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ANTI-INFLAMMATORY AND APOPTOSIS-STIMULATING PROPERTIES OF BIOACTIVE SUBSTANCES CONTAINED IN SWEET CLOVER AND CORN SILK IN THE PATHOGENESIS OF MALIGNANT CERVICAL TUMORS

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Abstract: Malignant cervical tumors are among the oncological diseases that pose a serious threat to women's health. In their pathogenesis, high-risk oncogenic human papillomavirus infection, chronic inflammation, oxidative stress, weakened immune surveillance, cell-cycle disruption, and impairment of apoptotic mechanisms occupy a central place. In recent years, phytochemical sources, particularly sweet clover (Melilotus officinalis) and corn silk (Zea mays L. stigma), have attracted scientific interest because of the anti-inflammatory, antioxidant, immunomodulatory, and apoptosis-stimulating properties of their bioactive substances. Coumarins, flavonoids, phenolic acids, and saponins contained in sweet clover have been studied for their potential to reduce inflammatory mediators, support microcirculation, and decrease oxidative stress. Corn silk is rich in flavonoids, maysin, luteolin, polysaccharides, phenolic compounds, sterols, and trace elements, and in certain experimental studies its effects on NF-kB, PI3K/Akt, the caspase system, p53, and mitochondrial apoptotic pathways are discussed. This article analyzes the role of inflammation and apoptosis in the pathogenesis of malignant cervical tumors, the possible molecular mechanisms of bioactive compounds from sweet clover and corn silk, and their preventive and additional scientific-practical significance. The available evidence indicates that these plants should be evaluated not as independent therapeutic agents, but as phytobiological sources that may be studied in integration with evidence-based medicine, screening, HPV vaccination, and a healthy lifestyle.

Keywords: Cervical cancer, HPV, inflammation, apoptosis, sweet clover, Melilotus officinalis, corn silk, Zea mays stigma, flavonoids, coumarins, oxidative stress, NF-kB, p53, caspase.

ПРОТИВОВОСПАЛИТЕЛЬНЫЕ И АПОПТОЗ-ИНДУЦИРУЮЩИЕ СВОЙСТВА БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ, СОДЕРЖАЩИХСЯ В ПАЖИТНИКЕ И КУКУРУЗНЫХ ПОЧАТКАХ, В ПАТОГЕНЕЗЕ РАКА ШЕЙКИ МАТКИ

Аннотация: Злокачественные опухоли шейки матки остаются одной из актуальных онкологических проблем женского здоровья. В их патогенезе важную роль играют инфекция вирусом папилломы человека высокого онкогенного риска, хроническое воспаление, окислительный стресс, нарушение иммунного контроля, расстройство клеточного цикла и подавление механизмов апоптоза. В последние годы особый интерес вызывают фитохимические источники, в частности Melilotus officinalis и кукурузные

рыльца Zea mays L. stigma, содержащие биологически активные вещества с противовоспалительным, антиоксидантным, иммуномодулирующим и потенциально проапоптотическим действием. Melilotus officinalis содержит кумарины, флавоноиды, фенольные кислоты и сапонины, которые изучались в связи со снижением воспалительных медиаторов, поддержкой микроциркуляции и уменьшением окислительного стресса. Кукурузные рыльца богаты флавоноидами, майзином, лютеолином, полисахаридами, фенольными соединениями, стеролами и микроэлементами; в экспериментальных исследованиях они рассматриваются в контексте влияния на NF-kB, PI3K/Akt, каспазную систему, p53 и митохондриальные пути апоптоза. В статье проанализирована роль воспаления и апоптоза в патогенезе злокачественных опухолей шейки матки, а также возможные молекулярные механизмы действия биоактивных соединений Melilotus officinalis и кукурузных рылец. Имеющиеся данные свидетельствуют о том, что эти растения следует рассматривать не как самостоятельное средство лечения рака, а как перспективные фитобиологические источники для дальнейшего изучения в рамках доказательной профилактики, скрининга, вакцинации против HPV и здорового образа жизни.

Ключевые слова: Рак шейки матки, HPV, воспаление, апоптоз, Melilotus officinalis, кукурузные рыльца, Zea mays stigma, флавоноиды, кумарины, окислительный стресс, NF-kB, p53, каспазы.

INTRODUCTION

Malignant cervical tumors are among the most urgent problems of modern oncogynecology. In many cases, this disease develops against the background of long-lasting viral infection, insufficient local immune response, disruption of molecular control mechanisms in epithelial cells, and chronic inflammation. According to WHO data, cervical cancer is the fourth most common type of cancer among women worldwide; in 2022, approximately 660,000 new cases and 350,000 deaths were recorded [1]. This indicator clearly demonstrates the global medical, social, and preventive significance of the disease.

The main etiological factor of cervical cancer is long-term persistent infection with high-risk oncogenic human papillomavirus, especially HPV types 16 and 18. However, HPV infection itself does not always lead to the development of cancer. In most women, the virus is eliminated by the immune system. For cancer to develop, the long-term persistence of the virus, a chronic inflammatory environment in the epithelium, oxidative stress, DNA damage, epigenetic changes, reduced activity of tumor suppressor proteins such as p53 and pRb, limitation of apoptosis, and increased proliferation create the necessary biological conditions [2, 3].

In recent years, bioactive substances obtained from plants have been widely studied from the standpoint of oncological prevention, regulation of inflammatory processes, and modulation of intracellular signaling pathways. The main purpose of this approach is not to present medicinal plants as miraculous remedies for cancer treatment, but to analyze the phytochemical compounds contained in them at the cellular and molecular levels. In this regard, sweet clover and corn silk are among the plant raw materials known in traditional medicine and whose composition and biological activity are being gradually studied in modern phytopharmacology.

Sweet clover (Melilotus officinalis) is a medicinal plant belonging to the legume family, and its composition has been shown to contain coumarins, melilotin, phenolic acids, flavonoids, saponins, tannins, and other secondary metabolites [4]. These substances may possess anti-inflammatory, antioxidant, microcirculation-improving, and cytoprotective properties under certain experimental conditions. Corn silk (Zea mays L. stigma) is known in traditional medicine as a diuretic and anti-inflammatory agent, and flavonoids, maysin, luteolin, phenolic compounds,

polysaccharides, sterols, vitamins, and mineral components have been identified in its composition [5, 6].

Because inflammation and apoptosis occupy a central place in the pathogenesis of malignant cervical tumors, the analysis of bioactive substances contained in sweet clover and corn silk specifically in these two directions is scientifically relevant. Control of inflammation may help stabilize the tumor microenvironment, reduce oxidative stress, and limit DNA damage. Stimulation of apoptosis supports the physiological mechanism for eliminating damaged cells that, under the influence of viral oncoproteins, tend toward uncontrolled division.

AIM OF THE STUDY

The aim of this article is to analyze the role of chronic inflammation and apoptosis disturbances in the pathogenesis of malignant cervical tumors and, based on the scientific literature, to elucidate the possible anti-inflammatory, antioxidant, immunomodulatory, and apoptosis-stimulating mechanisms of bioactive substances contained in sweet clover and corn silk.

MATERIALS AND METHODS

The article was prepared in a narrative-analytical format. For the analysis, scientific sources concerning the pathogenesis of cervical cancer, HPV infection, chronic inflammation, oxidative stress, apoptosis, NF-kB, PI3K/Akt, p53, pRb, the caspase system, the phytochemistry of sweet clover (Melilotus officinalis) and corn silk (Zea mays L. stigma), and their pharmacological properties were studied. The data were summarized on the basis of PubMed, PMC, WHO, IARC, GLOBOCAN, phytopharmacological reviews, and experimental studies.

In the analysis, plant-based agents were considered not as factors replacing clinical treatment methods, but as sources of bioactive substances that may exert theoretical and experimental effects on certain links of pathogenesis. Particular attention was paid to mechanisms associated with inflammatory mediators, oxidative stress, the cell cycle, mitochondrial apoptosis, caspase activation, and the tumor microenvironment.

The role of HPV, inflammation, and apoptosis in the pathogenesis of malignant cervical tumors - The development of cervical cancer is centered on the long-term persistence of high-risk HPV infection. After the virus enters epithelial cells, its E6 and E7 oncoproteins affect the most important intracellular tumor suppressor systems. The E6 protein suppresses p53 activity and limits the elimination of DNA-damaged cells through apoptosis. The E7 protein inactivates the pRb protein, creating conditions for the uncontrolled continuation of the cell cycle [2, 3]. As a result, damaged cells accumulate, proliferation intensifies, and an invasive tumor may form through stages of dysplasia.

Inflammation in this process is not merely an accompanying condition, but an active pathogenetic factor. Chronic cervicitis, sexually transmitted infections, imbalance of the vaginal microbiota, weakened local immunity, and damage to the epithelial barrier may enhance HPV persistence. Under inflammatory conditions, mediators such as interleukins, TNF-alpha, prostaglandins, COX-2, iNOS, and NF-kB are activated. This leads to an increase in free radicals within the cell, DNA damage, angiogenesis, epithelial-mesenchymal transition, and intensified invasion processes [7].

Suppression of apoptosis is one of the most important molecular features of cervical cancer. In healthy tissue, genetically damaged cells are eliminated through apoptosis. In HPV-infected cells, however, suppression of the p53 pathway, changes in the ratio of Bcl-2 family proteins, insufficient activation of the caspase system, and disruption of mitochondrial membrane

potential allow damaged cells to survive. Therefore, biological approaches aimed at restoring or stimulating apoptosis are important for understanding tumor pathogenesis.

Bioactive substances contained in sweet clover and their pathogenetic significance - Sweet clover (Melilotus officinalis) is one of the plants long used in traditional medicine, and its biological activity is mainly associated with the coumarins and phenolic compounds it contains. Phytochemical studies have shown that sweet clover contains coumarin, melilotin, phenolic acids, flavonoids, saponins, tannins, triterpenes, and other secondary metabolites [4]. Together, these substances may exert antioxidant, anti-inflammatory, and microcirculatory effects.

Coumarins are among the most important phytochemical groups in sweet clover. They have been studied in processes related to blood circulation, lymph flow, and tissue swelling. Under inflammatory conditions, impaired microcirculation, tissue hypoxia, and accumulation of metabolic waste products are observed. Theoretically, certain components contained in sweet clover may limit the long-term persistence of the inflammatory environment by supporting microcirculation. However, an important precaution is associated with coumarins. Some coumarin derivatives may affect the blood coagulation system; therefore, independent use of such plant agents may be dangerous in patients taking anticoagulant drugs, those prone to bleeding, or those preparing for surgery.

The flavonoids and phenolic acids contained in sweet clover are important from the standpoint of antioxidant protection. In the pathogenesis of cervical cancer, oxidative stress is considered one of the factors that intensify DNA damage in HPV-infected epithelial cells. Flavonoids may stabilize the cellular microenvironment by neutralizing free radicals, reducing lipid peroxidation, decreasing the expression of inflammatory mediators, and supporting the activity of antioxidant enzymes [4, 8].

The NF-kB signaling pathway occupies a special place in the anti-inflammatory mechanism. When NF-kB is activated, mediators such as TNF-alpha, IL-1 beta, IL-6, COX-2, and iNOS increase. These mediators not only maintain inflammation, but may also support the viability, invasion, and angiogenesis of tumor cells. From a scientific standpoint, the possibility that phenolic and flavonoid compounds contained in sweet clover may attenuate these inflammatory chains is an important direction; however, direct clinical efficacy against cervical cancer has not yet been sufficiently proven.

Evidence related to the apoptosis-stimulating effects of sweet clover currently relies mainly on general experimental oncological models. Some studies have reported that Melilotus officinalis extracts may reduce tumor cell proliferation, influence p53 expression, and enhance signs of apoptosis [9]. Such findings provide a scientific basis for studying the effects of phytocomplexes contained in sweet clover on cell death pathways. Nevertheless, these data are not sufficient for clinical application in cervical cancer. It is more appropriate to evaluate them as a hypothesis for subsequent laboratory, animal-model, and clinical studies.

Bioactive substances contained in corn silk and their pathogenetic significance - Corn silk (Zea mays L. stigma) is a plant raw material used in many traditional medical systems. Modern studies note that it is rich in flavonoids, maysin, luteolin, phenolic acids, polysaccharides, sterols, alkaloids, vitamins, and mineral substances [5, 6]. Its antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, and, under certain experimental conditions, antitumor properties are discussed [5].

Among the flavonoids in corn silk, maysin and luteolin deserve particular attention. Luteolin is a flavonoid found in many plants and has been studied in the scientific literature for its ability to modulate signaling pathways such as NF-kB, STAT3, PI3K/Akt, and MAPK [10]. These pathways are also important in the pathogenesis of cervical cancer, because they directly influence inflammation, proliferation, cell viability, and apoptosis.

Some reviews of corn silk extracts state that their bioactive components may modulate immune cell responses, enhance cytotoxicity, and increase pro-apoptotic markers such as p53, p21, caspase-9, and caspase-3 in certain cellular models [5, 6]. This is of particular scientific interest in the context of cervical cancer cell lines such as HeLa. Because HeLa cells belong to an HPV-associated tumor model, this direction represents an important experimental platform for studying the pathogenesis of cervical cancer.

Corn silk polysaccharides are also of particular importance. Polysaccharides may exert immunomodulatory effects and influence macrophage activity, cytokine balance, and oxidative stress. In some cancer models, plant polysaccharides have been reported to affect cell viability through PI3K/Akt, EGFR, or mitochondrial pathways [5]. However, these effects are not always uniform. In some animal models, even complex and context-dependent effects of polysaccharides on the inflammatory environment have been observed. Therefore, caution, standardization, and toxicological evaluation are necessary when considering the use of corn silk components in cervical cancer.

Phenolic compounds contained in corn silk may limit DNA damage in the cervical epithelium by reducing oxidative stress. Against the background of HPV persistence, an increase in reactive oxygen species may intensify the effects of viral oncoproteins, deepen dysplastic changes in the epithelium, and facilitate escape from immune surveillance. Antioxidant phytocompounds are theoretically significant in attenuating this process, but confirmation by clinical outcome indicators is required.

A general molecular model of the effects of sweet clover and corn silk - Bioactive substances contained in sweet clover and corn silk may influence several common chains in the pathogenesis of malignant cervical tumors. The first chain is associated with inflammatory mediators. The flavonoids and phenolic compounds contained in both plants are discussed in terms of their ability to reduce NF-kB activation, suppress COX-2 and iNOS expression, and decrease cytokines such as TNF-alpha, IL-1 beta, and IL-6 [5, 8, 10]. If this effect occurs in the cervical epithelium, the chronic inflammatory environment that supports HPV persistence may be relatively weakened.

The second chain is associated with oxidative stress. As a result of HPV-infected cells, inflammatory mediators, and immune cell activity, reactive oxygen species increase. This raises the risk of DNA mutations, chromosomal instability, epigenetic disturbances, and tumor transformation. Sweet clover flavonoids and phenolic acids, together with corn silk polyphenols, may theoretically limit this process through antioxidant protection [4, 5].

The third chain is associated with apoptosis. In cervical cancer, the HPV E6 protein suppresses p53 function. When p53 is suppressed, damaged cells become less prone to apoptosis. In some experimental models, the effects of corn silk bioactive substances have been reported in relation to the expression of p53, p21, caspase-9, and caspase-3 [5, 6]. The potential effects of sweet clover extracts on apoptotic signs in tumor cells have also been discussed [9]. These findings indicate that restoration of apoptosis is an important direction for oncopreventive and adjuvant studies.

The fourth chain is associated with angiogenesis and the tumor microenvironment. Chronic inflammation stimulates the formation of new blood vessels through VEGF, prostaglandins, and other mediators. Flavonoids and phenolic substances may attenuate signaling pathways that affect angiogenesis. This direction may serve as a promising scientific basis for studying the indirect effects of sweet clover and corn silk on the tumor microenvironment.

The fifth chain is associated with immunomodulation. Weakening of the local immune response plays an important role in HPV persistence. Plant polysaccharides and polyphenols may influence immune cell activity. However, immunomodulation does not always produce a positive

outcome, because in the tumor microenvironment some immune responses may, on the contrary, intensify inflammation or support immune tolerance. Therefore, the effects of such substances depending on dose, extract type, duration of use, and biological context require separate evaluation.

DISCUSSION

The central role of inflammation and apoptosis in the pathogenesis of malignant cervical tumors provides an important scientific basis for studying the bioactive components of medicinal plants. Although sweet clover and corn silk are widely known in traditional medicine, their use in oncogynecological diseases must be evaluated according to the criteria of evidence-based medicine. Existing phytochemical and experimental data show that the substances contained in these plants may affect inflammatory mediators, oxidative stress, and apoptotic pathways; however, this is not sufficient to recommend them as treatments for cervical cancer.

The first important point is that the strongest and most proven measures for preventing cervical cancer are HPV vaccination, regular screening, cytological examination, HPV testing, colposcopy, and, when necessary, timely treatment of precancerous cervical processes [1, 11]. Medicinal plants cannot replace these measures. They may be studied only as additional objects of scientific research within the concept of a healthy lifestyle and a general anti-inflammatory diet.

The second point is related to the lack of standardization of plant extracts. The composition of sweet clover and corn silk varies depending on the place of growth, time of collection, drying method, extraction solvent, storage conditions, and dose. An extract that showed an effect in a laboratory study may not be identical to an infusion prepared at home. Therefore, it would be erroneous to transfer scientific results directly to traditional use.

The third point concerns safety. Because sweet clover is rich in coumarins, it may affect the blood coagulation system. Particular caution is required in individuals taking anticoagulant or antiplatelet drugs, those with liver disease, and those at high risk of bleeding. Corn silk is known for its diuretic effect; therefore, its use without medical supervision is not advisable in patients with kidney diseases, electrolyte imbalance, or those taking diuretic drugs.

The fourth point is related to the complexity of cancer biology. The fact that a substance enhances apoptosis in cell culture does not mean that it will stop cancer in the human body. Concentrations used in cell culture, absorption in the body, metabolism, bioavailability, hepatic degradation, and the degree of delivery to tissues are entirely different issues. Therefore, future studies on sweet clover and corn silk should be conducted sequentially, including standardized extracts, toxicological evaluation, pharmacokinetics, cell models, animal models, and clinical observations.

Nevertheless, there is a basis for formulating a scientific hypothesis based on these plants. Coumarins, flavonoids, and phenolic acids contained in sweet clover are promising in terms of reducing inflammation and oxidative stress, while maysin, luteolin, polyphenols, and polysaccharides contained in corn silk are promising from the standpoint of inflammatory signaling pathways, immune response, and apoptotic mechanisms. In particular, the interrelationship of NF-kB and p53 pathways in HPV-associated epithelial transformation requires a deeper study of these phytocompounds.

PRACTICAL SIGNIFICANCE

The practical significance of this topic is manifested in several directions. First, in public education on the prevention of cervical cancer, interest in traditional medicine can be not rejected, but correctly directed toward scientifically grounded prevention. Second, local plant

raw materials such as sweet clover and corn silk may serve as promising objects for phytochemical and experimental studies. Third, laboratory models can be developed on the basis of these plants to evaluate their effects on markers of inflammation, oxidative stress, and apoptosis.

In future studies, it would be advisable to investigate the effects of sweet clover and corn silk extracts on cervical cancer cell lines such as HeLa, SiHa, and CaSki. In this regard, evaluation of cell viability, ROS level, NF-kB activity, IL-6, TNF-alpha, COX-2, p53, p21, Bax, Bcl-2, caspase-3, and caspase-9 indicators would be scientifically important. The toxicity of the extracts toward healthy epithelial cells should also be examined separately, because a promising phytopreparation has practical value only when it exerts a selective effect against tumor cells.

CONCLUSION

High-risk HPV infection, chronic inflammation, oxidative stress, weakened immune surveillance, and disruption of apoptotic mechanisms participate in an interrelated manner in the pathogenesis of malignant cervical tumors. HPV E6 and E7 oncoproteins disrupt tumor suppressor systems such as p53 and pRb, creating conditions for the survival and uncontrolled proliferation of damaged cells. Chronic inflammation further intensifies this process and forms the tumor microenvironment.

The coumarins, flavonoids, phenolic acids, and saponins contained in sweet clover are significant because of their potential anti-inflammatory, antioxidant, and microcirculatory effects. Maysin, luteolin, polyphenols, polysaccharides, and sterols contained in corn silk are being studied as bioactive compounds that may influence signaling pathways associated with NF-kB, PI3K/Akt, p53, and the caspase system. The components of both plants may theoretically affect the inflammation and apoptosis chains in the pathogenesis of cervical cancer.

The available data indicate that sweet clover and corn silk should be evaluated not as treatments for cervical cancer, but as phytobiological sources that require further in-depth laboratory and clinical studies. Proven prevention of cervical cancer is based on HPV vaccination, regular screening, reduction of risk factors, and timely treatment of early-detected precancerous processes. The use of medicinal plants may acquire scientific and practical significance only when it is integrated with medical consultation, safety criteria, and an evidence-based approach.

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