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THE MECHANISM OF POLYPHENOLIC COMPOUNDS ON PROSTATE CANCER

Abstract. Prostate cancer is the most common type of cancers and the second leading cause of cancer-related deaths among men in the US. In Kazakhstan, prostate cancer is at the 6th place. Despite the successful development of technology treatment of other cancers, the incidence of prostate cancer and mortality from this disease has not decreased over the years. This is due to increased resistance of prostate cancer cells to drugs and radiotherapy. This article presents the literature data on the mechanism of action of polyphenolic compounds on prostate cancer cells, in combination with chemotherapy alone and polyphenols themselves. Recent studies have shown that naturally occurring polyphenols are used against many types of cancer worldwide since they possess anti-cancer properties and are not toxic. Polyphenol compounds act as key modulators of signaling pathways and considered as ideal chemoprevention. Of particular interest is the ability of polyphenolic compounds to selectively inhibit the growth of tumor cells. In this connection, the polyphenols are promising for use as not only a preventive means, but also as adjuvants for enhancing the effectiveness of chemotherapy. Polyphenols present in vegetables and beverage products, and antioxidants are the most common in the human diet, they have antimicrobial, anti-inflammatory, antiviral, antitumor and immunomodulatory effects. This article also examined the mechanisms of action of polyphenolic compounds on prostate cancer cells such as stopping the cell cycle, apoptotic activity of polyphenolic compounds and signaling pathways involved in prostate cancer. We present a systematic review of polyphenolic compounds in prostate cancer, focusing on the types of polyphenols, which have a great impact on the prevention and treatment of prostate cancer.

Keywords: metabolism, biology, prostate cancer, polyphenols, carcinogenic, apoptosis, cell cycle, signaling pathway.

Introduction. Cancer is a complex disease involving multiple changes in cell physiology, which eventually leads to malignant tumors. The invasion of tumor cells into the surrounding tissues and distant organs is a major cause of morbidity and mortality in most patients. A biological process, which transforms normal cells into malignant tumor cells is the subject of much researches in the field of biological and medical sciences for many decades. Despite numerous scientific and research papers, treatment of metastatic cancer is difficult today as they were 40 years ago [1, 2].

Prostate cancer (PC) is the main cause of male cancer deaths at the ages of 55-74 and above 75 years, it is the second leading cause of death in North American men after lung cancer and bronchus cancer [3, 4]. All men with advanced disease, who have gone through androgen therapy, die due to the development of metastatic androgen-independent prostate cancer [5, 6, 7]. Thus, the highest death rate from prostate cancer is connected with the active dissemination of prostatic adenocarcinoma, which spreads to distant organs with a preference to the bone tissue [8]. There is a large amount of data which indicates that the progression of both primary and metastatic prostatic tumors is determined by the potential loss of apoptotic cells [9-10]. The incidence of prostate cancer increases steadily by 3% per year; that is why it was named by the epidemiologists as "oncologic time bomb". Annually in the world there are revealed more than 400 thousand new cases of prostate cancer and about 200 thousand people die of cancer every year [3].

According to the WHO predictions, the incidence and mortality from prostate cancer in the world will increase by 2 times by 2030. Prostate cancer is one of the leading causes of death in older men from malignant tumors in Kazakhstan. In the structure of morbidity among all malignant tumors, PC occupies the second place (5%).

The causes of prostate cancer are varied and not completely understood. However, nowadays, there is a huge amount of factual material, which explains the mechanisms of the pathogenesis of the disease [11-17].

The main aims of targeted anticancer drugs selectively affecting the transformed cells are key protein molecules. This area of medicine, which underwent rapid development over the past 10-15 years, thanks to the achievements of modern science can treat malignant tumors by therapeutic method with a sufficiently large capacity of relevant drugs. Some of them are already widely used in the clinic, and the majority undergoes II-III stage of clinical trials, including prostate cancer. On the other hand, it is clear that therapy of directed action is effective only when it "hits" simultaneously several, at least three or four, molecular targets. Because not only one, but a whole group of regulatory molecular mechanisms breaks down in the transformed cell; this mechanisms allow getting out from intracellular reparative and protective immune systems and give rise to a nascent tumor. This means that the doctor chemotherapist should appoint to cancer patients at least three or four of these drugs. It is better if they act on different links of carcinogenesis and block various biological targets, such as to inhibit proliferation, enhance the apoptosis of tumor cells and block tumor angiogenesis. However, each of them will have its limitations in application and range of undesirable side effects. Another possibility is to appoint a targeted therapy (drugs) in combination with standard anti-tumor hormonal drugs or chemotherapy efficiency with polyphenol compounds. Nevertheless, the literature described many examples of more or less successful use of this approach (though still only in the experiment), especially when trying to reduce the metastatic potential of tumors, including prostate cancer and breast cancer, leukemia [18-23].

Thus, the study of prostate cancer is a topical problem of modern oncology and biomedicine. In the case of disease progression, development of metastasis in tumor cells, all the work becomes ineffective or toxic. In this connection, further study of treatment for prostate cancer is the search for new drug targets – polyphenolic compounds.

Naturally occurring polyphenols in prostate cancer. Naturally occurring polyphenolic compounds become interesting as a chemoprevention because of low toxicity and high tolerability.

Polyphenols present in food and beverage products of plant origin (fruit, vegetables, cereals, herbs, spices, beans, nuts, olives, chocolate, tea, coffee and wine) and are the most abundant antioxidants in the human diet [24]. Epidemiological studies have shown that a diet rich for polyphenols can prevent a wide range of human diseases. Polyphenol compounds effects human health, including antimicrobial, anti-inflammatory, antiviral, anticancer and immunomodulatory effects [25-30].

Despite significant progress in the development of anti-cancer treatments, the incidence of cancer continues to grow worldwide. Recently, chemoprevention using natural nutrients became as a practical approach to reduce the increasing incidence of cancer. It was estimated that by making changes in the diet, more than two-thirds of human cancers can be prevented [31].

A defect in the mechanism of apoptosis is recognized as an important cause of carcinogenesis. Disregulation of proliferation is not sufficient for the development of cancer; the suppression of apoptotic signals is also required. Cancer cells acquire resistance to apoptosis by overexpression of anti-apoptotic proteins and/or suppression or mutations of proapoptotic proteins. A better understanding of the main events involved in carcinogenesis will facilitate the use of food components as one of the key strategies to prevent the development of cancer. Various studies indicate that nutritional components such as phytochemicals, may modulate the complex multistep process of carcinogenesis [32].

Cell-cycle block. Many plant polyphenols inhibit the growth of tumor cells, causing cell cycle delay. In this case, the mechanisms of action of polyphenol compounds in various tumor cell lines may vary [33-35], and in A431 epidermoid carcinoma cells it caused cycle delay in G1 phase [33]. Thus, resveratrol suspended transition from S phase into G2 phase in HL60 leukemia promyelocytic, in U937 lymphoma cells, in CaCo-2 colorectal cancer cells, in adenocarcinoma glandula mammaria, intestinal tract, prostate [37-40] and in A431 epidermoid carcinoma cells it caused the arrest of the cycle in the G1 phase [41].

Epigallocatechin-3-gallate (EGCG) causes cell cycle arrest in many human tumor cells [40-42]. In the cells of pancreas carcinoma, EGCG stops the cell cycle in G1 phase, adjusting the level of D1 cyclin,

CDK4 kinase, CDK6, p21 and p27 CDK inhibitors [45]. p21 protein levels increase under the influence of EGCG in prostate cancer cells, regardless of their sensitivity to androgens and availability of functionally active p53 gene [43]. It is known that the p53 protein, which is called as the "the main conservator of genome", in normal cells at DNA damage activates and provides the cell cycle suspension, and the p21 gene is its transcription target. p53 gene is inactivated in many tumors, so the ability of EGCG to the p21 protein induction and cell cycle arrest, regardless of the p53 gene is particularly important.

Apigenin (4 ', 5, 7-trihydroxyflavone) found in celery, parsley and other vegetables, stops the proliferation of cancer cells and enhances the expression of p21 protein and p53 by independent way [46]. In prostate cancer cells, its target is also inhibitory proteins as p27, INK4a/p16 and INK4c/p18, D1, D2, E cyclins and cyclin-dependent kinases (CDK2,4,6) [47, 48].

At the heart of the action of curcumin, which inhibits the proliferation of many cancer cells in vitro and has antitumor effects in vivo, lies its ability to exercise negative control of cyclins activity and cyclin-dependent kinases, and to enhance the expression of CDKI inhibitory proteins [49-51].

Apoptotic activity of polyphenols. Many plant polyphenols, along with a cytostatic action (cell cycle arrest) have cytotoxic effects (by inducing apoptosis) on precancerous and cancerous cells. Two basic ways of apoptosis is well known. In the first case the apoptosis is activated at the interaction of specific ligands with receptor proteins containing 'death domains' [52]. In particular, after connection with ligand, the receptor Fas/APO1/CD95 undergoes trimerization and recruits FADD protein; this leads to the formation of supramolecular complex with pro-caspase-8, which leads to its activation; caspase-8 activates caspase-3, the central "executor" caspase cells [52].

The role of mitochondria in apoptosis is complex and widely considered process. Since activation of mitochondria is considered as a "return point" in the process of apoptosis, manipulation of mitochondrial activation with proapoptotic intention was envisaged as a potential therapeutic approach. The mitochondrial way of apoptosis begins with the collapse of mitochondrial membrane potential and accompanied by the release of cytochrome C from the mitochondrial intermembrane space to the cytoplasm of the cell. Furthermore, other mitochondrial apoptosis-inducing factors also release, e.g. Apaf-1. Cytochrome c, Apaf-1, ATP, and procaspase-9 form a supramolecular complex (apoptosome) in which caspase-9 is activated by autocatalysis. Caspase-9, as well as caspase-8 activates central caspase-3, which starts the process of DNA destruction and DNA cytoskeleton and other caspases [51]. In the process of apoptosis, the inhibitory effects of IAPs are neutralized by the second mitochondria of caspase (Smac) activator, a direct IAP-binding protein with low isoelectric point (DIABLO) and/or the requirement to high temperature of protein-A2, which are released from the mitochondria [53].

Cancer cells tend to develop the resistance to apoptosis due to the overproduction of antiapoptogenic proteins and reducing apoptogenic proteins. Plant polyphenols start apoptosis of tumor cells by affecting various stages of the process. Importantly, causing the death of cancer cells, polyphenols (e.g., curcumin, EGCG, apigenin) show no cytotoxicity to normal cells, i.e. act selectively [54-56].

A huge experimental data summarized in several reviews [57-58] shows that some polyphenols have apoptogenic action, using a variety of cellular targets. Due to such pleiotropic effects of cancer cell lines, which apoptosis induces polyphenols, is very wide. Curcumin inhibits the delay in protein cytoplasm of cells BRCA1, which does not directly involve in apoptosis, but is responsible for DNA repair. The inability to repair serves as a signal for apoptosis. The ability of apoptosis to induce is found in apigenin on the model of on prostate cancer xenografts using enzyme immunoassay and Western blot analysis [33]. There are differences in the action of polyphenols in vitro and in vivo. Thus, resveratrol, inducing apoptosis of androgen-sensitive cells of LNCaP in vitro, inhibited the xenografts in the model and enhanced the tumor angiogenesis [58]. In both cases, resveratrol modulated the signaling pathways dependent on androgen receptor, and decreased expression of activated genes by androgens. Presumably, the activation of this signaling cascade occurs at low concentrations of resveratrol, while the activation of p53-dependent signaling pathway that induces apoptosis, requires a much higher concentration, which is not achievable in vivo [58].

Action of polyphenols on signaling cell ways. The factors responsible for cell cycle arrest, involving in apoptosis or promoting angiogenesis and metastasis of tumors, are controlled by signaling ways which are included in the existing network in the cell. One of the factord that activate the expression of genes encoding COX-2, iNOS, antiapoptotic proteins and proteins responsible for proliferation, is the nuclear

factor of transcription activation NF-kappaB (NF-kB). Under normal conditions, it presents in the cell cytoplasm as inactive trimeric complexes consisting of p50 and p65 subunits, and the inhibitory protein I-kB [58]. In normal cells, the activation of NF-kB factor occurs in response to mitogenic and other stimuli, but in many tumor cell types, its expression, and hence the expression of tumor growth factor for various reasons become the basis. In this connection, the NF-kB factor is considered as a possible target when searching anticancer therapeutic and prophylactic methods [59]. It has been found that many of the polyphenolic compounds have modulating action. Resveratrol, for example, inhibits phosphorylation of IkBa subunits and NF-kB of factor p65, and reduces its activity in myeloma cells in which NF-kB factor is constitutively active [60]. Curcumin acts similarly [59-60]. EGCG inhibits the degradation of IkBa subunit and thereby inhibit TNFa-induced activation of NF-kB factor [61] and silymarin flavonoids reduce both TNFa induced, and constitutive activation of NF-kB [63]. Consequently, the effect of polyphenols as modulators of cell proliferation, apoptosis, inflammation, angiogenesis and metastasis could be mediated by their effects on the NF-kB factor. Polyphenols can affect the signaling way components, especially on receptor tyrosine kinase (RTK) [63]. These include, in particular, receptors of vascular endothelial growth factor VEGFR, which include signaling cascade leading to proliferation of endothelial cells, their migration and differentiation with formation of capillary tubes. It is shown that tea catechins inhibit VEGFR receptors [64]. Another RTK class includes epidermal growth factor receptor (EGFR), which ligands are transforming growth factor a (TGF-a) and EGF, HER2 receptor (ligand is not identified), and receptor HER3 and HER4. RTK associated with the membrane cell. In normal cells after interaction of RTK with specific ligands, autophosphorylation occurs resulting in a corresponding activation of protein kinase of signaling ways (Ras/MAPK and PI3K/Akt). By sequential phosphorylation of other protein kinase cascade, the signal of activation is transmitted to transcription factors (c-jun, c-fos, ELK, AP-1, NF-kB). The cancer cells are often observed overexpression of different RTK and activating transcription signal becomes constant. RTK are targets of plant polyphenols. EGCG, for example, inhibits the autophosphorylation of EGFR, HER2 and HER3 receptors [52]. As the result, there is the inhibition of ERK, c-fos, transcription of D1 cyclin and anti-apoptotic proteins Bcl-X, which becomes the cause, respectively, of the cell cycle arrest and induction of G1 stage of apoptosis. EGFR receptor activation inhibitor is curcumin [37]. Modulating effect of plant polyphenols on gene expression in cancer cells is mediated by their effect on the protein kinase of signaling ways. Thus, resveratrol causes decrease of metalloproteinase-9 levels through inhibition of protein JNK and PKC kinases [65]. Anthocyanins reduce the expression of VEGF factor by inhibiting of PI3K/Akt cascade [66]. Tea catechins action on angiogenesis is also associated with inhibition of Akt protein kinase [67]. EGCG, moreover, negatively regulates NIK, PI3K, PKC, IKK, ERK1/2, p38, JNK protein kinase [30]. Inhibition of one of the components of signaling ways, definitely affects the other ways because they are interconnected, and the variety of targets of polyphenols are not inferior to the existing diversity of phenotypes of tumors. Thus, in tumor cells with abnormally activated Stat3 transcriptional factor, the resveratrol inhibits signaling cascade, which involves Stat3 and Src protein kinase [68].

Thus, polyphenols act as generators of active oxygen species that act as second messengers in cellular signal transduction. In prostate cancer cells, there are many targets, which may be affected by the polyphenolic compounds. NF-kB factor, however, can be considered as central target because it controls the expression of genes responsible for the proliferation, apoptosis, metastasis of tumors.

Conclusion. On the basis of literature data on the mechanisms of action of polyphenolic compounds on cancer cells it can be concluded that naturally occurring polyphenols have great potential to prevent the risk of prostate cancer, as well as the use of a combination with chemotherapy. Suitable polyphenols combination with existing chemotherapeutic agents will reduce side effects without reducing effects of chemotherapy. Further, polyphenol compounds are promising molecules for the chemoprevention of prostate cancer because they are safe and inexpensive.

The development of prostate cancer generally occurs due to signaling ways; therefore, there should be used multi-targeted approaches to avoid and prevent the development of drug resistance. In addition, numerous studies are necessary to find the specific purpose of each polyphenol in order to develop a combination therapy. Thus, the association of dietary polyphenols of natural origin and their influence on the risk of prostate cancer and treatment in combination with chemotherapy are very promising agents for the prevention and treatment of prostate cancer.

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ҚАТЕРЛІ ҚУЫҚ АСТЫ ІСІГІНЕ ТАБИҒИ ПОЛИФЕНОЛДАР ҚОСЫЛЫСТАРЫНЫҢ ӘСЕР ЕТУ МЕХАНИЗМДЕРІ

Аннотация. Қуық асты безі - әлем бойынша ер адамдарда жиі кездесетін сырқаттың кең таралған түрі. АҚШ-та аталған сырқат қатерлі ісік себептерінен екінің бірін өлімге әкелетін жағдайлар бойынша екінші орында болса, өз елімізде қуық асты безі бойынша өмірден өту қауіпі 6-шы орында. Қатерлі ісіктің қай түрі болмасын алдын алу және емдеу жолдары жағынан ғылыми технологиялардың кеңінен дамуына қарамастан аталған сырқаттан қайтыс болу салдары азаймай отыр. Бұл қатерлі ісік клеткаларының емдік препараттар мен сәулелі терапияға төзімділігі ерекшеліктеріне де байланысты. Мақалада полифенолдардың бөлек, сонымен қатар химиотерапиямен үйлескен қосылыстардың қуық асты безіне әсер етуіне әдеби деректері ұсынылған. Соңғы жылдардағы зерттеу жұмыстарының көрсеткіштері табиғи тектес полифенолдар токсинді емес және ісіктің алдын алатын қасиеті болғандықтан антиканцерогендік әсер көрсетеді. Полифенолдық қосылыстар сигналдық жолдарының негізгі модуляторы ретінде әрекет ететін болғандықтан жақсы химиопрофилактика болып саналады. Әсіресе қызығушылық тудырып отырғандардың бірі полифенолдық қосылыстар қатерлі қуық асты безінің өсуінің баяулауына арнайы әсер етуі.

Сонымен қатар полифенолдар әсері профилактикалық қана емес химиятерапиялық препараттардың тиімділігін арттыратын адъюванттар болып табылады. Полифенолдар тағамдық заттардың, өсімдіктектес сусындардың құрамында болатын антиоксиданттар ретінде кең таралған. Сонымен бірге адамның ағзасына микробқа, қабынуға, вирусқа, қатерлі ісікке қарсы және иммуномодуляторлық әсері бар.

Полифенолдарды қоспа түрінде және қатерлі ісікке қарсы препараттармен бірге қолдану, қартерлі ісіктерді тоқтату, жою барысында тиімді әсер береді.

Төмендегі мақалада полифенолдар қосындыларының немесе полифенолдар мен ісікке қарсы препараттардың қуық асты безі ісігіне: клеткалардың өсуінің тежелуі, сигналдық жолдарға әсері және апоптоз механизмдері туралы айтылған. Қуық асты ісігінің алдын алатын және емдейтін полифенолдың қоспалар түрлеріне назар аудара отырып, қуық асты қатерлі ісігі бойынша полифенол қосылыстарына шолу жасалынды.

Түйін сөздер: қуық асты безі, табиғи полифенолдар, тежелу, энергетикалық метаболизм, апоптоз, клеткалық цикл, клеткалық сигналдық жолдар.

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МЕХАНИЗМЫ ДЕЙСТВИЯ ПОЛИФЕНОЛЬНЫХ СОЕДИНЕНИЙ НА РАКОВЫЕ КЛЕТКИ ПРОСТАТЫ

Аннотация: Рак предстательной железы – распространенная злокачественная опухоль у мужчин в мире. В США рак предстательной железы является второй причиной смерти от злокачественных опухолей. В Казахстане опухоль простаты занимает 6-е место. Несмотря на успешное развитие технологий лечения ряда других форм рака, распространенность рака простаты и смертность от этой болезни не уменьшаются в течение многих лет. Это связано с повышенной устойчивостью раковых клеток простаты к лекарственным препаратам и лучевой терапии. В статье представлены литературные данные о механизмах действия полифенольных соединений на раковые клетки простаты, как в комбинации с химиотерапией и в отдельности самих полифенолов. Исследования последних лет показали, что полифенолы природного происхождения актуально используются против многих видов рака во всем мире. Так как они обладают противораковыми свойствами и не токсичны. Полифенольные соединения действуют в качестве ключевых модуляторов сигнальных путей и поэтому считаются идеальными химиопрофилактиками. Особый интерес вызывает способность полифенольных соединений к избирательному ингибированию роста опухолевых клеток. В связи с этим полифенолы перспективны для использования не только в качестве профилактических средств, но и в качестве адъювантов для усиления эффективности химиотерапевтических препаратов. Полифенолы присутствуют в продуктах питания и напитков растительного происхождения и являются наиболее распространенными антиоксидантами в рационе человека, обладают противомикробными, противовоспалительными, противовирусными, противоопухолевыми и иммуномодулирующими эффектами. Также в статье рассматривались действия полифенольных соединений на раковые клетки простаты такие как: остановка клеточного цикла, апоптогенная активность полифенольных соединений и сигнальных путей участвующих в раке простаты. Приводится систематический обзор полифенольных соединений при раке простаты, ориентируясь на виды полифенолов, которые оказывают большое влияние на профилактику и лечение рака простаты.

Ключевые слова: рак простаты, полифенолы природного происхождения, ингибирование, энергетический метаболизм, апоптоз, клеточный цикл, клеточные сигнальные пути

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