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REVIEW PAPER

Monika Stompor [1,2(ABFGH)], Rafał Podgórski [1,2(FG)], Tomasz Kubrak [1,2(FG)]

Combined effect of flavonoid compounds and cytostatics in cancer treatment

[1] Centre for Innovative Research in Medical and Natural Sciences,
University of Rzeszów, Poland
[2] Department of Biochemistry, Faculty of Medicine,
University of Rzeszów, Poland

ABSTRACT

Aim. The aim of the study was to review the literature on the combination of cytostatics with flavonoids as a promising way to improve the cancer therapy.

Material and methods. A review of Polish and foreign literature was performed. The following databases were searched: PubMed, Scopus, Science Direct, and Polish Medical Bibliography.

Literature analysis. Effective strategies to inhibit the progression of cancer are needed. Compounds of natural origin, including plant polyphenols, are a part of our diet. Due to their availability, and antioxidant properties, they may serve as efficacious adjuvants in cancer therapy, enhancing the effectiveness of chemotherapeutics. Epidemiological studies have shown an inverse relationship between diets rich in fruits, vegetables, and supplements, and the risk of all causes of death from cancer. Based on their diverse biological activity, flavonoids may be potential adjuvant therapeutic agents that act synergistically with cytostatics for treatment of many types of cancer. This review of the results is a summary the research on anticancer activity of flavonoids and may also raise consciousness of consumers, who will be able to compose their diet armed with the knowledge of preventive and therapeutic anticancer properties of food ingredients. There is need for further research on polyphenols of plant origin, including interactions among food components that coexist. Another important aspect is to understand how the activity of phytocompounds depends on concentration and the presence of additional factors (e.g. microflore, metal ions), which could possibly make a compound harmful, instead of having positive theraputics effect. Elucidation of the mechanisms involved in biological activity of the described phytocompounds is essential for a better understanding of their influence on an organism.

Keywords. flavonoids, anticancer drugs, co-delivery system, cytostatics

Corresponding author: Monika Stompor, e-mail: monika.stompor@gmail.com

Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

At the present time, a considerable portion of cancer diseases are attributed to lifestyle choices such as smoking. Unfortunately, in many cases prognosis for cancer patients is not optimistic and the survival period is usually no longer than a couple of years after diagnosis. The majority of tumors develop very slowly and worrying symptoms appear late. An additional difficulty in cancer therapy is the fact that cancer cells are capable of recurrence and dispersion among healthy cells, so that complete removal of a tumor by surgery is not possible. A large number of cancers are also highly resistant to pharmacotherapy. Using aggressive chemotherapy usually worsens the condition of patients, who suffer many devastating side effects. Many oncological drugs destroy cancer cells along with normal cells. For this reason there is a search for new effective therapies that would eliminate cancer cells by the process of programmed cell death and prevention of migration. Currently, there is a tendency to look for natural ingredients with interesting biological properties that would support pharmacological therapy. We still do not exactly know what role diet ingredients that are delivered with food play during therapy, especially those with confirmed antioxidant activity. Hence, there is a necessity to broaden knowledge of interactions between drugs and specific antioxidants inside cancer cells. Research indicates that a properly composed diet that contains natural antioxidants may reduce toxic effects of chemotherapy.[1]

Biologically active flavonoid compounds

Flavonoids belong to one of the most widespread groups of natural compounds in nature composed of over 7000 different chemical compounds with highly diverse chemical structures and biological properties. They are found in the leaves, flowers, fruits, seeds, roots and bark of plants. Flavonoids have been tested for inhibition of the key enzymes involved in the mitochondrial respiratory chain among other properties. Some flavonoids show inhibitory activity towards particular groups of enzymes such as: hydroxylases, oxidoreductases, DNA synthetases, RNA polymerases, phosphatases, protein phosphokinases and oxygenases. It was also shown that they have anti-inflammatory properties and may act as hormones. Flavonoid compounds are known to be scavengers of free radicals of various kinds, such as peroxide anion, peroxide radical or hydroxyl radical. They may also serve as singlet oxygen quenchers. Their capability to inhibit free radicals arises from their chemical structure. The presence of hydroxyl groups in the flavonoid ring is responsible for the ability to inhibit free radicals and prevent oxidative stress. Results of a recent study have shown that dietary flavonoids have a significant effect on complicated regulatory processes taking place in cancer cells. They may improve conditions of patients in various stages of cancer disease considerably. Many studies have been performed in order to find cytotoxic anticancer compounds in plants, especially in those that have been long-known in traditional medicine. Literature data indicates that plant-derived polyphenol compounds are promising "nutraceuticals" which combine nutritional value and pharmaceutical properties and may contribute to fighting various diseases such as diseases of the circulatory system, obesity, neurological diseases and cancers.

There is evidence that consumption of flavonoids considerably reduces the risk of certain types of cancers. A diet rich in isoflavones may lead to reduction in breast cancer occurrence in women and prostate cancer in men. The antitumor activity of flavonoids is considered to be related to interactions with the enzymes involved in neoplasia. A mechanism of flavonoid-induced blocking of DNA replication by inhibiting activity of enzymes such as DNA polymerase II and topoisomerases I and II are known. Flavonoid compounds also take part in inhibition of the cell cycle, which results in blocking proliferation and inducing apoptosis of cancer cells. Flavonoids are also capable of preventing oncogene activation by interactions with metabolic enzymes, for example, by inhibition of cytochrome P450s such as CYP1A1 and CYP1A2.[2]

Due to their pro-health properties, hop flavonoids and their synthetic derivatives have also been studied. Xanthohumol, the most important chalcone which constitutes 1% of hop-cone dry weight, has many biological properties. Apart from strong antioxidant activity, it also has antiviral, antimicrobial and anti-inflammatory properties.[3-5] Moreover, an *in vitro* study demonstrated that xanthohumol inhibits formation of new blood vessels during carcinogenesis and has antiproliferative properties against the human cancer cell lines: breast (MCF-6, MCF-7, T47-D), colon (HT-29), ovarian (A-2780) and prostate.[6-10]

Research over the last few years revealed that naringenin, which is a precursor of most flavonoids, may control fat tissue accumulation by induction of apoptosis in fat cells (adipocytes), inhibition of their formation (adipogenesis) and by increasing lipolysis.[11] There is also great interest in isoxanthohumol and 8-prenylnaringenin, compounds in hop cones 10 to 100 times lower in concentration than xanthohumol, as evidenced by a large number of scientific papers.[12] 8-Prenylnaringenin, a potential anticancer drug, demonstrates strong *in vitro* affinity for the estrogen receptor ERα found mainly in the mammary gland, the endometrium and the ovary. The binding affinity of 8-Prenylnaringenin is stronger than for coumestrol and genistein which are considered the most active flavonoids known.[13]

In addition to being promising agents in cancer therapy, flavonoid compounds may be used for prevention and treatment of anemia and circulatory disorders, in dermatology for treatment of atopic dermatitis, and as

anti-inflammatory agents. They may also prevent infections and the skin ageing process.[14] Moreover, recent research showed that naringenin may be used as an analgesic agent.[15] In lipopolysaccharide-activated mouse macrophages it efficiently inhibited expression of TNF-α gene, nitric oxide synthase, cyclooxygenase (COX-2) inhibiting release of inflammatory mediators (TNF-α, nitric oxide and prostaglandins).[16]

Additionally, flavonoids have a positive effect on the peripheral and central nervous systems by improving blood flow to the brain. This helps in formation of new blood vessels and growth of hippocampal neurons, which improves memory. Such properties help to maintain brain cognitive skills which may be important, for example, in Alzheimer's disease therapy. In research on hippocampus cells, naringenin (present in citrus fruits and tomatoes) was found to promote neurogenesis and to stimulate growth of damaged neurons.[17] Although plants have been used for a long time for therapy of various diseases, it is important to know the activity of individual compounds that they contain. According to research by Kuete et al., naringenin isolated from *Aframomum arundinaceum* was more toxic to drug resistant cancer cells than the plant extract itself.[18]

Bonina et al. provided evidence that quercetin, hesperetin and naringenin protect *in vitro* skin cells against UV radiation.[19] The mechanism proposed involved inhibition of peroxidation of phosphatidylcholine in liposome membranes and decreased production of malondialdehyde (MDA). The flavonoids decreased the amount of MDA, in direct proportion to concentrations used. Their activity can be ranked as follows: quercetin > hesperetin > naringenin. However, due to better absorption and the ability to penetrate into deeper skin layers, naringenin and hesperetin were the most profitable as active ingredients of protective preparations and cosmetics.[20] Plant polyphenols, due to their immunomodulatory properties and the ability to scavenge oxygen free radicals, may contribute to acceleration of wound healing. Recently, research has indicated that isoflavones and their derivatives may also be used in prevention of thyroid and lung cancers.[21] Isoprenylated flavonoid compounds may act as inhibitors of protein kinases, taking part in initiation of inflammation or cancer diseases. Studies carried out by Nishimura et al. demonstrated that prenylated flavonoids from hop (*Humulus lupulus* L.), namely xanthohumol and its derivatives, induced cancer cell apoptosis in the neuroblastoma cells IMR-32 and NB-39.[22] Prenyl, geranyl, furan and pyran derivatives of baicalein and 3,7-dihydroxyflavone obtained by chemical synthesis were tested for pro-apoptotic activity towards breast and lung cancer cell lines.[23] A remarkable inhibition of tumor cell growth was observed for derivatives containing a single geranyl group and also for the compounds with furan and pyran fused rings. Hisanaga et al. demonstrated that 8-prenylquercetin has stronger anti-inflammatory activity than its derivatives that lack a prenyl chain.[24] Substitution of the prenyl group increases the hydrophobicity of flavonoids and may modulate their absorption and excretion from the body.[25] This finding suggests that 8-prenylnaringenin reduces the rate of excretion of naringenin from blood, allowing for circulation in the blood stream for much longer periods than non-prenylated naringenin, so higher accumulation to target tissue may be achieved.

Combined action of flavonoids and cytostatics

Chemotherapy is a systemic method of cancer treatment with the use of cytostatics. Combination therapy (or polytherapy) involves using two or more anticancer drugs, which administered together are more effective.[26-27] In this form of treatment, flavonoids, which are contained in food, seem to be very promising. Numerous studies have confirmed the synergistic effect of natural polyphenols and cytostatics on the programmed cell death induction in cancer cells. They may increase susceptibility of cancer cells to subsequent lines of attack in chemotherapy.

Polyphenols may selectively enhance the activity of some cytostatics against tumor cells, and at the same time, exert a cytoprotective effect on normal tissues. The most often described mechanism of flavonoid anticancer activity is their ability to inhibit proliferation and induce programmed cell death in cancer cells. At the molecular level, this activity is related to inhibition of intramolecular signal transduction pathways necessary for cell survival such as the Ras/Raf/MEK/ERK, PI3K/Akt/mTOR, Ras/Ras protein, Raf/Raf kinase, MEK/mitogen activated protein kinase, ERK/extracellular signal regulated kinase, PI3K/phosphoinositide 3-kinase, Akt/PKB/protein kinase B, and mTOR/mammalian target of rapamycin kinase.

Paclitaxel, known also as Taxol, isolated from the bark of the Pacific yew (*Taxus brevifolia*) is widely used in treatment of breast, ovarian and lung cancers. Moreover, the combination of paclitaxel and cisplatin is an effective second-line therapy for patients with metastatic breast cancer. Paclitaxel analogues, such as docetaxel and cabazitaxel, are also used as anticancer drugs (for treatment of aggressive breast and prostate cancers). A recent study confirmed that prenylated compounds derived from hop (*Humulus lupulus L.*), such as isoxanthohumol, enhance *in vivo* activity of paclitaxel.[28] According to the literature, naringenin also enhances the sensitivities of cancer cells to doxorubicin both *in vitro* and *in vivo*.[29]

In another study, central nervous system cancer cells were used as an experimental model. This group of cancers is difficult to treat. The complex anatomical and histological structure of the central nervous system is the reason why complete removal of the cancer-affected tissue is often impossible. These types of cancer are also highly resistant to pharmacotherapy. Additional difficulty in the therapy is the necessity to protect neu-

rons from damage. It is a known fact that nerve cells are very sensitive to oxidative stress. Having high antioxidant activity, flavonoids may play an important role in preventing neuronal death during anticancer therapy. Therefore, the study on employment of flavonoids in combination therapy of the central nervous system cancers were preceded by the assessment of their impact on normal nerve cell survival.

Glioblastomas are brain cancers that arise from astrocytes in the glial tissue. One of the most malignant is an anaplastic astrocytoma (AA) (lat. astrocytoma anaplasticum, WHO grade III) and glioblastoma multiforme (GBM) (lat. glioblastoma multiforme, WHO grade IV). They represent about 50% of all brain tumors. Unfortunately, prognoses for patients with these diseases are not optimistic and the life expectancy from the time of diagnosis is about a year for GBM and 3-5 years for AA. Gliomas develop slowly and the symptoms appear late. An additional difficulty in therapy of gliomas is the ability of cancer cells to migrate and disperse through the normal brain cells, so it is impossible to completely remove cancer tissue. They are also resistant to pharmacotherapy. The drug frequently used for treatment of glioblastomas is temozolomide (Temodal®, TMZ). This is an alkylating agent and its anticancer activity is based on formation of O^6-methylguanine in the DNA strand, which mispairs with thymine instead of cytosine during the next DNA replication cycle. This leads to prolonged G2-M arrest in glioma cells and ultimately cell death. An *in vitro* study revealed that using quercetin in combination with temozolomide enhances the therapeutic effect of this drug. Among others, stronger inhibition of cancer cells growth was observed, along with higher level of caspase-3, an important marker of apoptosis, compared to temozolomide alone.

Another promising example of using quercetin in combination chemotherapy was a study carried out with MOGGCCM astrocytoma cells. Preincubation of the glioblastoma cell line with this flavonoid increased sensitivity of the cells to induction of programmed cell death by means of Temodal. Interestingly, the type of programmed cell death induced by these two compounds was dependent on quercetin concentration. Incubation of the astrocytoma cells with Temodal and this flavonoid at the concentration of 1-5 μM effectively inhibited autophagy, whereas higher concentrations of the natural compound (about 30 μM) induced apoptosis.[30]

Another compound used in anticancer therapy, which is acts synergistically with quercetin in apoptosis induction, is doxorubicin, belonging to anthracyclines. In doxorubicin-resistant human pancreatic carcinoma cell lines EPP85-181 this flavonoid inhibited expression of P-glycoproteins, which are responsible for multi-drug resistance. In consequence, the tested cell line became more sensitive to the antibiotic-induced apoptosis. An additional advantage of this therapy is the ability of quercetin to protect normal cells from death, which was often observed in the case of treatment with daunorubicin alone.[31] Moreover, this flavonoid acted synergistically with doxorubicin, another anthracycline antibiotic, as inhibitor of breast cancer cells proliferation, and with tamoxifen as angiogenesis inhibitor in this cancer.[32] Similar results were obtained in treatment of a drug-resistant breast cancer with the help of quercetin or luteolin combined with doxorubicin (cytostatic) and tamoxifen (anti-estrogen), which led to inhibition of both proliferation and angiogenesis of the cancer cells.[33-34]

The most recent literature reports indicate that also other flavonoids are used as adjuvants in cancer therapies.[35-44] Chrysin in combination with celecoxib may help in treatment of diseases associated with COX-2 cyclooxygenases inhibition.[45-46] Whereas, naringenin administered with ABT-737, a drug being Bcl-2 protein inhibitor, enhanced its cytotoxic effect to gastric cancer cells.[35]

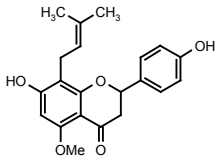
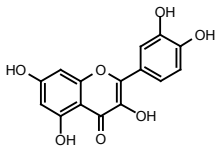
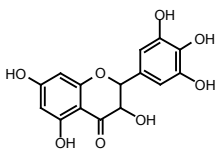
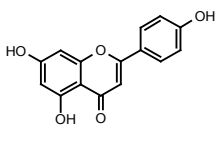
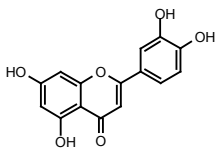
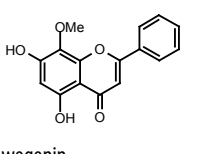
Similar research showed that quercetin also enhanced proapoptotic and pro-autophagic properties of the anticancer agent sorafenib (Nexavar) used in treatment of kidney cancer.[47] The molecular mechanism of this drug is based on inhibition of Raf serine/threonine kinase which plays a key role in the intracellular Ras/Raf/MEK/ERK signal transduction pathway, which in consequence leads to inhibition of cell proliferation. Combination of sorafenib and quercetin significantly increased sensitivity of MOGGCCM cells to induced apoptosis mediated by the mitochondrial pathway.

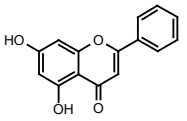
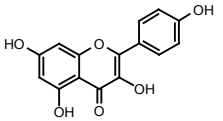
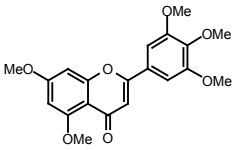
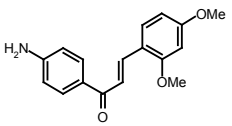
The combination of chrysin with cytostatics is more effective in induction of programmed cell death than using single chemotherapeutics. For the majority of tested cancer cells, changes in the mechanisms regulating cell cycle progression were observed. Mutual action of anticancer drugs and other flavonoids, such as combination of temozolomide and quercetin, significantly increased apoptosis of human glioblastoma cells induced by temozolomide, the anticancer drug used in treatment of brain cancers. Moreover, quercetin administered at the proper concentration considerably increased the chemosensitivity of breast and liver cancer cells to doxorubicin, and therefore enhanced the response of tumors to chemotherapy.[48] Luteolin and silibinin in combination of 20 μM and 50 μM, respectively were more effective than temozolomide (100 μM), the commonly used chemotherapy for glioblastoma.[49] Flavonoid compounds that have been used in combination therapy with cytostatics are listed in Table 1.

Summary

Clinical use of anticancer drugs is limited due to their dose-dependent side effects. Food intervention with the use of plants containing a proper composition of bioactive compounds may be a safe and effective way to pre-

Table 1. Combined effect of flavonoids and cytostatics in cancer therapy

Flavonoid compound	Anticancer drug	Biological model	Type of experiment	Ref.
		Flavanones		
 isoxanthohumol	paclitaxel	rats	in vivo	Krajnović et al. 2016
 quercetin	tamoxifen	rats breast cancer therapy	in vivo	Silva et al. 2017
	adriamycin	mice after P388 cell inoculation	in vivo	Han et al. 2014
			in vitro	Han et al. 2015
	doxorubicin	SMMMC7721 liver cancer cell	in vitro	Wang et al. 2012
		MCF-7 MDA-MB-231 MCF-10A	in vitro	Staedler et al. 2011
	daunorubicin	EPP85-181P EPP85-181DB human pancreatic carcinoma	in vitro	Borska et al. 210
	cisplatin	HeLa human cervix carcinoma	in vitro	Jakubowicz-Gil et al. 2005
	sorafenib	T98G MOGGCCM Human anaplastic astrocytoma and glioblastoma multiforme	in vitro	Jakubowicz-Gil et al. 2014
 dihydromyricitein	paclitaxel doxorubicin	A2780 SKOV3 IOSE80 ovarian carcinoma	in vitro	Xu et al. 2017
	nedaplatin	SMMC7721 QGY7701 HL7702 human hepatocellular	in vitro	Jiang et al. 2015
		Flavones		
 apigenin	cisplatin	PC3 prostate cancer	in vitro	Erdogan et al. 2017
	paclitaxel	HeLa cells	in vitro	Xu et al. 2011
 luteolin	tamoxifen	MCF-7, BT-483, BT-474; ER– cells: MDA-MB-231 human breast cancer	in vitro	Tu et al. 2013
	cisplatin	Mice (male C57BL)	in vivo	Kang et al. 2011
	doxorubicin	MCF-7 MDA-MB-453	in vitro	Sato et al. 2015
 wogonin	cisplatin	AMCHN2, -HN3, -HN4, -HN5, and -HN9, and SNU-1041, -1066, and -1076 human head and neck cancer	in vitro	Kim et al. 2016
		A549 lung cancer		He et al. 2012

 chrysin	doxorubicin	BEL-7402 hepatocellular carcinoma	in vitro	Gao et al. 2013
 kamferol	cisplatin	OVCAR-3 ovarian cancer	in vitro	Luo et al. 2010
 3',4',5',5,7-pentamethoxyflavone	cisplatin	A549 lung cancer	in vitro	Hou et al. 2015
Chalcones				
	cisplatin	ES-2 Hey-A8 human ovarian cancer	in vitro	Su et al. 2017

vent life-style diseases, including cancers. *In vitro* studies may contribute to a better understanding the role of antioxidants in chemotherapy, because at the moment, the effects of antioxidant supplementation are still unclear. Not only do antioxidants directly participate in free-radical reactions, but also have influence on the activity of many enzymes and expression of genes participating in apoptosis and DNA repair. Due to synergistic action, it could be possible to decrease drug dose, while providing the same therapeutic effect. Additionally, there is a possibility of reducing harmful side effects of chemotherapeutics on normal cells without loss of effectiveness of the treatment, because antioxidants can stabilize DNA and contribute to strengthening the antioxidant barrier, which is highly beneficial to chemotherapy. Preclinical and clinical studies with cancer patients is a serious challenge in this area. There is a need to perform more detailed studies that would lead to the development of new, innovative molecularly targeted therapeutic approaches for cancer treatments.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflicts of interest.

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