Jopkiewicz Sylwia. The process of cancer. Part III. Selected vitamins in cancer Chemoprevention. Journal of Education, Health and Sport. 2019;9(5):442-453. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3233449
http://ojs.ukw.edu.pl/index.php/johs/article/view/6953

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.03.2019. Revised: 15.03.2019. Accepted: 28.05.2019.

The process of cancer. Part III. Selected vitamins in cancer Chemoprevention

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Summary:

Introduction and objective: Free radicals (ROS), affect the course of each step of the process of carcinogenesis. Antioxidants that interact with ROS inactivates them, resulting in a positive effect both in preventing and inhibiting the progression of cancer. Vitamins such as A, C, E and D have anticancer properties. The article gives an overview of the problems of comp contribution of each vitamin in the chemoprevention of cancer. Its purpose is to present some antioxidants for its potential anti-tumor and to provide modifications to their effect on the carcinogenesis process.

Description of knowledge: Vitamin A inhibits inter alia, lipid peroxidation and influences the growth and differentiation of epithelial cells to prevent neoplastic transformation. Vitamin E inhibits inter alia, angiogenesis, growth and proliferation of

diseased cells. It also has the ability to stop the cell cycle. It prevents the formation of carcinogenic nitrosamines. Vitamin D inhibitor of vascular endothelial growth factor, and factors stimulating cell proliferation. Suppressive affects COX-2 enzyme. Increases the synthesis of E-cadherin. Vitamin C contributes to the proper functioning of the immune system by stimulating the activity of B and T lymphocytes is an electron donor for protecting cell components against oxidation. Stimulates cells to produce hyaluronidase inhibitor. Induces the synthesis of proteins p73 and MLH1.

Conclusions: Imbalance redox system can lead to neoplastic transformation. Taking antioxidant supplements is associated with the risk of delivering them in too large a dose. Consequently, there is a support of the oxidation processes. The best way to protect against cancer and support cancer therapy is to provide antioxidants in their natural form, ie in the form of fresh vegetables and fruits.

Keywords: antioxidants, carcinogenesis, vitamins

Introduction

Oxidative stress, which is due to impaired balance between the formation of free radicals (ROS) and their elimination from the body may be a direct or indirect cause of a variety of disorders and diseases [1], this may initiate the process of carcinogenesis [2]. As a result of oxidative stress DNA damage occurs, which will disturb the processes of transcription and replication, and lead to mutagenesis. Free radicals have an impact on the course of each of the steps in the process of carcinogenesis. The accumulation of mutations in the genetic material of the cells results in a loss of control on the process of differentiation and growth resulting in neoplastic transformation [3,4]. Oxidative stress may aggravate the process of metastasis. With the increase in the number of oxidative DNA damage occurs to enhance the metastatic potential of [5].

The activity of free radicals in the human body is limited by the endogenous enzyme systems and non-enzymatic antioxidants, most of which are supplied with nutrients. Antioxidants have the ability to enter the ROS interact and causetheir inactivation. A major role in this area plays a vitamin, and the specificity of those which are classified as antioxidant vitamins, namely A, C and E [1,6]. These vitamins

except that eliminate ROS can affect the modulation of the redox state of the cells and the regulation of signaling pathways inside the cell. Scientific studies on colorectal cancer has shown that oxidative stress reduces the levels of these vitamins, and their supplementation may positively affect the slowing progression of the disease [7].

Antioxidants directly or indirectly contribute to reducing the risk of cancer and slow down progression of the disease. For this reason, it is considered reasonable approximation of the role of antioxidant vitamins in the chemoprevention of cancer.

Vitamin A

Dioxygenase enzyme-mediated β-carotene molecule breaks up into two molecules of retinal. As a result of the reduction which occurs by retinal reductase produced retinol, or vitamin A. It is a fat soluble and alcohol. May exist in two forms: as biologically active as vitamin A and carotene, or pro-vitamin A. Conversion of carotenoids into vitamin A in humans occurs only in the liver [8].

Retinol exhibits inhibitory effect on tumor development, mainly due to the antioxidant activity. It may react with peroxide radicals (ROO). This results in the inhibition of lipid peroxidation and the formation of hydroperoxides (ROOH). Reduces the incidence of chromosomal aberration and reduces DNA damage caused by the impact of ROS cells. In addition, Vitamin A prevents malignant transformation of epithelial cells due to influence their growth and differentiation [9].

Retinoids are compounds that fulfill the role of vitamin A. In the group of retinoids distinguished by their three generations: Natural which include, among others Retinol and its metabolites, monofragrant compounds obtained synthetically and retinoids polifragrant [10]. Both the natural retinoids as their synthetic derivatives have chemopreventive treatment, since they have an impact on the proliferation and differentiation of tumor cells. Therefore they show proapoptotycznie action. In cancer of the colon it has been observed that decrease the activity of MMP-2 and -9 and reduce the metastatic potential of the [11,12].

Retinoids the metabolic transformation bind to and cause the activation of specific nuclear receptors (the so-called. Hormone response sequences), which results in the transcription of the respective genes. Receptors located in the cell nucleus divides into [10]:

- RAR (retinoic acid receptors) - receptors for retinoic acid. These receptors recognize a ligand three acids: all-trans-retinoic acid, 9- cis retinoic acid and 13- cis retinoic acid.

- RXR (retinoid X receptors) - retinoid X receptors, these receptors only recognize as Lingan acid, 9 - cis retinoic acid.

Acid, trans-retinoic (ang. All-trans retinoic acid, ATRA) are activated by p53 which arrests the cell cycle in the G1 phase, thus allowing repair of DNA. The result is inhibition of tumor cell growth. ATRA reduces the expression of Bcl-2 and Bcl-X. Too high activity of Bcl-2 protein acts limited to the process of apoptosis. Further, ATRA causing release of mitochondrial cytochrome c, leads to reduced gene expression antyapoptycznego Bcl-2, while increasing pro-apoptotic protein expression of Bax, which induces apoptosis [11].

The tumors of the gastrointestinal tract was observed that ATRA decreases the expression of VEGF (vascular endothelial growth factor). Inhibits mediator AP-1, which is a transcription factor contributing to the reduction of the expression of the p21 protein thus acting anti-apoptotic [11].

Research indicates that retionol along with other vitamins (E, β-carotene) and trace elements (selenium) reduce mortality in patients with cancer of the stomach and esophagus [13]. Vitamin A and kartenoidy also reduce the risk of, among others, tumors of prostate, lung, breast, cervical, colon, endometrial [14,15].

Vitamin E

Vitamin E is a group of fat-soluble compounds which are among the most important natural antioxidants. It prevents oxidation of unsaturated fatty acids in cell membranes, and effectively reduces free radicals. It also protects vitamins A, C and beta carotene from the destructive effects of reactive oxygen species. It is necessary to activate vitamin B_{12}. It protects the body from the harmful effects of mercury and lead. It consists of four tocopherols (alpha, beta, gamma, delta) and 4 tokotrienolów (epsilon, zeta, eta, theta). Vitamin E is sensitive to light, in particular UV rays. Very easily reaches its oxidation. It shows resistance to heat, acids and bases. In the human body this vitamin is stored for a relatively short time. Provided with food tocopherols (T) accumulate predominantly in adipose tissue. Their action in the body is limited, because they are immediately metabolized in the liver and excreted the bile or urine. Their role in preventing the emergence of diseases and The manipulation of gene expression is much weaker compared to tokotrienolów (T3) [8,16,17]. Research carried out in 2013 for 16 weeks in animal models suffering from pancreatic cancer suggest that tocotrienol supplementation results in significantly

longer survival (70%). For comparison, the group of animals who were given placebo, the survival rate was 10%, while in the group of rodents which were administered a standard drug used in chemotherapy- gemcitabine survival was 30%. In combination therapy, which included gemcitabine tocotrienol and 90% of patients survived rodents [18].

Tocotrienols contribute to the inhibition of angiogenesis and growth and proliferation of tumor cells [19]. In addition, block enzym- HMG-CoA reductase, which is required for tumor cells to metastasize. T3 also increases the sensitivity of cancer cells to standard chemotherapy [20].

Tocopherols react with peroxide radicals. The result of this process is the creation of stable radicalstokoferylowych, which they are less reactive. Tocopherols have a propensity to disrupt the lipid peroxidation chain [21]. By means of raising the activity of the protein p27, which is a cyclin-dependent kinase inhibitor, α-tocopherol effect on the cell cycle arrest in patients with prostate cancer. In contrast, γ- tokeferol inhibit cell cycle in S phase in the course of prostate cancer [22,23]. Furthermore, by decreasing the protein kinase activity (PKC) reduce the proliferation of tumor cells [24].

Compounds T and T3They have the ability to cell cycle arrest, induce apoptosis of tumor cells, modulate the activity of transcription factors and intracellular signaling pathways so that they can be used in the chemoprevention of cancer [25]. In addition, Vitamin E prevents the formation of nitrosamines [26].

Vitamin D

Vitamin D is determined by two main components which include the vitamin D_2 and vitamin D_3. The common name for this group is calciferols. Vitamin D_2 is formed of ergosterol and is called ergocalciferol. While provitamin of vitamin D_3 is 7-dehydrocholesterol and is called cholecalciferol. Vitamins D_2 and D_3 have no biological activity. In the hydroxylation (metabolic conversion), which occurs in the liver is formed of 25-hydroxyvitamin D [25 (OH) D] is also called kalcydiolem. Then, in the kidney there is a transformation kalcydiolu of calcitriol, the active form of vitamin D known as 1,25 dihydroxyvitamin-1,25 (OH) $_2$D [27,28]. The active metabolite functions as a hormone acting autocrine and endocrine. It reaches the tissue effector, and then binds to the vitamin D_3 receptor (VDR). These receptors are occupied 2776 genomic locations, and therefore the concentration of the vitamin D

plays a role in numerous physiological processes [29,30]. Calcitriol modulates the growth and differentiation of various cell lines of tissue [31] and the activity of about 500 genes [32] (including genes encoding cytokines, genes for production of proteins necessary for proper cell operation).

Research shows that calcitriol shows the inhibitory effect on VEGF and factors stimulating proliferation. Vitamin D, when combined with VDR results in binding to the promoters of the genes p21 and p27. This results in their increased expression, which in turn inhibits the activity of cyclin-dependent kinases and cell cycle arrest in the G1 phase [33, 34]. Calcitriol acts to suppress cyclooxygenase-2 (COX-2) [35]. This is the enzyme that is involved in the development and progression of cancer [36]. High activity of this enzyme effect on the inhibition of apoptosis through the activation of the serotonin-threonine kinase and the increase in the activity of anti-apoptotic proteins (Bcl-2) [37]. Furthermore, the overexpression of this enzyme is important in the process of angiogenesis. COX-2 affects the formation and growth of new vessels.

Vitamin D increases the synthesis of E-cadherin, which is forming the so-called transmembrane glycoprotein. Connection fitting (ang.*adherence junctions*) between cells. It is responsible for contacting the cells with the extracellular matrix. It is important in apoptosis, cell migration, differentiation and proliferation. One of the causes of metastasis is the loss of glycoprotein or disorder in their structure on tumor cells, which consequently leads to a loss of adhesion of tumor cells in the primary tumor metastases thereby forming a [41,42,43].

Vitamin D decreases the amount of oxidative stress and DNA damage. Furthermore, the preventive action in the process of tumorigenesis can result from its influence on the regulation of the energy path in the case of non-cancerous cell [44].

Results of scientific research suggests that vitamin D plays a significant role as a chemopreventive agent in the carcinogenesis process. It has a beneficial effect both in preventing the onset and progression of tumors, among others, colon, prostate, ovarian, breast [45].

Vitamin C

Vitamin C, or ascorbic acid (AA) is a derivative of saccharides. This compound is a highly biologically active. It fulfills an important function in many reactions and changes that directly influence the course of many biochemical processes in the human body. Vitamin C is involved in the synthesis of corticoids, cortisol, collagen

biosynthesis, as well as substitution of proline hydroxyproline and folic acid, folinic. Activates a cytochrome P450 and facilitates the removal of harmful substances exogenous [8.46]. It plays a significant role in immunomodulatory and stimulate the synthesis of interferon, which affects the proper functioning of the immune system. It stimulates the activity of B and T lymphocytes, which are involved in the elimination of cancer cells. Vitamin C is a powerful antioxidant. Removes free radicals and reactive oxygen species nierodnikowe. Being an electron donor has a protective activity of other cell components against oxidation. Inhibit lipid peroxidation in sera and cell membranes through the regeneration α-tokeferolu its radical form. Reduces the amount of damage to proteins [47,48,49]. By the modulation of the redox state of the cell vitamin C affects the process of DNA repair. cell cycle and cell signaling [50]. In addition, vitamin C has the ability to block the nitrosation reaction nitrate nitrosamines, by reduction of nitrite to nitrogen, oxygen inhibition of the action of bacteria involved in the conversion of nitrates to nitrites [48]. Vitamin C by promoting the synthesis of collagen stimulates cells to produce hyaluronidase inhibitor. Hyaluronidase is an enzyme that degrades intracellular binder, specifically hyaluronate, which is the main component of the extracellular matrix. Hyaluronan (HA) is a glycosaminoglycan synthesized on the inner surface of the cell membrane. It can be important in processes such as differentiation and maturation, proliferation, migration of the cells within the tissue, the expression of genes of various cytokines and chemokines, and angiogenesis. Its increased amount is produced in the course include ovarian cancer and colon cancer. This promotes progresowi tumor and tumor cell proliferation. HA has the ability to protect against malignancies of the immune system by creating a physical protection. Some tumors synthesize the enzyme hyaluronidase, and the resulting hyaluronan oligosaccharides contribute to the angiogenesis and migration of cancer cells [51].

Collagenase produced by tumor cells contribute to the breakdown of collagen and connective tissue, which in turn leads to metastasis. Vitamin C due to its ability to stimulate the production of collagen increases the stability of tissue that acts as a barrier between the normal tissue and the neoplastic lesion. As a result, vitamin C is involved in reducing the possibility of metastasis diseased cells. The antitumor activity of the vitamin C is also apparent from the fact that it induces the synthesis of protein MLH1 protein and p73. The first of these satisfies an important role in the repair of mismatched bases, and the second protein is responsible for the induction of cell death

[52]. Furthermore, research shows that the vitamin C contributes to the reduction of IKK kinase activity, which in turn is essential for the activation of NF-KB Consequently it comes to inhibiting the activity of NF-? B. This vitamin is also affected by the reduction in COX-2 expression [53].

Conclusions

1. The imbalance oxidation-reduction system can lead to neoplastic transformation. Preparation of increased amounts of reactive oxygen species also occurs in tumor cells, which in turn leads include to decrease cellular sensitivity to chemotherapy. Antioxidants balance the action of reactive oxygen species in the human body by inhibiting the degree of oxidation of the particles and causing them to conversion into inactive derivatives.

2. Taking antioxidant supplements is associated with the risk of delivering them in too large a dose. Consequently, there is a support of the oxidation processes, as antioxidants at high concentrations become prooksydacyjnych properties. Therefore, the use of synthetic vitamins may paradoxically contribute to increased risk for the development of the process of carcinogenesis. Furthermore, during use of medical oncology the use of vitamins in this form may negatively affect the absorption and metabolization of drugs and to cause the occurrence of various kinds of adverse interactions.

3. The best way to protect against cancer and support cancer therapy is to provide antioxidants in their natural form in the form of fresh vegetables and fruits. Their anticancer effect based on the mutual strengthening of their properties. All these vitamins, which are important in cancer prevention should be introduced into the body in the form of consumption of these food products, which have been proved scientifically that their inclusion in the daily diet is associated with a reduced risk of developing cancer.

List of references:

[1] Kulczyński B. Znaczenie stresu oksydacyjnego i wolnych rodników w rozwoju chorób cywilizacyjnych. Food Forum 2017; 3(19): 98-104.

[2] Rahman T, Hosen I, Islam M, et al. Oxidative stress and human health. Adv Biosci Biotechnol 2012; 3: 997-1019.

[3] Evans MD, Dizdaroglu M, Cooke MS. Oxidative DNA damage and disease: induction, repair and signifi cance. Mutat Res 2004; 567: 1–61.

[4] Cooke MS, Evans MD, Dizdaroglu M, et al. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J 2003; 17: 1195–1214.

[5] Olinski R, Gackowski D, Foksinski M i wsp. Oxidative DNA damage: assessment of the role in carcinogenesis, atherosclerosis, and acquired immunodefi ciency syndrome. Free Radic Biol Med 2002; 33: 192–200.

[6] Lesiów KM, Krupa K, Komarnicka KU, Walencik KP. Białka błony zewnętrznej Fusobacterium Nucleatum jako potencjalny czynnik promocji nowotworu jelita grubego. Wiadmości Chemiczne 2018; 72(7-8): 585-596.

[7] Gackowski D, Banaszkiewicz Z, Rozalski R i wsp. Persistent oxidative stress in colorectal carcinoma patients. Int J Cancer 2002; 101: 395–397.

[8] Wiąckowski KS. Żywienie, żywność, składniki pokarmowe a zdrowie. Wydawnictwo Stanisław K. Wiąckowski, Kielce 2005.

[9] Palace VP, Khaper N, Qin Q, et al. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med 1999; 26: 746–761.

[10] Marona H, Gunia A, Pękala A. Retinoidy – rola w farmakologii w aspekcie komórkowego mechanizmu działania. Farm Pol 2010; 66(3): 187-192.

[11] Hoffman E, Mielicki PW. Kwas całkowicie *trans*-retinowy (ATRA) w prewencji i terapii nowotworów. Postepy Hig Med Dosw 2010, 64: 284-290.

[12] Badian M, Dzierżanowski T. Suplementacja witamin u chorych onkologicznych. Część II. – witamina C i witaminy rozpuszczalne w tłuszczach oraz pierwiastki: wapń i żelazo. Med Paliat 2018; 10(4): 176-183, DOI: https://doi.org/10.5114/pm.2018.83274.

[13] Rutkowski M, Grzegorczyk K, Malinowska K. Witaminy A, C, E − rola ich działania antyoksydacyjnego w prewencji ontogenezy. Probl Ter Monitor 2010; 21(4): 251-257.

[14] Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Aspects Med. 2005; 26: 459–516.
[15] Markowska A, Jaszczyńska-Nowinka K, Kaysiewicz J, et al. Rola witamin antyoksydacyjnych w złośliwych nowotworach ginekologicznych. Curr Gynecol Oncol 2016; 14(1): 39-52.
[16] Nogala-Kałucka M, Siger A. Tocochromanols – bioactive compounds of oilseeds. From biosynthesis to biomarkers. Oilseed Crops 2011; 32: 9-28.
[17] Zielińska A, Nowak I. Tokoferole i tokotrienole jako witamina E. Chemik 2014; 68(7): 585-591.
[18] Husain K, Centeno BA, Chen DT, et al. Vitamin E δ-tocotrienol prolongs survival in the LSL-KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre (KPC) transgenic mouse model of pancreatic cancer. Cancer Prev Res (Phila) 2013; 6(10): 1074-1083.
[19] Witkowski S. Tokotrienole- mniej znana strona witaminy E. Herbalism 2016; 2(1):7-21.
[20] Norsidah KZ, Asmadi AY, Azizi A, et al. Palm tocotrienol-rich fraction reduced plasma homocysteine and heart oxidative stress in rats fed with a high-methionine diet. J Physiol Biochem 2013; 69(3): 441-449.
[21] Burton GW. Vitamin E: molecular and biological function. Proc Nutr Soc 1994; 53: 251–262.
[22] Gysin R, Azzi A, Visarius T. Gamma-tocopherol inhibits human cancer cell cycle progression and cell proliferation by down-regulation of cyclins. FASEB J 2002; 16: 1952–1954.
[23] Venkateswaran V, Fleshner NE, Klotz LH. Modulation of cell proliferation and cell cycle regulators by vitamin E in human prostate carcinoma cell lines. J Urol 2002; 168: 1578–1582.
[24] Breyer I, Azzi A. Differential inhibition by alpha- and beta-tocopherol of human erythroleukemia cell adhesion: role of integrins. Free Radic Biol Med 2001; 30: 1381–1389.
[25] Ju J, Picinich SC, Yang Z, et al. Cancer-preventive activities of tocopherols and tocotrienols. Carcinogenesis 2010; 31(4): 533-542.
[26] Kong P, Cai Q, Geng Q, et al. Vitamin intake reduce the risk of gastric cancer: meta-analysis and systematic review of randomized and observational studies. PLoS One 2014; 9(12): e116060.

[27] Wawer I. Para witamin: D_3 i K_2. Zdrowe kości a wapń. Food Forum 2017; 2(18): 6-10.
[28] Olędzka R. Witamina D w świetle badań ostatnich lat. Bromatol Chem Toksykol 2013; 46: 121-131.
[29] Ramagopalan S, Heger A, Berlanga A, et al. .AChP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. Gen Res 2010; 20:1352-1360.
[30] Myszka M, Klinger M. Immunomodulacyjne działanie witaminy D. Postepy Hig Med Dosw 2014; 68: 865-878.
[31] Lorenc R, Karczmarewicz E, Kryśkiewicz E i wsp. Zasady suplementacji i standardy oceny zaopatrzenia organizmu w witaminę D w świetle jej działania plejotropowego. Stand Med, Pediatr 2012; 9: 595-604.
[32] Souberbielle J, Body J, Lappe J, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev 2010; 9:709-715.
[33] Christakos S, Dhawan P, Verstuyf A, et al. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 2016, 96: 365–408.
[34] Mess E, Pająk W, Ornat M. Spojrzenie na witaminę D w aspekcie chorób nowotworowych. Med Paliat 2019; 11(1): 21-26, DOI: https://doi.org/10.5114/pm.2019.83841.
[35] Krishnan A, Feldman D. Review Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol 2011; 51: 311-336.
[36] Williams SC, Mann M, DuBois NR. The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 1999; 18(55): 7908–7916.
[37] Leahy MK, Koki TA, Masferrer LJ. Role of cyclooxygenases in angiogenesis. Curr Med Chem 2000; 7(11): 1163–1170.
[38] Somiari BS, Shriver DC, Heckman C, et al. Plasma concentration and activity of matrix metalloproteinase 2 and 9 in patients with breast disease, breast cancer and at risk of developing breast cancer. Cancer Lett 2006; 23 (1): 98–107.
[39] Schwab MJ, Schluesener JH, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol? Lancet 2003; 361(9362): 981–982.
[40] Zheng W, Tayyari F, Gowda GA, et al. 1,25-dihydroxyvitamin D regulation of glucose metabolism in Harvey-ras transformed MCF10A human breast epithelial cells. J Steroid Biochem Mol Biol 2013; 138: 81-89.

[41] Janik-Papis K, Błasiak J. Molekularne wyznaczniki raka piersi. Progresja i nowi kandydaci- część II. Nowotwory J Oncol 2010; 60(4): 341-350.
[42] Berx G, Van Roy F. Review The E-cadherin/catenin complex: an important gatekeeper in breast cancer tumorigenesis and malignant progression. Breast Cancer Res 2001; 3: 289-293.
[43] Krakowiak M, Knopik-Skrocka A. Komórki nowotworowe- mocny przeciwnik. Czy potrafimy stworzyć skuteczną terapię nowotworową? Tutoring Gedanensis 2018; 3(1): 6-15.
[44] Bednarek A, Chudek J, Karwasiecka D, Niedobory witaminy D u kobiet z rakiem piersi i niepewne korzyści z jej suplementacji. Prz Lek 2015; 72(11): 669-672.
[45] Kulik-Kupka K, Nowak J, Koszowska A i wsp. Witaminy w walce z nowotworami. Med Rodz 2016; 1(19): 26-31.
[46] Mullak A, Hołysz H, Totoń E, Rubiś B. Witamina C jako modulator skuteczności terapii przeciwnowotworowej. Farm Współczesna 2018; 11: 245-253.
[47] Kalemba-Drożdż M. Witamina C w leczeniu nowotworów i profilaktyce chorób niezakaźnych. Państwo i Społeczeństwo 2018; 3: 94-104.
[48] Szymańska-Pasternak J, Janicka A, Bober J. Witamina C jako oręż w walce z rakiem. Onkol Prakt Klin 2011; 7(1): 9–23.
[49] Lunec J, Holloway KA, Cooke MS, et al. Urinary 8-oxo-2'-deoxyguanosine: redox regulation of DNA repair in vivo? Free Radic Biol Med. 2002; 33: 875–885.
[50] Carr AC, Maggini S. Vitamin C and Immune Function. Nutrients 2017; 3, 9(11), doi: 10.3390/nu9111211.
[51] Krasiński R, Tchórzewski H. Hialuronian jako czynnik regulujący proces zapalenia. Postepy Hig Med Dosw 2007; 61: 683-689.
[52] Catani MV, Costanzo A, Savini I, et all. Ascorbate up-regulates MLH1 (Mut L homologue-1) and p73: implications for the cellular response to DNA damage. Biochem J 2002; 364: 441–447.
[53] Han SS, Kim K, Hahm ER, et al. L-ascorbic acid represses constitutive activation of NF-kappaB and COX-2 expression in human acute myeloid leukemia, HL-60. J Cell Biochem 2004; 93: 257–270.