herba polonica
International journal edited by the Institute of Natural Fibres and Medicinal Plants
National Research Institute
Vol. 69 No. 2 2023

Received: 2023-04-10
Accepted: 2023-05-30
Available online: 2023-06-30

DOI: 10.5604/01.3001.0053.7211

REVIEW ARTICLE

Selected substances of natural origin with anticancer activity

FILIP PRZERWA[1], AGNIESZKA JANIEC[2], JAKUB BYRSKI[1], JUSTYNA ALEKSANDRZAK[1], MATEUSZ GUTOWSKI[1], KAROL ADAMCZYK[1], KATARZYNA KOTRYCH[3], IZABELA UZAR[4]*

[1] Student Science Club
Department of General Pharmacology and Pharmacoeconomics
Pomeranian Medical University in Szczecin
Szczecin, Poland

[2] Department of Endocrinology, Metabolic and Internal Diseases
Pomeranian Medical University in Szczecin
Szczecin, Poland

[3] Department of General and Dental Radiology
Pomeranian Medical University in Szczecin
Szczecin, Poland

[4] Department of General Pharmacology and Pharmacoeconomics
Pomeranian Medical University in Szczecin
Szczecin, Poland

*corresponding author: e-mail: uzari@wp.pl

Summary

Cancer is one of the most serious problems facing modern medicine. Research on new methods of treating this disease is being conducted. Existing methods are increasingly effective, but they also have risks to human health. The attention of scientists is focused on compounds of natural origin, as they are less toxic to human body than traditional chemotherapeutics. They are also much more accessible and their production is much less complex and expensive. There are several natural compounds with anticancer potential. In this article, we present three groups of potential therapeutic importance - polyphenols, brassinosteroids, and flavonoids.

Key words: ***natural substances, anticancer activity, polyphenols, brassinostreoids, flavonoids***

Słowa kluczowe: ***substancje naturalne, działanie antynowotworowe, polifenole, brassinosteroidy, flawonoidy***

INTRODUCTION

Despite recent significant advances in oncology, cancer remains one of the biggest problems that modern medicine is facing. The 2019 coronavirus pandemic (COVID-19) has led to delays in cancer diagnosis and treatment due to disruptions in healthcare, and patient concerns about exposure to the virus. Although the most serious consequences of the pandemic appear to be over, its effects are still present. In 2023, an estimated 1.2 million people will die from cancer in Europe [1], while in the USA the number exceeds 600,000 [2]. However, thanks to the efforts of doctors and scientists around the world, cancer mortality has been steadily declining since 1991. This is a result, both of advances in treatment and increasing public awareness of the disease. Better screening, improved treatments such as postoperative adjuvant chemotherapy and the development of targeted drugs and immunotherapies, and declining smoking rates in the population are all factors contributing to the reduction in cancer mortality.

Cancer treatments include chemotherapy, radiation therapy, immunotherapy, surgical treatment, photodynamic therapy, and stem cell treatment. Despite the increasing efficacy of the above treatments, each carries several potential risks, side effects, and other factors that can negatively affect the course of treatment. Hence, research is constantly being conducted to minimize harm while increasing the effectiveness of treatment. Developing new therapeutic methods and increasing their specificity seems to be the future of cancer control [3].

Chemotherapeutic agents are cytostatic and cytotoxic drugs that have shown promising results when used alone or in combination with other anticancer drugs. They have relatively high efficacy against a broad spectrum of cancers, but they also have numerous limitations – they have a lot of dangerous side effects and their production is complicated and expensive. Side effects of chemotherapeutics are associated with various acute and late symptoms of toxicity. These include general side effects, such as anaemia, neutropenia, nausea, vomiting, diarrhoea, and mucositis, however, toxic effects on the kidneys, nervous system, lungs, and hearing organs are also widespread [4].

Currently, the goal of many scientists is to search for compounds of natural origin that can potentially aid cancer therapy, while having much less severe side effects. A collection of natural anti-cancer compounds of plant origin can be found in the Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target Database (NPACT, https://webs.iiitd.edu.in/raghava/npact/), where 1574 substances have been documented [5]. This paper focused on three chemical groups – polyphenols, brassinosteroids, and flavonoids.

POLYPHENOLS

Polyphenols are defined as compounds with one or more hydroxyl groups attached to at least one aromatic ring. Polyphenols are a broad category of natural plant compounds and metabolites considered complex antioxidants, which are abundant in our daily diet. They are particularly abundant in fruits, pulses, spices, cocoa, vegetables, coffee, nuts, beer, wine, and olive oil [6]. It is estimated that the average daily intake of polyphenols is about 1 g [7]. Polyphenols have physiological functions and are responsible for antioxidant activity, prevention of cardiovascular disease, anticancer activity, and inhibition of microbial growth [8]. The anticancer properties of natural polyphenols are largely attributed to their potent antioxidant and anti-inflammatory effects, as well as their ability to modulate molecular targets and signalling pathways involved in cell survival, proliferation, differentiation, migration, angiogenesis, hormonal activity, detoxifying enzyme activity, immune response and also induction of apoptosis [9, 10]. Based on chemical structure, natural polyphenols can be divided into five classes, including flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols. Phenolic acids and flavonoids are the most common classes.

Due to their chemical properties, these compounds can have a wide range of applications in medicine, both in the prevention and control of diseases. Epidemiological studies show that a diet rich in polyphenols is an effective protection against chronic diseases such as cardiovascular disease, neurodegenerative diseases, and cancer [11]. In addition, findings from animal studies suggest that dietary polyphenols can be potentially used in the treatment of type 2 diabetes, also by inhibiting intestinal absorption of glucose [12]. The substances in question also have immunosuppressive properties (they inactivate NF-κB, modify mitogen-activated protein kinase pathways and reduce prostaglandin synthesis) which gives hope for their effective use in the treatment of chronic inflammatory diseases [13]. Polyphenols can also exert beneficial effects on human intestinal microbiota, e.g. by promoting the growth of beneficial microorganisms such as *Akkermansia* spp. [14] , whose presence improves

glucose metabolism and reverses the adverse consequences of a high-fat diet. Unfortunately, due to different bioavailability and complex interactions of polyphenols among themselves and the activity of their metabolites, the effective use of polyphenolic compounds in medicine requires further thorough research [15]. Due to the abovementioned activity, the described compounds have long been of interest to scientists for their anticancer use. The hope is the possibility that polyphenols are able to modulate the activity of activated 5'AMP kinase (AMPK), which is a key enzyme in the regulation of energy pathways (causes a shift in the AMP:ATP ratio in favour of AMP leads, among other things, to an increase in insulin secretion by the pancreas and thus to an increase in glucose uptake by muscles). Glucose and its metabolism play an important role in the growth and development of cancer, so the possibility of disrupting this process is promising in the fight against cancer [16]. Obesity and especially breast, colorectal, and liver cancer are also factors in cancer development [17]. In this field, also the use of polyphenols such as resveratrol seems promising, which, according to studies, show positive properties in obesity prevention by reducing adipocyte viability, inhibiting preadipocyte proliferation and differentiation, reducing triglyceride accumulation, and stimulating lipolysis and β-oxidation of fatty acids. The key here seems to be the involvement of mTOR kinase which plays an important part in cellular metabolism and which, according to studies, can be stimulated by some polyphenols [18], but whose function in this process has not been fully understood. Studies show that polyphenols may be important in the prevention and treatment of colorectal cancer. Their action targets two different areas because they affect both small intestinal cells and the intestinal microbiota. Natural polyphenols have a preventive effect by improving the functioning of the microbiota, reducing inflammation, and inhibiting the invasion of pathogenic bacterial strains. Studies have shown that polyphenols present in green tea affect the composition of the intestinal microbiota in rats. The presence of *Peptostreptococcaceae* associated with the CRC phenotype significantly decreased, while the abundance of Bacteroidetes and Oscillospira associated with the lean phenotype increased [19]. Experiments on a new curcumin analogue, GO-Y030, have shown that decreasing the activity of the STAT3 pathway, shortens the life of cancer cells, reduces the formation of the tumorigenesis zone, and stimulates cancer stem cells to apoptosis [20].

Resveratrol is a natural polyphenolic chemical that acts as an antioxidant and exhibits anti-cancer effects. In a study of male transgenic mice with prostate adenocarcinoma, they were fed resveratrol (625 mg resveratrol per kg of AIN-76A diet) or a control diet without phytoestrogens (AIN-76A) from 5 weeks of age. Mechanism of action and histopathological studies were performed at 12 and 28 weeks of age, respectively. Dietary resveratrol reduced the incidence prostate adenocarcinoma (7.7-fold). In the ventral part of the prostate, resveratrol significantly reduced cell proliferation and phosphorylation of ERK 1 and 2, but did not alter insulin-like growth factor IGF-1 receptors. In the dorsal part of the prostate, resveratrol inhibited cell proliferation, increased the activity of the androgen receptor, oestrogen receptor β, and insulin-like growth factor-1 receptor, and significantly decreased the activity of insulin-like growth factor IGF-1 and phosphorylated extracellular regulatory enzyme 1 (phosphorylated ERK1). Serum levels of total testosterone, free testosterone, estradiol, and dihydrotestosterone in the prostate were unchanged in mice treated with resveratrol. The 12-week-old mice received 625 mg of resveratrol per kg of diet for 3 weeks. Down-regulation of phospho-ERKs 1 and 2, decreased cell proliferation and potent growth factor IGF-1, and an increase in the putative tumour suppressor oestrogen receptor β, provide evidence that resveratrol inhibits prostate cancer development [21].

Another recent study found that resveratrol treatment significantly increased ATP2A3 expression by increasing lysine 27 H3 acetylation on the ATP2A3 gene promoter and decreasing DNMT activity and expression levels of the DNA methyl-binding proteins MeCP2 and MBD2. In addition, HDAC inhibitors increased the expression level of ATP2A3 [22]. The ATP2A3 gene, which plays an important role in intracellular Ca2+ processing and normal cell death processes, has been identified in breast cancer. In another study, resveratrol combined with grape seed proanthocyanidins significantly reduced DNMT and HDAC activity in breast cancer cell lines [23]. In addition, this study showed that resveratrol and proanthocyanidins synergistically inhibited breast cancer cell growth, while AhR agonists increased BRCA1 promoter methylation in breast cancer [24]. They found that when mothers took resveratrol, the expression of AhR repressors increased, and BRCA1 gene expression increased in the offspring [25]. Therefore, the results suggest that resveratrol prevents breast cancer development by modulating BRCA1 expression through the regulation of AhR signalling.

Human pancreatic cancer stem cells (CSCs) CD133+, CD44+, CD24+, and ESA+ have high tumorigenic potential and form subcutaneous tumours in NOD/SCID mice. Compared to normal pancreatic tissue and primary pancreatic cancer cells, the expression of Nanog, Oct-4, and Notch1 is also significantly higher. Resveratrol inhibits the self-renewal capacity of pancreatic CSCs in primary human tumours and KrasG12D mice. Resveratrol induces apoptosis in human CSCs through the activation of caspase-3/7 and suppression of Bcl-2 and XIAP expression. Resveratrol inhibits pluripotency maintenance factors (Nanog, c-Myc, and Oct-4) and the ABCG2 drug resistance gene in CSCs. Inhibition of Nanog by shRNA increases the inhibitory effect of resveratrol on CSCs' ability to self-renew. Finally, resveratrol inhibits CSC migration and invasion and markers of epithelial-mesenchymal transition (Slug and Snail). This data suggests that resveratrol has the potential for use in the prevention and treatment of pancreatic cancer [26].

BRASSINOSTEROIDS

Brassinosteroids (BR) include about 70 poly-hydroxylated sterol derivatives and are endogenous plant hormones that are essential for the proper regulation of various physiological processes required for normal growth and development, hence the high prevalence of these hormones in the plant kingdom. They are composed of a cholesterol backbone with various hydroxyl substituents and attached functional groups [27], making them structurally very similar to animal hormones [28]. They are involved in the control of processes related to plant growth, such as flowering and cell development. In addition, they affect the activity of complex metabolic pathways, regulate the expression of many genes, contribute to the control of cell division and differentiation, and influence the activity of complex metabolic pathways. They are also secreted in stressful situations, such as high temperatures and drought [29]. BRs are widely distributed in the plant kingdom and have been isolated from 64 plant species [30]. These hormones have been detected in all plant organs studied, including pollen, seeds, leaves, stems, roots, flowers, and seeds – but they reach their highest concentrations in pollen and seeds [31].

The mechanism of action of brassinosteroids in animals was shrouded in mystery for a very long time. Only intensive research in recent years has enabled a partial understanding of the process. By their structural similarity, BR animal cells can bind to hormone receptors of cells, allowing activation or inhibition of the transcription rate of specific genes [32, 33].

There have also been recent advances in BR bioactivity studies in various animal models, suggesting significant potential for therapeutic applications. BRs have been shown to have anti-viral activity against herpes simplex virus (HSV) types 1 and 2, vesicular stomatitis virus (VSV), measles virus, and polio [34, 35]. Synthetic brassinosteroid analogues, including stigmasterone and androstenedione derivatives, are also immuno-modulators that act as anti-inflammatory steroids [36]. Phytosterols inhibit the gut's ability to absorb cholesterol, resulting in a reduction in plasma total cholesterol and LDL fraction cholesterol. It has been suggested that BRs, being an oxidized form of phytosterols, may potentially have similar properties, but further research in this area is needed [37]. Given the positive effects of BRs on oxidative stress, their potential impact on some neurological diseases has also been suggested [38]. Animal studies have also demonstrated the anabolic effects of 28-homobrassinolide, increasing their food intake and lean body mass gain [39].

In recent years, the mechanism of the potential anticancer effects of brassinosteroids has been the subject of many studies. One of their most important goals is to understand the effects of these substances on steroid receptors [40]. It is suspected that brassinosteroids inhibit the cell cycle and, as a result, limit cell proliferation. In addition, hormone-sensitive cell lines yield a potentially better response to treatment. This is indicated by the fact that BR administration at any phase of the cell cycle can induce apoptosis of breast cancer cells [41]. Similarities between BR and human steroids have also been demonstrated – 28-homocastasterone has been shown to inhibit the growth of human microvascular endothelial cells (HMEC-1). In contrast, a synthetic analogue of BR called cholestanone, in addition to the above action, also has antagonistic effects on human oestrogen receptor-α and oestrogen receptor-β. Another potential anticancer mechanism exhibited by BRs is their antiangiogenic effect. Angiogenesis, the process of blood vessel formation, is one of the key processes in the progression of cancer, as vascularization enables the delivery of nutrients and oxygen to tumour cells and, as a result, their faster growth. Blocking angiogenesis will limit growth and ultimately slow the progression of the disease.

It has been demonstrated that 24-epibrassinolide and 28-homocastasterone and 24-epibrassinolide significantly inhibit the migration of endothelial cells derived from the human umbilical vein [33].

In the aforementioned studies on the mechanism of action of the two brassinosteroids, their inhibitory effects on hormone-sensitive (MCF-7) and hormone-insensitive (MDA-MB-468) breast cancer cell lines were demonstrated by affecting and blocking the cell cycle [41].

Studies have shown that the brassinosteroid substance epibrasinolide (EBR) acts on colon cancer cells *in vivo*, promoting their apoptosis and reducing their lifespan as a result. It works by interacting with several cellular factors, interfering with relevant signalling pathways. It has been shown that EBR can affect JNK, CHOP, and caspase-12, causing apoptosis of colon cancer cells [42]. Other studies have shown that EBR also causes inhibition of PARP, an enzyme involved in DNA repair [43], but its blockage is also associated with cancer cell death. Another anticancer mechanism of epibrasinolide is the activation of caspases, which are responsible for cell destruction, hence their activation in cancer cells is associated with their apoptosis. The PI3K/Akt/mTOR signalling pathway is highly active in many types of cancer and regulates a broad spectrum of cellular mechanisms, including metabolism, growth, proliferation, angiogenesis, and metastasis. FOXO3 is an important target molecule of this pathway. Decreases in this protein are associated with carcinogenesis [44]. In contrast, EBR increased FOXO3a levels, which induced apoptosis in HT-29 and HCT116 colon cancer cells [45].

BRs also exhibit cytotoxic effects against prostate cancer cells, as indicated by numerous studies. Brassinosteroids induced apoptosis in PC-3 cells through the activation of caspases [46]. Another study demonstrating the effects of BR on this cell line was by Obakan *et al.* where they also showed that they could activate caspases in PC3, but also induce apoptosis of PC3 prostate cancer cells independent of p53 expression [47]. Other studies have shown that BR substances can inhibit the growth of DU-145 and LNCaP cell lines. In the former, the effect was achieved by inhibiting the cell cycle at the G2/M level, resulting in reduced expression of cyclins responsible for mitotic divisions. In contrast, in the LNCaP cell line, brassinosteroids inhibited the cell cycle at the G1 level [48]. Subsequent studies on the same cell lines showed yet another mechanism of action of brassinosteroids – the apoptosis of cancer cells was caused by the activation of enzymes responsible for the degradation of polyamines, resulting in increased concentrations of such compounds as aldehydes and hydrogen peroxide, which had cytotoxic effects on the cells [49]. Studies conducted on the 2019 DU-145 and LNCaP prostate cancer cell lines also demonstrated the potential use of brassinosteroids as a therapeutic agent against this cancer. Catasterone, a precursor of BR synthesis, has shown effects that disrupt the integrity of the cell membrane of these cells and at higher concentrations, it also inhibited the cell cycle at the G0/G1 level [50].

Brassinosteroids have also shown therapeutic effects on some lung cancer cell lines. Apoptosis of SCLC line cancer cells was induced by the activation of the Wnt signaling pathway. The effect of BR was seen on both drug-resistant (VPA17) and sensitive (NCI-H69) cells. It was also shown that the addition of epibrassinolide reduced the drug concentrations required for therapeutic action against this tumour, which could potentially reduce the doses required for administration [51]. Another study, conducted on the A549 line, showed that BRs could increase the concentration of reactive oxygen species (ROS) in these cells, which subsequently led to structural damage and ultimately death [52].

A study conducted by Obakan et. al in 2022 also demonstrated the potential therapeutic effect of BR on neuroblastoma cancer cells and more specifically the SK-N-AS cell line, by inducing apoptosis of the mitochondria of these cells through increased production of reactive oxygen species. In addition, phosphorylation of GSK3β is inhibited, which in effect prevents translocation of the β-catenin protooncogene [53].

In addition to studying potential anti-proliferative mechanisms, scientists are still trying to learn about the direct effects of brassinosteroids on cancer cells. However, the studies of cancer cell apoptosis so far have only been *in vitro* studies, hence more experimental studies in animals are needed to definitively confirm their effects as inhibitors of tumor growth.

FLAVONOIDS

Flavonoids are polyphenolic compounds synthesized by plants – bioactive secondary metabolites responsible for colour, aroma, and pharmacological activity [54, 55]. Flavonoids are most abundant in fruits and vegetables. They are also present in cocoa products (cocoa powder, chocolate), black tea, green tea, and red wine [56]. Among fruits, they are abundant in berries, plums, cherries, and apples, while tropical

fruits are considered poor in flavonoids. Among vegetables, such as: olives, broad beans, onions, spinach, the spring onions possess the most flavonoids [57, 58].

Flavonoids have attracted the attention of researchers because they are potent antioxidants that protect plants from adverse environmental conditions. They have been the subject of many scientific studies to evaluate their beneficial effects on the course of numerous acute and chronic diseases in humans; including anti-inflammatory, immunomodulatory, and anti-cancer effects [59, 60].

The anti-inflammatory mechanism of action of flavonoids (e.g., quercetin-galanin, apigenin, baicalin) is mainly due to the inhibition of 5-lipoxygenase and cyclooxygenase activity. These enzymes are involved in the synthesis of prostaglandins and leukotrienes (mediators of the inflammatory response) from arachidonic acid [61].

In addition to the general anti-inflammatory effect, some flavonoids have been shown to have anti-allergic effects. In addition, flavonoids have been shown to act on immune cells. Their actions include inhibition of lymphocyte proliferation, suppression of the synthesis of antibodies of Ig E, G, M, and A classes, and inhibition of cytokine release. They can also inhibit the activity of lysosomal enzymes involved in inflammatory and allergic processes [62].

There is ample evidence that dietary intake of flavonoids contributes to reducing the risk of cardiovascular mortality. Numerous epidemiological studies have confirmed an inverse relationship between the consumption of products containing large amounts of flavonoids (drinking about four cups of green tea a day, red wine, eating large amounts of apples, onions, and broccoli) and the incidence of cardiovascular disease. The antioxidant activity of these compounds contributes to inhibiting lipid peroxidation in cell membranes, protecting low-density lipoproteins (LDL) from oxidation, and increasing the HDL fraction of cholesterol) [63, 64].

Atherosclerosis is a multifactorial disease, and its pathogenesis is complex. One of the many triggers of atherosclerotic lesions is endothelial dysfunction [65]. One of the main mediators of this process is nitric oxide (NO), which under normal conditions has an antioxidant and anti-inflammatory effect on blood vessels, and also contributes to their diastole [66]. Flavonoids not only inactivate NO and its derivatives but also inhibit the inflammatory response in atherosclerotic altered blood vessels by inhibiting the entry of leukocytes into the focus of inflammation [67].

The onset of diabetes is associated with decreased insulin production and secretion or the cells' insensitivity to the hormone, leading to elevated blood glucose levels. Experimental studies have shown that some flavonoids are associated with antidiabetic effects. *In vitro* studies have shown that epicatechin compounds can stimulate insulin synthesis, increase cAMP levels in pancreatic β cells and stimulate the secretion of this hormone. In addition, the conversion of proinsulin to insulin becomes more intense, increasing blood insulin levels. Flavonoids (quercetin in particular) have also been found to prevent cataracts in diabetics [68].

The main cause of this condition is the accumulation of sorbitol in the eye, whose synthesis is catalysed by aldol reductase [69].

Fruits and vegetables contain large amounts of flavonoids, which are used as chemopreventive agents, such as quercetin and aflavone, found in fruits and vegetables, especially onions and apples. Quercetin is used in the treatment of prostate, lung, stomach, and breast cancer [70]. Many biological properties of flavonoids and isoflavonoids have been shown to prevent cancer. Molecular biological mechanisms of action of flavonoids include cell cycle arrest, inhibition of heat shock proteins, inhibition of tyrosine kinases, increase in p53 protein levels, estrogen receptor binding capacity, inhibition of Ras protein, and Ras protein expression. Most genetic disorders in human cancers are based on the presence of abnormal p53 protein. This protein can be regulated by flavonoids. Flavonoid-mediated expression of the p53 protein can restrict cancer cell division in the G2 and migration phases of the cell cycle. Tyrosine kinase is considered a growth factor that transmits signals to the cell nucleus. The expression of this protein is involved in carcinogenesis. Anticancer drugs can inhibit tyrosine kinase activity. Quercetin has been used in human phase I clinical trials against tyrosine kinase activity. The results showed that it can be considered a relatively safe anticancer agent [71]. It inhibits the cell cycle of proliferating lymphoid cells. Flavonoids inhibit heat shock proteins in malignant cancer cells such as leukemia, colorectal cancer, and breast cancer [72].

In 1967–1991 in Finland, a clinical trial involving 9959 men and women for 24 years was conducted. This study showed an inverse relationship between flavonoid intake and lung cancer [73]. Of the data available in the study, some observations showed that lung cancer was reduced by 50% in the highest

quartile of flavonoid intake. Flavonoids prevent cancer and are also effective in treating it. In addition, they can induce cell cycle arrest in the G1/S and G2/M phases, as well as in the G1/S and G2/M phases, and repair DNA damage caused by chemicals with oxidative potential.

Flavonoids and isoflavonoids have high anti-proliferative properties, and the compounds in them are useful for cell cycle inhibition and apoptosis induction. In cell lines, they have been shown to be effective in arresting G1/S and G2/M cell cycles. For example, quercetin (30-100 mM), as demonstrated in several studies, had the ability to arrest the cell cycle of human colon COLO320 and leukaemia T cells in G1/S and induce apoptosis [74].

CONCLUSIONS

In this article, we have taken a closer look at three groups of natural compounds with potential anti-cancer effects – polyphenols, brassinosteroids, and flavonoids. We focused on these compounds because they have been shown to have anti-proliferative properties. They exhibit various mechanisms of action, ranging from cytotoxicity, induction of apoptosis, antioxidant activity, and inhibition of cancer cell growth. Additional advantages are their low toxicity to healthy cells in the body, their high availability, and the relatively uncomplicated process of obtaining them. Another positive aspect of natural compounds, compared to traditional chemotherapeutics, is that they are more environmentally friendly and less toxic to the environment [75].

Therefore, natural compounds have the potential to aid in the development of safer anti-cancer drugs. However, further research is needed, especially given that most of the work has been conducted *in vivo* and only a few have reached the clinical trial stage. This is a huge potential that should be investigated in the future.

Ethical approval: The conducted research is not related to either human or animal use.

Conflict of interest: Author declares no conflict of interest.

REFERENCES

1. Malvezzi M, Santucci C, Boffetta P, et al. European cancer mortality predictions for the year 2023 with focus on lung cancer [published online ahead of print 2023 Jan 27]. Ann Oncol 2023; S0923-7534(23)00048-0. https://dx.doi.org/10.1016/j.annonc.2023.01.010

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics 2023. CA Cancer J Clin 2023; 73(1):17-48. https://dx.doi.org/10.3322/caac.21763

3. Tsimberidou AM, Fountzilas E, Nikanjam M, Kurzrock R. Review of precision cancer medicine: Evolution of the treatment paradigm. Cancer Treat Rev 2020; 86:102019. https://dx.doi.org/10.1016/j.ctrv.2020.102019

4. Zraik IM, Heß-Busch Y. Management of chemotherapy side effects and their long-term sequelae. Urologe A 2021; 60(7):862-871. https://dx.doi.org/10.1007/s00120-021-01569-7

5. Mangal M, Sagar P, Singh H, Raghava GP, Agarwal SM. NPACT: Naturally occurring plant-based anti-cancer compound-activity-target database. Nucleic Acids Res 2013; 41(Database issue): D1124-D1129 https://dx.doi.org/10.1093/nar/gks1047

6. Vinson JA, Su X, Zubik L, Bose P. Phenol antioxidant quantity and quality in foods: fruits. J Agric Food Chem 2001; 49(11):5315-5321. https://dx.doi.org/10.1021/jf0009293

7. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000; 130(8S Suppl): 2073S-85S. https://dx.doi.org/10.1093/jn/130.8.2073S

8. Li J, Zhong X, Zhao Y, Shen J, Pilapong C, Xiao Z. Polyphenols as lung cancer chemopreventive agents by targeting microRNAs. Molecules 2022; 27(18):5903. Published 2022 Sep 11. https://dx.doi.org/10.3390/molecules27185903

9. Li F, Li S, Li HB, Deng GF, Ling WH, Xu XR. Antiproliferative activities of tea and herbal infusions. Food Funct 2013; 4(4):530-538. https://dx.doi.org/10.1039/c2fo30252g

10. Cazarin CB , Kelly Jda Silva , Colomeu TC et al. Intake of *Passiflora edulis* leaf extract improves antioxidant and anti-inflammatory status in rats with 2,4,6-trinitrobenzenesulphonic acid induced colitis. Journal of Functional Foods 2015; 575–586. https://dx.doi.org/10.1016/j.jff.2013.04.016

11. Luca SV, Macovei I, Bujor A, et al. Bioactivity of dietary polyphenols: The role of metabolites. Crit Rev Food Sci Nutr 2020; 60(4):626-659. https://dx.doi.org/10.1080/10408398.2018.1546669

12. Kim Y, Keogh JB, Clifton PM. Polyphenols and glycemic control nutrients 2016; 8(1):17. Published 2016 Jan 5. https://dx.doi.org/10.3390/nu8010017

13. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients 2018; 10(11):1618. Published 2018 Nov 2. https://dx.doi.org/10.3390/nu10111618

14. Tomás-Barberán FA, Selma MV, Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health. Curr Opin Clin Nutr Metab Care 2016; 19(6):471-476. https://dx.doi.org/10.1097/MCO.0000000000000314

15. Di Lorenzo C, Colombo F, Biella S, Stockley C, Restani P. Polyphenols and human health: the role of bioavailability. Nutrients 2021;13(1):273. Published 2021 Jan 19. https://dx.doi.org/10.3390/nu13010273

16. Hu Z, Li M, Cao Y, Akan OD, Guo T, Luo F. Targeting AMPK signaling by dietary polyphenols in cancer prevention. Mol Nutr Food Res 2022;66(2):e2100732. https://dx.doi.org/10.1002/mnfr.202100732

17. Kolb R, Sutterwala FS, Zhang W. Obesity and cancer: inflammation bridges the two. Curr Opin Pharmacol 2016; 29:77-89. https://dx.doi.org/10.1016/j.coph.2016.07.005

18. Cao Y, Han S, Lu H, et al. Targeting mTOR signaling by dietary polyphenols in obesity prevention. Nutrients 2022; 14(23):5171. Published 2022 Dec 5. https://dx.doi.org/10.3390/nu14235171

19. Wang J, Tang L, Zhou H, et al. Long-term treatment with green tea polyphenols modifies the gut microbiome of female sprague-dawley rats. J Nutr Biochem 2018; 56:55-64. https://dx.doi.org/10.1016/j.jnutbio.2018.01.005

20. Lin L, Liu Y, Li H, et al. Targeting colon cancer stem cells using a new curcumin analogue, GO-Y030. Br J Cancer 2011; 105(2):212-220. https://dx.doi.org/10.1038/bjc.2011.200

21. Harper CE, Patel BB, Wang J, Arabshahi A, Eltoum IA, Lamartiniere CA. Resveratrol suppresses prostate cancer progression in transgenic mice. Carcinogenesis 2007; 28(9):1946-1953. https://dx.doi.org/10.1093/carcin/bgm144

22. Izquierdo-Torres E, Hernández-Oliveras A, Meneses-Morales I, Rodríguez G, Fuentes-García G, Zarain-Herzberg Á. Resveratrol up-regulates ATP2A3 gene expression in breast cancer cell lines through epigenetic mechanisms. Int J Biochem Cell Biol 2019; 113:37-47. https://dx.doi.org/10.1016/j.biocel.2019.05.020

23. Gao Y, Tollefsbol TO. Combinational proanthocyanidins and resveratrol synergistically inhibit human breastcancer cells and impact epigenetic-mediating machinery. Int J Mol Sci 2018; 19(8):2204. Published 2018 Jul 27. https://dx.doi.org/10.3390/ijms19082204

24. Donovan MG, Selmin OI, Doetschman TC, Romagnolo DF. Epigenetic activation of BRCA1 by genistein *in vivo* and triple negative breast cancer cells linked to antagonism toward aryl hydrocarbon receptor. Nutrients 2019; 11(11):2559. Published 2019 Oct 23. https://dx.doi.org/10.3390/nu11112559

25. Papoutsis AJ, Selmin OI, Borg JL, Romagnolo DF. Gestational exposure to the AhR agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induces BRCA-1 promoter hypermethylation and reduces BRCA-1 expression in mammary tissue of rat offspring: preventive effects of resveratrol. Mol Carcinog 2015; 54(4):261-269. https://dx.doi.org/10.1002/mc.22095

26. Shankar S, Nall D, Tang SN, et al. Resveratrol inhibits pancreatic cancer stem cell characteristics in human and KrasG12D transgenic mice by inhibiting pluripotency maintaining factors and epithelial-mesenchymal transition. PLoS One 2011; 6(1):e16530. Published 2011 Jan 31. https://dx.doi.org/10.1371/journal.pone.0016530

27. Haubrick LL, Assmann SM. Brassinosteroids and plant function: some clues, more puzzles. Plant Cell Environ 2006; 29(3):446-457. https://dx.doi.org/10.1111/j.1365-3040.2005.01481.x

28. Clouse SD. Brassinosteroids. Arabidopsis Book 2011; 9:e0151. https://dx.doi.org/10.1199/tab.0151

29. Nolan TM, Vukašinović N, Liu D, Russinova E, Yin Y. Brassinosteroids: multidimensional regulators of plant growth, development, and stress responses. Plant Cell 2020; 32(2):295-318. https://dx.doi.org/10.1105/tpc.19.00335

30. Bajguz, A. Brassinosteroids – occurence and chemical structures in plants. In: Brassinosteroids: A Class of Plant Hormone 2011; 1-27. https://dx.doi.org/10.1007/978-94-007-0189-2_1

31. Oklestkova, J., Rárová, L., Kvasnica, M. et al. Brassinosteroids: synthesis and biological activities. Phytochem Rev 2015; 14, 1053–1072. https://dx.doi.org/10.1007/s11101-015-9446-9

32. Kim TW, Wang ZY. Brassinosteroid signal transduction from receptor kinases to transcription factors. Annu Rev Plant Biol 2010; 61:681-704. https://dx.doi.org/10.1146/annurev.arplant.043008.092057

33. Rárová L, Zahler S, Liebl J, et al. Brassinosteroids inhibit *in vitro* angiogenesis in human endothelial cells. Steroids 2012; 77(13):1502-1509. https://dx.doi.org/10.1016/j.steroids.2012.08.011

34. Wachsman, M.B. et al. Antiherpetic mode of action of (22S,23S)-3*β*-bromo-5α,22,23-trihydroxystigmastan-6-one *in vitro*. Int. J. Antimicrob. Agents 2004; 23(5):524-526. https://dx.doi.org//10.1016/j.ijantimicag.2003.10.002

35. Wachsman MB, López EM, Ramirez JA, Galagovsky LR, Coto CE. Antiviral effect of brassinosteroids against herpes virus and arenaviruses. Antivir Chem Chemother 2000; 11(1):71-77. https://dx.doi.org/10.1177/095632020001100107

36. Adaucto Bellarmino Pereira-Netto. Brassinosteroids: practical applications in agriculture and human health, Bentham Science Publishers 2012. https://dx.doi.org/10.2174/97816080529811120101

37. Moghadasian MH. Pharmacological properties of plant sterols *in vivo* and *in vitro* observations. Life Sci 2000; 67(6):605-615. https://dx.doi.org/10.1016/s0024-3205(00)00665-2

38. Bajguz A, Bajguz A, Tryniszewska E. Recent advances in medicinal applications of brassinosteroids, a group of plant hormones. Stud Nat Chem 2013. https://dx.doi.org/10.1016/B978-0-444-59603-1.00002-3

39. Esposito D, Komarnytsky S, Shapses S, Raskin I. Anabolic effect of plant brassinosteroid. FASEB J 2011; 25(10):3708-3719. https://dx.doi.org/10.1096/fj.11-181271

40. Swaczynova J, Sisa M, Hnilickova J, Kohout L, Strnad M. Synthesis, biological, immunological and anticancer properties of a new brassinosteroid ligand. Pol J Chem 2006; 80:629–636.

41. Malíková J, Swaczynová J, Kolár Z, Strnad M. Anticancer and antiproliferative activity of natural brassinosteroids. Phytochemistry 2008; 69(2):418-426. https://dx.doi.org/10.1016/j.phytochem.2007.07.028

42. Obakan-Yerlikaya P, Arisan ED, Coker-Gurkan A, et al. Calreticulin is a fine tuning molecule in epibrassinolide-induced apoptosis through activating endoplasmic reticulum stress in colon cancer cells. Mol Carcinog 2017; 56(6):1603-1619. https://dx.doi.org/10.1002/mc.22616

43. Chen A. PARP inhibitors: its role in treatment of cancer. Chin J Cancer 2011; 30(7):463-471. https://dx.doi.org/10.5732/cjc.011.10111

44. Myatt, Stephen S. and Eric Wing-Fai Lam. "The emerging roles of forkhead box (Fox) proteins in cancer." Nat Revi Canc 2007: 847-859. https://dx.doi.org/10.1038/nrc2223

45. Coskun D, Obakan P, Arisan ED, Çoker-Gürkan A, Palavan-Ünsal N. Epibrassinolide alters PI3K/MAPK signaling axis *via* activating Foxo3a-induced mitochondria-mediated apoptosis in colon cancer cells. Exp Cell Res 2015; 338(1):10-21. https://dx.doi.org/10.1016/j.yexcr.2015.08.015

46. Wu YD, Lou YJ. Brassinolide, a plant sterol from pollen of *Brassica napus* L., induces apoptosis in human prostate cancer PC-3 cells. Pharmazie 2007; 62(5):392-395.

47. Arisan ED et al. CDK inhibitors induce mitochondria-mediated apoptosis through the activation of polyamine catabolic pathway in LNCaP, DU145 and PC3 prostate cancer

cells. Curr Pharm Des 2014; 20(2):180-188. https://dx.doi.org/10.2174/13816128113199990029

48. Steigerová J, Rárová L, Oklešťková J, et al. Mechanisms of natural brassinosteroid-induced apoptosis of prostate cancer cells. Food Chem Toxicol 2012; 50(11):4068-4076. https://dx.doi.org/10.1016/j.fct.2012.08.031

49. Obakan P et al.. Activation of polyamine catabolic enzymes involved in diverse responses against epibrassinolide-induced apoptosis in LNCaP and DU145 prostate cancer cell lines. Amino Acids 2014; 46(3):553-564. https://dx.doi.org/10.1007/s00726-013-1574-1

50. Huskova Z, Steigerova J, Oklestkova J, Rarova L, Kolar Z, Strnad M. Molecular mechanisms of plant steroids and study of their interaction with nuclear receptors in prostate cancer cells. Food Chem Toxicol 2020; 137:111164. https://dx.doi.org/10.1016/j.fct.2020.111164

51. Sadava D, Kane SE. The effect of brassinolide, a plant steroid hormone, on drug resistant small-cell lung carcinoma cells. Biochem Biophys Res Commun 2017; 493(1):783-787. https://dx.doi.org/10.1016/j.bbrc.2017.08.094

52. Kisselev PA, Panibrat OV, Sysa AR, Anisovich MV, Zhabinskii VN, Khripach VA. Flow-cytometric analysis of reactive oxygen species in cancer cells under treatment with brassinosteroids. Steroids 2017; 117:11-15. https://dx.doi.org/10.1016/j.steroids.2016.06.010

53. Obakan Yerlikaya P, Nahmadova S. Epibrassinolide triggers apoptotic cell death in SK-N-AS neuroblastoma cells by targeting GSK3β in a ROS Generation-Dependent Way. Eur J Biol 2022; 81(2): 240-250. https://dx.doi.org/10.26650/EurJBiol.2022.1191701

54. Nabavi SM, Šamec D, Tomczyk M, et al. Flavonoid biosynthetic pathways in plants: Versatile targets for metabolic engineering. Biotechnol Adv 2020; 38:107316. https://dx.doi.org/10.1016/j.biotechadv.2018.11.005

55. Scarano A, Chieppa M, Santino A. Looking at flavonoid biodiversity in horticultural crops: A colored mine with nutritional benefits. Plants (Basel) 2018; 7(4):98. Published 2018 Nov 7. https://dx.doi.org/10.3390/plants7040098

56. Braicu C, Ladomery MR, Chedea VS, Irimie A, Berindan-Neagoe I. The relationship between the structure and biological actions of green tea catechins. Food Chem 2013;141(3):3282-3289. https://dx.doi.org/10.1016/j.foodchem.2013.05.122

57. Arts IC, van De Putte B, Hollman PC. Catechin contents of foods commonly consumed in The Netherlands. 2. Tea, wine, fruit juices, and chocolate milk. J Agric Food Chem 2000; 48(5):1752-1757. https://dx.doi.org/10.1021/jf000026+

58. Fattorusso E, Iorizzi M, Lanzotti V, Taglialatela-Scafati O. Chemical composition of shallot (*Allium ascalonicum* Hort.). J Agric Food Chem 2002; 50(20):5686-5690. https://dx.doi.org/10.1021/jf020396t

59. Rodríguez-García C, Sánchez-Quesada C, J Gaforio J. Dietary flavonoids as cancer chemopreventive agents: An updated review of human studies. Antioxidants (Basel) 2019; 8(5):137. Published 2019 May 18. https://dx.doi.org/10.3390/antiox8050137

60. Abotaleb M, Samuel SM, Varghese E, et al. Flavonoids in cancer and apoptosis. Cancers (Basel) 2018; 11(1):28. Published 2018 Dec 28. https://dx.doi.org/10.3390/cancers11010028

61. Woodman OL, Chan ECh. Vascular and antioxidant actions of flavonols and flavones. Clin Exp Pharmacol Physiol 2004; 31(11):786-790. https://dx.doi.org/10.1111/j.1440-1681.2004.04072.x

62. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. Scientific World Journal 2013; 2013:162750. Published 2013 Dec 29. https://dx.doi.org/10.1155/2013/162750

63. Woodman OL, Chan ECh. Vascular and antioxidant actions of flavonols and flavones. Clin Exp Pharmacol Physiol 2004; 31(11):786-790. https://dx.doi.org/10.1111/j.1440-1681.2004.04072.x

64. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996; 125(5):384-389. https://dx.doi.org/10.7326/0003-4819-125-5-199609010-00005

65. Valenzuela A, Sanhueza J, Nieto S. Cholesterol oxidation: health hazard and the role of antioxidants in prevention. Biol Res 2003; 36(3-4):291-302. https://dx.doi.org/10.4067/s0716-97602003000300002

66. Fuhrman B, Aviram M. Flavonoids protect LDL from oxidation and attenuate atherosclerosis. Curr Opin Lipidol 2001; 12(1):41-48. https://dx.doi.org/10.1097/00041433-200102000-00008

67. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996; 125(5):384-389. https://dx.doi.org/10.7326/0003-4819-125-5-199609010-00005

68. Sanderson J, McLauchlan WR, Williamson G. Quercetin inhibits hydrogen peroxide-induced oxidation of the rat lens. Free Radic Biol Med 1999; 26(5-6):639-645. http://dx.doi:10.1016/s0891-5849(98)00262-7

69. Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetic property. Asian Pac J Trop Biomed 2012; 2(4):320-330. https://dx.doi.org/10.1016/S2221-1691(12)60032-X

70. Brusselmans K, Vrolix R, Verhoeven G, Swinnen JV. Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. J Biol Chem 2005; 280(7):5636-5645. https://dx.doi.org/10.1074/jbc.M408177200

71. Duthie GG, Duthie SJ, Kyle JA. Plant polyphenols in cancer and heart disease: implications as nutritional antioxidants. Nutr Res Rev 2000; 13(1):79-106. https://dx.doi.org/10.1079/095442200108729016

72. Lamson DW, Brignall MS. Antioxidants and cancer, part 3: quercetin. Altern Med Rev 2000; 5(3):196-208.

73. Knekt P, Järvinen R, Seppänen R, et al. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997; 146(3):223-230. https://dx.doi.org/10.1093/oxfordjournals.aje.a009257

74. Veeramuthu D, Raja WRT, Al-Dhabi NA, Savarimuthu I. Flavonoids: Anticancer properties. IntechOpen 2017. https://dx.doi.org/10.5772/68095

75. Iqbal I, Abbasi BA, Mahmood T, et al. Plant-derived anticancer agents: A green anticancer approach. Asian Pac J Trop Biomed 2017; 1129-1150. https://dx.doi.org/10.1016/j.apjtb.2017.10.016