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The role of polyphenols in the prevention and treatment of cancer

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Abstract

Introduction: Polyphenolic compounds are widespread in nature, contained in large quantities especially in fruits, vegetables, cereals and nuts. In recent years numerous attempts have been made to characterize their biological effects, with particular emphasis on their protective potential against the development of chronic diseases, including cancer.

Purpose of the study: The aim of the study was to collect and analyze publications on the use of polyphenols in the prevention and treatment of cancer, with particular emphasis on breast cancer, colon cancer, prostate cancer and lung cancer - the four most common cancers in the Polish population.

Material and methods: A review of the literature available on PubMed was performed using various combinations of keywords: 'polyphenols' + 'cancer', 'polyphenols' + 'oncology', ‘polyphenols’ + ‘chemoprevention’, ‘polyphenols’ + ‘chemotherapy’, 'polyphenols' + 'lung cancer', 'polyphenols' + 'breast cancer', ‘polyphenols’ + ‘colorectal cancer’, 'polyphenols' + 'prostate cancer'/'prostate gland cancer'.

Results: The analysis of the collected publications allows to conclude that polyphenols exert multidirectional anticancer effect through antioxidant, antiproliferative, anti-inflammatory, immunomodulatory and prosenescence activity. This effect has been demonstrated, among others, in relation to cellular models of colorectal cancer, prostate cancer, breast cancer, cervical cancer and lung cancer. Polyphenols also reduce side effects associated with the use of conventional anticancer therapies and increase their effectiveness.

Conclusions: Polyphenols - both as independent compounds and components of complex anticancer treatment regimens - have chemopreventive and potentially chemotherapeutic effects. By influencing various stages of carcinogenesis - initiation, promotion and progression of cancer - they constitute a promising direction for the development of new, more effective forms of therapy and prevention of cancer.

Key words: cancer, chemoprevention, chemotherapy, polyphenols, breast cancer, colorectal cancer

Introduction

Polyphenols constitute one of the most common groups of phytochemicals [1]. This term covers organic compounds from the phenol group that have at least two hydroxyl groups connected to an aromatic ring. [2] In terms of the structure of the basic carbon skeleton, they

are divided into phenolic acids and flavonoids, which are the best-described class of polyphenols. Flavonoids can be further divided into flavans, isoflavans, flavonols, flavones, isoflavones, dihydroflavanols, flavanones, anthocyanidins and chalcones.

The flavonoid molecule is composed of two benzene rings, between which there is a heterocyclic pyran or pyrone ring. The fact that carbon molecules within the rings can undergo various modifications - including: hydroxylation, methylation and glycosidation - causes these compounds to be very diverse. The antioxidant effect of polyphenols, which is important from the point of view of oncology, results from the presence of hydroxyl groups. Their number and location determine the strength of the antioxidant effect [3].

Polyphenols are found in fruits, vegetables, legumes, cereal seeds, spices, herbs, vegetable oils, wine, beer, coffee and tea [4]. Under natural conditions, they play various roles - many of them are necessary for the physiological functions of plants, while some are involved in plant defense mechanisms, acting as phytoalexins - substances secreted by the plant as a result of contact with a pathogenic factor. They are toxic to pathogenic microorganisms and fungi, which is why they have protective effect. Flavanols, flavones and chalcones determine the yellow color of plant fragments, while anthocyanins cause blue, red or purple coloration. Polyphenol compounds also determine the taste and smell of fruits and flowers. In addition to the functions mentioned above, polyphenolic compounds protect plants against the harmful effects of UV radiation. This is possible due to the presence of chromaphore systems in the flavonoid molecule - an aromatic ring and conjugated double bonds. This mechanism allows the protection of cell membranes, proteins, DNA and the photosynthetic apparatus against oxidative damage. [5] More than 8,000 different polyphenolic compounds of plant origin have been described so far, but - due to the constant appearance of mutations in response to environmental changes - their number is constantly growing. [6]

The health benefits of polyphenols consumed in the diet depend on the dose of the substance and its bioavailability. The content of polyphenols in plants is influenced by many factors - including growing conditions, climate and industrial processing. [6] The type and proportion of catechins in tea vary, for example, depending on the season, climate, degree of ripeness of the leaves and production practices used. The quercetin content in tomatoes depends on their size - in the case of miniature tomatoes it is approximately 30 mg/kg, while for standard-sized tomatoes - 5 mg/kg. Significant changes in the content of polyphenols also occur during food processing. [3] The above facts make accurate determination of polyphenol intake in the diet a very difficult task.

The systemic effect of a substance also depends on its bioavailability, which in the case of polyphenols is low when administered orally. This is due to their low solubility in water, rapid biotransformation and the mass of the molecules. [8] Flavonoids can exist in nature as free molecules called aglycones or in a form bound to sugars as glycosides. [9] Most in vitro and in vivo studies on animal models concern the form of aglycones, while in natural plant sources these molecules occur in the form of glycosides showing less biological activity than the corresponding aglycones. [10] Moreover, although bacteria of the human intestinal microflora have the ability to transform glycosides into aglycones, thanks to the intestinal barrier and the first-pass effect, polyphenols undergo glucuronidation, methoxylation or transformation to other conjugated forms. This fact means that aglycones rarely appear in the systemic circulation. [11, 12] It should therefore be remembered that the results of in vitro studies on polyphenols cannot be transformed into clear guidelines regarding the recommended intake of polyphenols in the diet.

The low bioavailability of polyphenols after oral administration has recently led to the initiation of numerous studies on new strategies potentially increasing their bioavailability. The main concept includes the introduction of drug delivery systems using such agents as lipid nanoparticles/nanostructured lipid carriers, nanocrystals, liposomes, emulsions, niosomes, micelles, cyclodextrins, implants and systems based on food macromolecules (food macromolecule based deliver). [13] Moreover, in order to increase bioavailability, solutions such as microencapsulation and the use of an alternative, non-oral route of polyphenol administration have been proposed. [13, 14]

Numerous attempts to characterize the biological effects of polyphenols are facilitated by the fact that their extraction process is relatively easy (e.g. extraction using ultrasonography), and after the sterilization process they retain most of their properties. [4] Many polyphenols, in addition to the already mentioned antioxidant effects, also have anti-inflammatory, immunomodulatory, antimicrobial and prosenescent effects. [15-18] The multidirectional mechanism of their action in the pathogenesis of many diseases, such as neurodegenerative diseases, cardiovascular diseases and endocrine disorders, is observed both in vitro and in vivo in animal models. [19-22].

The process of carcinogenesis

We can distinguish three main stages in the carcinogenesis process: initiation, promotion and progression. During the initiation stage, numerous irreversible mutations occur, the accumulation of which leads to the formation of a cell that is resistant to the action of

differentiation and cytotoxic factors, but sensitive to the action of growth factors. [2, 23] A cell is considered "initiated" in which a mutation has occurred (and survived) in critical genes responsible for the control of the cell cycle - e.g. regulatory, suppressor or proto-oncogene genes.

At the promotion stage, abnormalities mainly concern epigenetic mechanisms that lead to increased proliferation and inhibition of apoptosis, and, as a result, to the growth of a selective clone of initiated cells. Oncogenes are activated and the synthesis of factors responsible for cell growth and multiplication is increased. At the same time, further mutations occur and are not repaired. Described processes lead to phenotypic changes, preneoplastic transformations, and ultimately - to the loss of cell function and its connection with other cells.

The final stage of carcinogenesis is progression, including invasion of adjacent tissues and the formation of distant metastases. It mainly involves the occurrence of subsequent molecular disorders, which cause primarily changes in the karyotype. This is an irreversible stage, which inevitably leads to the development of cancer. [24]

Methodology

The aim of this study was to investigate the potential of polyphenols in the treatment of cancer, with a primary focus on the four most prevalent cancers in the Polish population: colorectal, breast, prostate, and lung. To achieve this objective, we conducted a comprehensive literature review. Our approach adhered to the literature review methodology outlined by Snyder (2019) [25]. The following research questions were formulated::

1. What is the anticancer effect of polyphenols
2. How polyphenols may influence the treatment of breast cancer
3. How polyphenols may influence the treatment of colorectal cancer
4. How polyphenols may influence the treatment of prostate cancer
5. How polyphenols may influence the treatment of lung cancer

To address these research questions, we conducted a search on PubMed between November 15th and December 10th, 2023. The search strategy incorporated the following keywords: 'polyphenols' + 'cancer', 'polyphenols' + 'oncology', ‘polyphenols’ + ‘chemoprevention’, ‘polyphenols’ + ‘chemotherapy’, 'polyphenols' + 'lung cancer', 'polyphenols' + 'breast cancer', 'polyphenols' + 'colorectal cancer'/'CRC', ‘polyphenols’ + ‘colorectal cancer’, 'polyphenols' + 'prostate cancer'/'prostate gland cancer'. They were searched as keywords in titles and abstracts.

The inclusion criteria were as followed:

1. It analyzed the potential impact of polyphenols on carcinogenesis
2. it is a peer-reviewed empirical study or theoretical paper, technical report, book/chapter, thesis
3. the full text is available in English

Additionally, we performed a grey literature search by reviewing the websites of various international and national organizations specializing in new anticancer treatments or polyphenol research.

The search process was carried out independently by two researchers. Each researcher continued their search until they felt that saturation of relevant material had been achieved. Subsequently, all researchers reviewed the collected material collectively. They assessed whether the papers met the inclusion criteria and whether the gathered data was adequate to fulfill the study's objectives. After the initial search phase, consensus was reached among all authors that the compiled material was sufficient.

For data extraction, two researchers independently analyzed the materials related to each research question, highlighting key information. Subsequently, they compared their findings. In instances where discrepancies arose, discussions were held until a consensus was reached. If consensus could not be achieved, a third researcher was consulted for a final decision.

Following the extraction process, all researchers reassessed the data saturation. Unanimously, they concluded that the available information was adequate to address the research questions.

Anticancer effect of polyphenols

Polyphenols affect all three stages of carcinogenesis. They influence the initiation process, among others mechanisms, by eliminating reactive oxygen species and preventing their interaction with DNA, and in the event of DNA damage, increasing the effectiveness of repair. [26, 27]

The anti-promoting and anti-progressive effect is primarily related to the stimulation of cell differentiation, inhibition of proliferation, induction of apoptosis, inhibition of angiogenesis, impact on the tumor microenvironment and reduction of invasive potential. [26-29]

These actions are achieved by influencing various metabolic pathways, the most important of which seem to involve nuclear factor-kappa β, mitogen activated protein kinases

MAPK, Wnt/β-catenin and phosphatidylinositol 3-kinase and protein kinase B via selective actions on various components of the network. [30, 31]

Polyphenols and breast cancer

Breast cancer is the most common malignant tumor among women in Poland. According to epidemiological data collected in The Polish National Cancer Registry, the number of cases shows a constant increasing trend - the projected number of cases in 2024 is 23,285 with 19,620 cases in 2019. Statistical data clearly show that breast cancer also remains one of the leading causes of mortality among women. [32]

There are many clinical features that influence the selection of the best form of treatment for patients. These include the patient's age, tumor size, axillary lymph nodes involvement, histological type and molecular status - expression of progesterone, estrogen and HER2 receptors. Cancers called triple negative do not express any of the above-mentioned receptors. [32]

Conventional methods widely used in the treatment of breast cancer (chemotherapy, hormone therapy, radiotherapy, surgical interventions) are associated with significant side effects. [33] Their use is also limited by increasing resistance to classical chemotherapeutics previously used in breast cancer treatment protocols. [34] This fact implies the need for research to develop new potential therapeutic strategies that would increase the effectiveness of treatment while reducing the incidence of side effects.

Due to the multidirectional potential of biological action of phytochemicals - substances of plant origin, which also include polyphenols - in recent years, special attention has been paid to the possibility of their use in oncology. Studies conducted mainly in vitro have shown that polyphenols have chemopreventive and chemotherapeutic effects on breast cancer cells by influencing numerous molecular pathways. [35-39] They inhibit, among others, DNA-methyltransferase (DNMT) and histone deacetylase (HDAC), which - through increased acetylation and demethylation of suppressor genes - contributes to the prevention of proliferation and migration of breast cancer cells. [35, 36, 37] Polyphenols also inhibit STAT3 - signal inducer and activator of transcription - thereby inhibiting the expression of genes involved in cell proliferation, as well as in the processes of angiogenesis and metastasis. [35, 36, 38, 39] In recent years, attention has also been paid to the importance of overexpression of PD-L1 - programmed death ligand 1 - in various stages of carcinogenesis, metastasis and treatment resistance. In relation to breast cancer, polyphenols reduce PD-L1

expression. [40] Several studies have also demonstrated their potential to inhibit the activity of aromatase responsible for the conversion of androgens to estrogens. [41, 42]

Moreover, polyphenols influence the so-called Warburg effect related to glucose metabolism. Altered energy metabolism is one of the characteristics of a cancer cell - increased glucose consumption and induction of glycolysis, even in the presence of oxygen, result in excessive lactate production. In vitro studies have shown that polyphenols inhibit glucose transport and also block the uptake of glucose and lactate by cancer cells. It results in a reduction in the supply of cells with the two most important energy substrates. [43]

Polyphenols and colorectal cancer

According to data from The Polish National Cancer Registry in 2019 colorectal cancer (treated as a malignant tumor of the colon, colon-sigmoid bend, rectum and anus) was the third most common cancer in men, after prostate and lung cancer, and the third most common cancer in women, after breast and lung cancer. There were 18,514 new cases, making colorectal cancer a significant public health problem. [32, 44] Over the last four decades, the number of cases of colorectal cancer has increased almost 5-fold among men and more than 3-fold among women. [44] Globally, more than half of colorectal cancer cases occur in economically developed countries. The risk factors for colorectal cancer include, among others, a high-fat, low-fiber diet, obesity, a positive family history of colorectal cancer and - according to the latest research - dysregulation of the composition of the intestinal microbiota. The data collected so far suggest that the lack of proper dietary habits and lifestyle may influence the risk of occurrence and progression of intestinal diseases developing on the basis of chronic inflammation, including colorectal cancer. In inflammatory bowel diseases (IBD), chronic inflammation leads to mucosal damage with associated excessive production of reactive oxygen species (ROS), causing potential tumor progression and spread of metastases. [45, 46]

In addition to the immunomodulatory, pro-apoprotic, anti-proliferative and anti-inflammatory effects of polyphenols, what is worth remembering in relation to colorectal cancer is the fact that they influence the composition of the intestinal microbiota. In recent years, the intestinal microbiome has become the subject of numerous studies focused primarily on its role in the development, maturation and functioning of the host's immune system. The constant interaction between the intestinal microbiome and the mechanisms of innate and adaptive immunity also regulates the homeostasis of intestinal epithelial cells. Dysbiosis and loss of control over the aforementioned process leads to inflammatory

disorders that may promote carcinogenesis. Polyphenols have a prebiotic effect - they stimulate the growth of normal intestinal microflora and reduce the development of pathogenic microorganisms, thus contributing to limiting the inflammatory process. Moreover, the role of the intestinal microbiota is emphasized not only at various stages of carcinogenesis, but also in modulating the therapeutic response to treatment, especially with the use of immune checkpoint inhibitors. [45-49]

Another important issue is the problem of resistance to conventional chemotherapy treatments used in colorectal cancer treatment protocols. Currently, most of them involve the use of chemotherapy at various stages of treatment - most often in the form of adjuvant therapy after surgical interventions. Despite the fact that anticancer therapy using classic cytostatics such as 5-fluorouracil, platinum derivatives, vincristine, doxorubicin and irinotecan limits tumor growth and prolongs the average survival time of patients with colorectal cancer, when resistance develops, it becomes palliative chemotherapy for most patients. [50] Data from the literature indicate that in over 90% of patients with metastases treatment failure is related to the development of resistance to chemotherapeutic agents. [50, 51] For this reason, it is necessary to look for new strategies to reverse resistance. Among the tested polyphenols, the resistance-reversing effect was demonstrated, among others, for curcumin - a compound naturally contained in the rhizomes of turmeric, also called turmeric longa. Curcumin blocks the progression of epithelial-mesenchymal transition (EMT) - a process that results in depriving the cell of communication with other cells, increasing its mobility and gaining the ability to migrate. Moreover, it inhibits the overexpression of P-gp and the expression of HSP-27 (heat shock protein-27) - proteins associated with drug resistance mechanisms. [51, 52, 53] Resveratrol (occurring naturally mainly in grapes) influences the chemosensitization of model cell lines to 5-fluorouracil by strengthening intercellular connections. [51, 54] Resveratrol also has the potential to reverse oxaliplatin resistance by increasing cellular drug accumulation. [51, 55]

The data collected so far suggest that the use of polyphenols in monotherapy may be less effective than their combination with conventional chemotherapeutics. Synergistic effects were demonstrated by, among others, curcumin in combination with 5-fluorouracil and resveratrol metabolites in combination with oxaliplatin. [56] Moreover, several studies using a mouse xenographic model demonstrated, in addition to the chemosensitizing effect, an additional radiosensitizing effect against colorectal cancer cells. [57, 58]

Polyphenols and prostate cancer

Prostate cancer is the most common cancer among men in Poland - over 17,638 new cases were diagnosed in 2019. It is estimated that in 2024 this number will increase to approximately 27,000 cases. [32] Due to its high prevalence in the population, slow rate of growth and progression and long latency period prostate cancer is a promising subject of research on cancer chemoprevention. It is a cancer whose development from the precancerous stage (ASAP - atypical lobular proliferation, HG PIN - high-grade prostatic intraepithelial neoplasia) to the invasive stage takes from several to a dozen or so years. Such a long period of development creates opportunities for potential intervention to inhibit or reverse the process of carcinogenesis. [2]

The anticancer activity of polyphenols in the case of prostate cancer is also achieved in many directions - in molecular terms, they influence the expression of genes regulating the cell cycle, the process of apoptosis and angiogenesis, and they also take part in the metabolism of xenobiotics with carcinogenic potential. [2, 26, 59]

Also, worth emphasizing is the anti-androgenic effect of polyphenols, which is very important from the point of view of the treatment of hormone-dependent prostate cancer. This effect is probably achieved by one of three mechanisms - direct competitive effect due to the structural similarity of androgens and polyphenols, inactivation of androgen receptors or inhibition of androgen receptor transactivators. [60]

Epigallocatechin gallate (EGCG) present in green tea extract affects many molecular pathways important in the carcinogenesis process: the MAPK (mitogen-activated protein kinase) pathway involved in the regulation of cell proliferation and death, and pathways related to nuclear factor kappa B (NF-kappaB) responsible for the induction of inflammation, immune response and growth of cancer cells, with IGF (insulin-like growth factor) influencing the growth and development of cancer tumors and with EGF (epidermal growth factor)) increasing proliferation and invasiveness. [61-64] EGCG and green tea extract block 5-alpha reductase activity, modulate androgen receptor gene and protein expression in cancer cells. [65]

In the case of prostate cancer, apart from in vitro and in vivo studies, epidemiological observations were also carried out, which also showed an inverse correlation between green tea consumption and the risk of developing prostate cancer. The largest study conducted involving nearly 50,000 Japanese people showed that drinking more than 5 cups of green tea a day significantly reduces the risk of developing clinically significant prostate cancer. The

chemopreventive effect is also attributed in this case to the above-mentioned epigallocatechin gallate. [66]

Polyphenols and lung cancer

Lung cancer is the second most common cancer in both women and men. However, what deserves special attention, is the fact that for many years lung cancer has been the leading cause of mortality among all cancers. Histologically, there are two types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which accounts for 80% of cases. [32]

In the context of the use of polyphenols in chemoprevention and chemotherapy of lung cancer, the most data has been collected on polyphenolic compounds contained in green tea, catechins - epigallocatechin gallate (EGCG), epicatechin gallate, epigallocatechin and epicatechin. Epigallocatechin gallate was shown to inhibit the expression of programmed cell death ligand 1 (PD-L1) induced by both interferon-gamma and epidermal growth factor (EGF). [67, 68] In non-small cell lung cancer cells, the use of epigallocatechin gallate also reduced the invasive potential of the cells by reducing the levels of MMP-2 - extracellular matrix metalloproteinase 2 - and uPA (urokinase-type plasminogen activator). ECOG used in the treatment also showed a synergistic effect with cisplatin in inducing cytotoxicity and leading to cell death by inducing apoptosis, dysregulation of the mitochondrial membrane potential and activation of caspase 3 and 9. [69]

In-vivo studies conducted using a lung cancer cell model showed that EGCG acted as an alternative immune checkpoint inhibitor. [70]

Luteoin, naturally contained in green leaves of vegetables such as celery or parsley, in turn, reduced the invasive potential of lung cancer cells by blocking the kinase signaling pathway. [71]

The study conducted by Gu's team showed that resveratrol contained in grapes and red wine used in combination with arsenic trioxide (As_2O_3) had a synergistic effect, causing an increase in cytotoxicity and apoptosis at the tested concentration. Moreover, resveratrol administered simultaneously with cisplatin resulted in an increase in its antiproliferative effect. Another study showed that resveratrol induces apoptosis by depolarizing the membrane potential of the mitochondrial membrane, releasing cytochrome c from the mitochondrion into the cytosol, and changes in the expression of Bcl-2 and Bax proteins, which are associated with the process of programmed cell death. [72]

Summary

The data collected during the literature review clearly indicate a wide potential for the use of naturally occurring polyphenolic compounds in chemoprevention and chemotherapy of many chronic diseases - inflammatory disorders, cardiovascular diseases, diabetes and cancer, which still constitute a very big challenge for modern medicine. The anticancer effect of polyphenols has also been demonstrated against the most common cancers in the Polish population - breast cancer, prostate cancer, lung cancer and colorectal cancer - which were the focus of the above study. This fact makes polyphenolic compounds of particular interest also in the context of public health and health promotion. The beneficial multi-pronged biological effects of polyphenols are achieved through various molecular and metabolic mechanisms, which are still the subject of intensive research. Despite the promising results of completed and currently ongoing clinical trials, caution should be exercised in formulating conclusions regarding the effects of polyphenols on the human body, because this area requires further exploration.

Supplementary materials

Not applicable.

Authors contribution

Conceptualization: Aleksandra Szypuła, Beniamin Michalik; methodology: Beniamin Michalik; software: Iwona Galasińska; check: Katarzyna Hajduk-Maślak, Adrianna Skóra; formal analysis: Iwona Galasińska; investigation: Aleksandra Szypuła, Katarzyna Hajduk-Maślak; resources: Michał Sęk, Iwona Galasińska; data curation: Michał Sęk; writing - rough preparation: Adrianna Skóra; writing - review and editing: Katarzyna Hajduk-Maślak; visualization: Michał Sęk, Adrianna Skóra; supervision: Beniamin Michalik; project administration: Aleksandra Szypuła

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Data Availability Statement

The data presented in this study are available upon request from the correspondent author.

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