restricted evidence which suggests folate protects against these cancer danger . Many types of research and reports about the relationship between folic acid and diseases especially cancer had been effected or non-effected in low or normal doses of folic acid as well as the target tissue, age of the patient, family history and genetic factors, all these factors contributed of the main job of these vitamins. The original case for dietary folic acid is reducing the incidence of neural tube defects and folic acid a good option as anti hyperhomocysteinemia and lipid-lowering.

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Conflicts of interest

The author declares no conflict of interest.

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