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The influence of certain plant substances and their chemopreventive activity in ovarian cancer

Wpływ wybranych substancji roślinnych i ich chemoprewencyjne działanie w raku jajnika

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Abstract

A steadily growing number of studies have confirmed the beneficial effects of plant-derived substances (preparations) on the effectiveness of pharmacotherapy for ovarian cancer. A prior or parallel application of plant-derived substances and chemotherapy could be the way to strengthen the classic pharmacological treatment.

Our paper presents several plant-derived substances with proven antiproliferative activities, in which phenolic and flavonoid bioactive compounds dominate, with particular emphasis on ovarian cancer cells.

We are of the opinion that our paper will contribute to better understanding of the molecular basis for the positive interaction effect of concomitant application of the abovementioned plant substances with certain cytostatics. Also, this work may increase the number of preclinical in vivo experiments using these and other phenolic, flavonoid-rich plant substances to better understand their efficacy and safety and, in the future, to initiate clinical trials in this field.

Key words: **ovarian cancer** / **plant extracts** / **antiproliferative activity** /

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Streszczenie

Znaczna liczba doniesień potwierdza korzystny wpływ preparatów pochodzenia roślinnego na efektywność farmakoterapii raka jajnika. Obiecujące wydaje się być stosowanie preparatów roślinnych przed rozpoczęciem chemioterapii lub jako leczenie jednoczasowe.

W poniższym opracowaniu przedstawiono kilka substancji pochodzenia roślinnego o udowodnionej aktywności antyproliferacyjnej ze szczególnym uwzględnieniem ich działania na komórki raka jajnika.

Prezentowana praca pozwoli na lepsze zrozumienie molekularnych podstaw interakcji pomiędzy substancjami pochodzenia roślinnego a wybranymi cytostatykami. Ponadto może przyczynić do wzrostu liczby przedklinicznych badań in vivo dotyczących powyższych preparatów, co będzie skutkowało poznaniem wydajności i bezpieczeństwa substancji pochodzenia roślinnego w terapii onkologicznej.

Słowa kluczowe: **rak jajnika** / **ekstrakty roślinne** / **działanie antyproliferacyjne** /

Introduction

Platinum and taxane drugs, which are used in the treatment of epithelial ovarian cancer (EOC), are often associated with severe systemic toxicity and numerous side effects. Moreover, tumors acquire resistance to these drugs at various stages of therapy. Current adjuvant chemotherapy usually includes paclitaxel, and either cisplatin or carboplatin given every 3 weeks for six cycles. Also, bevacizumab is being incorporated as first-line therapy with standard-of-care chemotherapy on EOC. Regardless, the classic pharmacological treatment of ovarian cancer sometimes fails to bring the expected therapeutic effects. Therefore, it is critical to develop new, effective strategies for the management of these patients in order to determine the role of consolidation chemotherapy, development of new chemotherapeutic agents, chemoresistance modulators, as well as new approaches to the treatment.

Examples of positive interactions between flavonoids and certain cytostatics in ovarian cancer cells

Several herbs have been suggested to possess antitumor activity and they may become the main sources of anticancer drugs [1]. It is postulated that plant substances or their bioactive compounds may be administered before or parallel to conventional treatment in order to minimize side effects. Numerous studies have indicated that chemopreventive phytochemicals, especially phenolic compounds, flavonoids or anthocyanins possessing antiproliferative and antioxidant properties, can overcome problems of chemoresistance and nonspecific toxicity towards normal cells that are associated with chemotherapy [2, 3, 4, 5]. One of these studies highlighted that low concentrations of quercetin can increase the sensitivity of SKOV-3, EFO27, OVCAR-3 and A278OP ovarian cancer cells to cisplatin and paclitaxel [5]. A strong synergism was also observed between quercetin or curcumin and cisplatin and oxaliplatin in A2780 and its cisplatin-resistant form (A2780(cisR)) of human epithelial ovarian cancer cells, especially when either quercetin or curcumin was added first, and followed by platinum drugs 2h later [3, 4].

Furthermore, silybin (at concentrations of 0.1-20 μM) was revealed to exert a dose-dependent growth inhibitory effect on OVCA 433, wild type of A2780 ovarian cancer cells, and in MCF-7 doxorubicin (DOX)-resistant breast cancer cells (IC50 = 4.8-24 μM). Both, L and D diastereoisomers have been shown to effectively inhibit the growth of A2780 cells (IC50 = 14 and 20 μM, respectively). Flanonolignan exerted a dose-dependent inhibition of clonogenic efficiency of cells derived from three ovarian tumors (IC50 = 7.4, 4 and 6.4 μM, respectively). Moreover, at concentrations of 0.1 and 1 microM, it potentiated the effect of cisplatin (CDDP) (0.1-1 micrograms/ml) in inhibiting A2780 WT and CDDP-resistant cell growth. Similar results were obtained on MCF-7 DOX-resistant cells when silybin (0.1 microM) was associated with doxorubicin (0.1-10 micrograms/ml) [2].

However, another study failed to show the inhibitory effect of silybin in A2780 cells, at concentrations described previously by Scambia et al. [6]. In that experiment, silybin alone up to 10 μM was unable to produce a relevant *in vitro* growth inhibition of A2780 cells and acted much weaker than cisplatin (CDDP) (IC50 values = 0.5+/-0.14 μM). The concomitant treatment with silybin and CDDP resulted in a dose-dependent and statistically significant ($p<0.05$) increase in CDDP activity (IC50 = 0.35+/-0.07 μM for CDDP and 0.263+/-0.004 μM for silybin at concentrations of 1 and 10 μM, respectively). Furthermore, in an *in vivo* experiment, a bioavailable derivative of silybin - IdB 1016 (silipide) (1350 mg/kg) acted synergistically with cisplatin, causing potentiation of the antitumor activity and giving the tumor weight inhibition (TWI) of 90%, while IdB 1016 alone did not significantly affect tumor growth (TWI=80%). The concomitant administration of IdB 1016 (1800 mg/kg) enhanced CDDP antitumor activity, with 68% TWI. That study also demonstrated an antiangiogenic effect of IdB 1016 in an *in vivo* experimental model [6]. Recently, a synergism of action between several flavonoids from *Scutellaria barbata* and CDDP in ovarian cancer cells was also observed [7].

Our study describes several plant-derived substances with proven antiproliferative and antioxidant activity, in which phenolic, flavonoid, and anthocyanin bioactive compounds dominate, with particular emphasis on ovarian cancer cells.

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Antiproliferative and chemopreventive properties of certain plant substances and extracts

Currently, the development of adjuvant therapies offering additive or synergistic effects is attracting much attention and dietary phytochemicals could be such agents. They have the potential to increase drug efficacy by either modulating the disease process itself, or affecting specific cellular pathways known to cause resistance to standard cytotoxic agents. Over 60% of all anticancer drugs are speculated to be plant-derived [1].

Also, multidirectional mechanism of formulations based on herbal substances and a widespread acceptance of herbs and plant-derived preparations as relatively safe have been the topic of much discussion. Indeed, plant extracts and compounds isolated from plants are frequently used in cancer treatment, but these compounds are often not sufficiently selective and cause damage to normal cells and tissues, resulting in severe side effects. A plant extract is a complex mixture of different, often closely related, compounds that can act on different targets, making it an active mixture of natural origin. Owing to generally low concentration of the constituents, the toxicity is mostly low, with a high level of desired activity due to synergism between different constituents [1].

In addition, by acting as chemo-sensitizers, plant-derived products, i.e. dietary phytochemicals, may improve the therapeutic effect of drugs used in cancer treatment and reduce side effects of cytotoxic drugs by simply reducing the dose of drugs needed for the effect.

One of the most extensively studied herbal substances, examined for its chemopreventive properties in ovarian cancer and also being one of the most widely consumed beverages worldwide, is *Camellia sinensis* (common name: green tea) (*Theaceae*) [8]. About a third of its solid mass are polyphenols known as catechins, which may be responsible for anti-mutagenic and anti-carcinogenic activities of green tea. Major catechins include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) [8, 9]. Several studies have demonstrated cancer preventive properties of *C. sinsensis* extracts.

A great number of *in vitro* experiments and some *in vivo* studies have shown that *C. sinsensis* polyphenols were anti-carcinogenic through induction of apoptosis, inhibiting enzymes crucial for cancer growth (e.g. urokinase) [10]. The possible mechanism consists in the stimulation of detoxification systems, antioxidant and free-radical scavenging [10]. An *in vitro* study on ovarian cancer cell lines (SKOV-3 p53 negative cells, OVCAR-3 mutant type p53 cells, PA-1 wild type p53 cells) revealed that one of the main compounds of *Camellia sinensis*, EGCG (epigallocatechin-3-gallate) shows an inhibitory effects on cell growth. These effects were mostly time- and dose-dependent, and they were mediated by apoptosis, cell cycle arrests, and regulation of several genes expression [11].

Also, several clinical studies with *C. sinensis* infusions have been conducted. One of the cohort studies (lasting over 3 years) in 244 patients with histopathologically confirmed EOC showed that adjusted death hazard ratio for tea drinkers, compared to non-drinkers, was 0.55 (95% CI=0.34-0.90). Moreover, patients with I or II FIGO stage constituted 73% of the survivors and 4% of the deaths. These authors demonstrated that chemopreventive efficacy of green tea was higher in patients with a lower-stage cancer [12].

There was only one clinical trial which enrolled 16 patients (500 mL of tea/daily; brewed from 35 g/L leaves in water; contained 639.6 +/- 95.7 mg/L of EGCG) with advanced FIGO stage III-IV serous or endometrioid ovarian cancer after surgery. Results of the phase I trial (duration: 18 months) showed that EGCG-enriched green tea supplementation does not seem to be a promising agent for reduction of recurrence risk in ovarian cancer - in that study only 5 women were free of recurrence. However, it has been postulated that results among patients with earlier stages of carcinogenesis might be more promising [13]. Although the mechanism of action of *C. sinensis* extracts and their major bio-active metabolites have relatively well-examined, there is a clear need to conduct some epidemiological studies evaluating the effect of *C. sinensis* intake on ovarian cancer occurrence and its enhancing effect during chemotherapy in further, especially long-term, double-blinded, placebo-controlled clinical trials.

Several studies have shown that *Scutellaria barbata* (*Lamiaceae*) extracts (SBE) possess anticancer activity. *Scutellaria barbata* D. Don is one of the herbs belonging to perennial plants. In traditional Korean (known as Ban-Ji-Ryun) and Chinese (known as Huang Qin) medicine it has been used as anti-inflammatory and antitumor agent against human leiomyoma, mammalian, and ovarian cancers [14, 15]. Several studies have proven induction of apoptosis (down-regulation of the expression of Bcl-2 protein) and antiproliferative activities of the SB extract in leiomyoma cells [14, 15, 16, 17].

However, the issue whether the effect of SB results from the direct action on the cells themselves or indirectly via immune action on the environments remains to be the topic of much heated debate [14, 15, 16, 17]. For example, in myometrial and leiomyomal smooth muscle cells (SMCs), *S. barbata* water extract inhibited their proliferation through the induction of expression of SMC differentiation markers such as alpha-smooth muscle actin (alpha-SMA), calponin H1 and cyclin-dependent kinase inhibitor p27 proteins (without the involvement of cell-cycle-related gene products from the G1 phase; cyclin E and cdk2 proteins) [14, 15]. Powell et al., revealed a cytotoxic activity of an aqueous extract of *Scutellaria barbatae* herb (HSB) to eleven of actively proliferating ovarian lines (A2780 Parent, A2780 CP70 (cisplatin-resistant of A2780), A2780 V (vector control transfected cell line), A2780 MP53 (stably transfected cell line expressing dominant negative p53 protein), SKOV3, HA8, HEY, HEY-C2, OVCAR-3, CAOV3 and OCC). The dilution of HSB that resulted in 50% reduction of the OD540 in the cell viability assay (ID50) for these cell lines spanned between 1:455 – 1:73, respectively. The mechanism determining sensitivity to killing by HSB was probably p53 mutation-independent and the inhibition of cell proliferation was especially evident in the G1 phase of the cell cycle. Although the cytotoxic activity was in this case maintained in the aqueous solution only, these authors hypothesized that many fractions may be responsible for this activity and may act in a synergistic or additive fashion [18]. Further studies demonstrated that inhibition of growth and invasiveness of cancer cells during the aqueous extract of *S. barbata* (SB) treatment may occur via inhibition of phosphorylated IkBa which decreased NFkB activation and subsequently suppressed NFkB activated metastasis-promoting proteins [1], for the active constituents in

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SB are mainly alkaloids and flavonoids such as baicalein, baicalin, wogonin, and oroxylin A [19]. In an experiment performed by Kavandi et al., dose-dependent cell growth inhibition was observed following higher doses in all studied cell lines (growing normal and malignant ovarian cells (HOSE 642, OVCA 420, and OVCA 429) which were cultured continuously in the absence or presence of different concentrations of SB (1.5 – 500 mg/mL)). In OVCA 420 and OVCA429 cancer cells, the IC50 values for SB were 45.73 and 56.44mg/mL, respectively. Immortalized ovarian epithelial cells (HOSE 642) were less sensitive to these treatments (IC50 = 247.73 mg/mL; duration of experiment = 120 h) [1]. Recent studies have indicated synergistic effects of several flavonoids from *Scutellaria barbata* with CDDP in ovarian cancer cells. However, some authors postulate that such interaction did not directly correlate with their redox properties, but could be associated with the positions of hydroxyl group and methoxy group of flavonoids [7].

Another plant evaluated for cytotoxic activity against cancer cell lines was *Plantago major* (*Plantaginaceae*). *Plantago* spp. leaf infusion is widely used to wash wounds and treat skin infections. Although the key bioactive compound, believed to be responsible for the cytotoxic activity, is the major flavonoid present in *Plantago* species - a luteolin-7-O-beta-glucoside, the exact mechanism of action of *Plantago* spp. extracts remains to be fully elucidated. So far, results of several studies attempting to determine the cytotoxic effect of *Plantago* sp. have been published. For example, it has been observed that 1 ug/ml methanol extract (leaves and seeds) of *Plantago major* resulted in 22% decrease in OVCAR cells survival after 72h, although concentrations of 10 and 100 ug/ml did not show cytotoxic activity against cancer cell line [20].

Alpinia spp. representatives (*Zingiberaceae*) were also tested for their anticancer properties. *Alpinia purpurata* ethyl acetate leaf extract showed potential anticancer activity against PA1 ovarian cell line with IC50 value of 110.25 ug/ml, after 48h incubation. It exhibited dose-dependent decrease in cell count for all of the tested concentrations. The results of cell viability were compared with cisplatin at the same concentration and time. There was no statistical difference between plant extract and ovarian cancer drug. IC50 for cisplatin was 52.32 ug/ml and 110.25ug/ml for *A. purpurata* [21]. Furthermore, crude methanol and fractioned (hexane, chloroform, water) extracts from leaves, rhizomes, roots and pseudo stems of *Alpinia scabra* were evaluated for cytotoxicity against SKOV-3 (human ovarian carcinoma cells). Cells were administered with 1, 10, 20, 50, 75 or 100 ug/ml concentrations of methanol extract and then incubated for 24, 48 and 72h. The results have shown that the highest inhibitory effect was observed with the leaf (hexane and chloroform) and rhizome (chloroform) extracts. The chloroform extract from the leaves was fractionated in search of fraction with excellent cytotoxic properties and selectivity against SKOV-3 cell line. The results have demonstrated that there was only one fraction which had toxic activity with IC50 value of 11.12 ug/ml (72h incubation). It was fractionated to 17 sub-fractions, and only one of them exhibited very good toxic effects against cancer cell lines, with IC50 value of 10.89 ug/ml. At the same time, it was non-toxic against human lung fibroblast cells (MRC-5), IC50 >100ug/ml. It was shown that the cytotoxic effect of the obtained plant extracts and fractions, was caused by induction of cell apoptosis (characterized by apoptotic morphological changes and DNA fragmentation) [22].

Isothiocyanates (ITCs) kave been known to induce phase II enzymes related to detoxification processes of chemical carcinogens to prevent the start of carcinogenesis. They also exhibit antitumor activity at post-initiation phase, suggesting their additional role in cancer prevention. Sulforaphane is the most extensively studied isothiocyanate and it is mainly found in broccoli and other cruciferous. In a dose-dependent manner, ITCs inhibit cell viability of several cancer cells, i.e. human cervical cancer cells, human pancreatic cancer cells, human hepatocellular carcinoma cells, and human ovarian cancer cells [23]. Thus, an extract of broccolini seeds (BSE; a dichloromethane extract from seeds of *Brassica oleracea Italica* × *Alboglabra* ((*Brassicaceae*), a hybrid of broccoli and kai-lan, (Chinese broccoli), induced apoptotic, morphological and subcellular changes (cell membrane shrinkage, condensation and fragmentation of nuclear chromatin, formation of apoptotic bodies) in OVCAR-3 cells (IC50 value of BSE was 78.6 µg/ml) in a dose-dependent manner (90-120 µg/ml of extract) [24].

Evidence of chemopreventive activities of cranberries (*Vaccinium* sp. representatives), cranberry products, and isolated cranberry components mainly in *in vitro* experiments have also been investigated. Polyphenolic compounds, flavonoids, especially proanthocyanidins, anthocyanins, and flavonols have attracted major research attention in this field [25, 26, 27]. In an experiment performed by Singh et al., treatment of SKOV-3 ovarian cancer cells with isolated proanthocyanidin fractions (PACs; the so-called PAC-1 and PAC-2 fractions from the whole *Vaccinium* extract) induced classic apoptotic changes. SKOV-3 cancer cells were more sensitive to PAC-1 than to PAC-2 or other flavonoid fractions examined in the study. They acted synergistically with paraplatin in SKOV-3 cells. Moreover, pretreatment with PACs (106 microg/ml) resulted also in a significant reduction of the paraplatin IC50 value [Singh et al., 2009]. These authors hypothesized that the differences may be the result of the specific oligomers in PAC-1/2 extracts due to differences in the material source and processing vs. PAC oligomeric compositions tested by others. Also, it is known that the type of linkages in PACs strongly influences their biological activity. For example, the A-type linkage containing dimers and trimers was more cytotoxic than dimers and trimers with only B-type linkages against i.e. GLC4 lung and COLO 320 colon carcinomas [27]. It is believed that PACs may act as effective chemosensitizers by significantly reducing the dosages of chemotherapeutic agents required to achieve similar or improved efficacy [27].

Ethanol plant extracts from five plants (*Morus alba*, *Musa sapientum*, *Arnebia decumbens*, *Arnebia echioides*, *Arnebia linearifolia*), each at several concentrations of 12.5, 25, 50 and 100 ug/ml, have been used as chemosensitizers to explore the possibility of overcoming multidrug resistance phenomenon. Every extract combined with cisplatin (anticancer drug) was administered under *in vitro* conditions to A2780/cp (cisplatin resistant ovarian cancer cell line). The best synergistic and chemosensitizing effects were obtained with the highest tested concentrations of each plant extract (increase of the cytotoxic effects of cisplatin in a dose-dependent manner). It has been also estimated that IC50 values of cisplatin were about four

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times lower (when combined with these extracts). Moreover, the studied plant extracts showed an antagonistic effect on HF2 cells (normal fibroblast cell line) when combined with doxorubicin, so they potentially have chemopreventive properties on normal/healthy cells during chemotherapy [28].

Conclusions

A steadily growing number of studies have confirmed a beneficial effect of plant-derived substances (preparations) on the effectiveness of pharmacotherapy for ovarian cancer. Application of plant-derived substances before chemotherapy could be the way to strengthen the classic pharmacological treatment. Our paper presents several plant-derived substances with proven antiproliferative activities, in which phenolic and flavonoid bioactive compounds dominate, with particular emphasis on ovarian cancer cells.

We are of the opinion that our paper will contribute to better understanding of the molecular basis for the positive interaction effect of concomitant application of the abovementioned plant substances with certain cytostatics. Also, this work may increase the number of preclinical *in vivo* experiments using these and other phenolic, flavonoid-rich plant substances to better understand their efficacy and safety and, in the future, to initiate clinical trials in this field.

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