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ANTI-CANCER POTENCY OF PHYTOCHEMICALS AGAINST VARIOUS TYPES OF CANCER (REVIEW ARTICLE)

There have been several promising breakthroughs in cancer treatment during the past decades, especially by means of novel approaches like nanomedicine, targeted therapy, and immunotherapy. Despite these progresses, chemoresistance has remained the biggest challenge in achieving success in eliminating cancerous cells. Furthermore, chemotherapy usually induces a variety of side-effects in cancer treatment as it cannot tell normal cells apart from cancer cells and targets both. Therefore, phytomedicines are considered as an option not only for their use as an adjuvant therapy, but also in view of their comparatively low toxicity, diminishing adverse effects of chemotherapy in cancer patients. Natural products and their derivatives can be used as novel therapeutic interventions with improved pharmacological properties targeting tumor cells. Since, currently, natural sources supply 60% of anticancer agents (through various mechanisms of actions), the present review article aims to discuss the role of some of the most beneficial phytochemicals used in cancer treatment. Alkaloids are important biochemical compounds occurring in blooming plants with antiproliferative and anti-neoplastic properties. The anticancer activity of flavonoids is realized by multiple cancer-related pathways, such as action on cellular processes, induction of apoptosis, inhibition of angiogenesis and cytotoxicity. Experimental pharmacology has also revealed chemoprotective properties and some related mechanisms of action of tannins. The antimutagenic qualities of essential oils are responsible for their chemopreventive characteristics.

Key words: *alkaloids, essential oils, flavonoids, tannins, anti-cancer, phytochemicals.*

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ПРОТИПУХЛИННА ЕФЕКТИВНІСТЬ ФІТОХІМІЧНИХ РЕЧОВИН ПРОТИ РІЗНИХ ВИДІВ ОНКОЛОГІЧНИХ ЗАХВОРЮВАНЬ

За останні десятиліття відбулося кілька перспективних відкриттів у терапії онкологічних захворювань, особливо за допомогою нових підходів лікування, таких як наномедицина, таргетна терапія та імунотерапія. Незважаючи на ці успіхи, хіміорезистентність залишається найбільшою проблемою у досягненні успіху у знищенні пухлинних клітин. Крім того, хіміо-

терапія зазвичай викликає безліч побічних ефектів, оскільки вона не може відрізнити нормальні клітини від пухлинних клітин та націлена на обидві. Тому фітопрепарати розглядаються як варіант не тільки їх використання як ад'ювантної терапії, а й через їх порівняно низьку токсичність, що зменшує побічні ефекти хіміотерапії у онкологічних хворих. Рослинні компоненти та їхні похідні можуть бути використані як нові терапевтичні засоби з покращеними фармакологічними властивостями, що впливають на пухлинні клітини. Оскільки натепер природні джерела забезпечують 60% протипухлинних препаратів (за допомогою різних механізмів дії), метою цієї оглядової статті є обговорення ролі деяких найефективніших фітохімічних речовин, що використовуються для лікування пухлин. Алкалоїди є важливими біохімічними сполуками, що містяться в квітучих рослинах, мають антипроліферативні та протипухлинні властивості. Протипухлинна активність флавоноїдів реалізується декількома патогенетичними шляхами розвитку онкологічних захворювань, такими як дія на клітинні процеси, індукція апоптозу, інгібування ангіогенезу та цитотоксичність. Експериментальна онкофармакологія виявила хіміопротекторні властивості та деякі пов'язані з ними механізми дії дубильних речовин. Антимутагенні властивості ефірних олій зумовлюють їхні хіміопрофілактичні властивості.

Ключові слова: *алкалоїди, ефірні олії, флавоноїди, дубильні речовини, протипухлинні, фітохімічні речовини.*

According to GLOBOCAN 2020, estimates of incidence and mortality worldwide for 36 cancers in 185 countries, cancer is categorized as a leading cause of death with an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths in 2020 (Sung et al., 2021, p. 209). There have been promising developments in cancer treatments during the last decades especially by the means of novel approaches like nanomedicine, targeted therapy, and immunotherapy (Zhang & Chen, 2018, p. 1773–1781). Despite these advances, chemoresistance has remained the chief hurdle in eliminating cancerous cells (Elgendy et al., 2020, p. 155). Indeed, chemoresistance is associated with transformation of tumor cells into a more aggressive and/or metastatic type and is considered the principal reason of death in cancer patients (Vasan, Baselga, & Hyman, 2019, p. 299). Furthermore, chemotherapy commonly induces a variety of side-effects in patients as a result of nonspecific action against both normal cells and cancerous cells. Therefore, phytomedicines should be considered as an option not only for adjuvant therapy, but also in view of their comparatively low toxicity and ability to diminish adverse effects of chemotherapy in cancer patients. Natural products and their derivatives can be used as novel therapeutic interventions with improved pharmacological properties targeting tumor cells (Chowdhury et al., 2019, p. 133–148). Although natural compounds are valuable sources for developing anti-cancer agents, they possess some pharmacokinetic characteristics which restrict clinical usage of these therapeutic products, such as reduced bioavailability, distribution, water insolubility, short half-life, rapid clearance and excessive toxicity. In order to improve the therapeutic potential of natural products and overcome their restrictions, natural nanomaterials are being considered as an innovation in cancer therapy because of their unique characteristics (Douer, 2016, p. 840–847). The integration of phytochemicals into conventional cancer treatments through modern technology platforms such as "-omics" technologies (genomics, epigenomics, transcriptomics and proteomics), DNA/RNA sequencing and network pharmacology, may be a valuable approach in increasing novel cancer therapy efficacy, on one hand, and overcoming drug resistance, on the other hand (Efferth et al., 2017, p. 50284–50304). Since, currently, natural sources supply 60% of anticancer agents (through various mechanisms of actions) (Martino et al., 2018, p. 2816–2826), the present review article aims to discuss the role of some of the most beneficial phytochemicals used in cancer treatment.

Alkaloids are important biochemical compounds occurring in blooming plants with antiproliferative and anti-neoplastic properties (Mondal, Gandhi, & Bishayee, 2019, p. 172472). Vinca alkaloids (vincristine, vinblastine, vinorelbine, vindesine, and vinflunine) obtained from the plant *Catharanthus roseus* (whose anticancer properties are well-established), act via targeting microtubules, thereby inhibiting mitotic division of tumor cells, and are widely used in the treatment of hematological and lymphatic neoplasms (Martino et al., 2018, p. 2816–2826). Vincristine's high affinity to neuronal microtubules limits its use in higher doses, particularly in patients with high body surface area. Liposomal vincristine (vincristine sulfate liposome injection, VSLI) is nanoformulated vincristine with altered pharmacokinetics that makes the drug more potent with higher efficacy and safety, permitting higher dose of the drug to be prescribed (Markman, Rekechenetskiy, & Ljubimova, 2013, p. 1866–1879). The specific chemical structure of VSLI enables prolonged circulation of vincristine in blood, enhancing tumor drug exposure. The novel drug shows higher organ and bone marrow infiltration with reduced adverse events compared to vincristine. Several *in vitro* and *in vivo* investigations testify that VSLI is superior to vincristine for treating adult ALL, although the effect of the drug on complete remission duration, toxicity and overall survival still is under investigation (Ghanbari-Movahed, Kaceli, & Bishayee A, 2021, p. 480). Captothecin (CPT) is classified as an indole alkaloid, originating from the plant *Camptotheca acuminate* and possesses antileukemic and anti-tumor effects. CPT represents its cytotoxic effect by binding to the DNA-topoisomerase I (Topo I) complex, preventing DNA re-ligation which leads to a

disruption of DNA processing and subsequent apoptosis (Hertzberg, Caranfa, & Hecht, 1989, p. 4629–4638). Yen et al. (2014, p. 11591) revealed that CPT-loaded micelles dramatically suppress tumor growth, enhancing tumor elimination of urothelial carcinoma in rat populations. Lu and colleagues (2020, p. 119666) suggested that CPT-loaded micelles with good stability both *in vitro* and *in vivo* effectively penetrate the blood-brain barrier, reaching glioma sites and markedly increase antitumor effect with laser irradiation.

The anticancer activity of *flavonoids* is realized by multiple cancer-related pathways, such as action on cellular processes, induction of apoptosis, inhibition of angiogenesis and cytotoxicity (Sridevi Sangeetha, Umamaheswari, & Narayana Kalkura, 2016, p. 3924). Flavones, a sub-class of flavonoids, can improve outcomes in cardiovascular and neurodegenerative diseases. Moreover, flavones represent anticancer properties by inhibiting numerous protein kinases involved in the development of cancer. Furthermore, flavones induce oxidative stress, activating apoptosis pathways in human gastric carcinoma cells, human tongue cancer SCC-4 cells and human breast cancer MCF-7 cells. Interestingly, flavones present either antioxidant or pro-oxidant activity depending upon the dose (Khan et al., 2021, p. 100010). According to Liskova and coauthors (2020, p. 1498), flavonoids prevent cancer cell invasiveness by inhibiting migration, invasion and inflammatory processes involved in the development of metastasis; as well as regulating different signaling pathways contributing to proliferation, migration and invasion of tumor cells. Malignant cells are reported to show different sensitivity toward flavonoids. For instance, the anticancer effect of flavonoids on hematological tissues depends on the origin of the blood cells. Also, the cytotoxic influence of flavonoids on breast and prostate cancer is related to the distribution of hormone receptors (Sak, 2014, p. 122–146). The beneficial effects of flavonoids in combination with chemotherapeutic drugs are observed in the treatment of acute promyelocytic anemia (APL) and various solid tumor cells. Several investigations have revealed that flavonoids enhance sensitivity of malignant cells to conventional anticancer agents (Kikuchi, Yuan, & Okazaki, 2019, p. 1517).

Experimental pharmacology has also revealed chemoprotective properties and some related mechanisms of action of *tannins* and related compounds. Studies on mouse skin carcinogenesis models have shown the ability of tannic acid (TA, hydrolysable tannin) to impede specific cytochrome P450 isoforms, reducing carcinogen-DNA adduct formation in mouse epidermis and tumorigenesis initiation in mouse skin. Additionally, translocation and activity of protein kinase C (PKC) isozymes modulated by tannic acid is evidence for anti-promotional activity of this substance in mouse skin tumors (Baer-Dubowska, Szaefe, & Krajka-Kuźniak, 2020, p. 28–37). Recent investigations found new intracellular mechanisms modulated by TA in prostate cancer cells. Tannins in Terminalia bellirica inhibit hepatocellular carcinoma growth by regulating epidermal growth factor receptor (EGFR) signaling (Chang et al., 2021, p. 3720). Also, inhibitory effect of TA on lung cancer progression has been validated by Sp and co-researchers (2020, p. 3209). They have proved that TA induces G0/G1 cell cycle arrest and intrinsic apoptosis pathways in non-small cell lung cancer (NSCLC).

Several investigations have been performed in order to demonstrate the combinatorial therapeutic effects of tannins and antineoplastic drugs. Geng and co-authors (Geng et al., 2019, p. 2108–2116) concluded that TA markedly increases potency of cisplatin (cis-dichlorodiamine platinum, CDDP) against liver cancer cells by inducing mitochondria-mediated apoptosis in HepG2 cells. It is notable that TA, when bound to different metal ions, forms stable metal nanoparticles with interesting properties. For instance, TA-stabilized gold nanoparticles (TA/AuNP) showed higher cytotoxic activity against different cancer cell lines (HCT116, MCF7 and HepG2) and improved stability with less toxicity on normal cells (HEK 293) compared to free TA (A Youness, Kamel, & A Farag, 2021, p. 1486). More recently, advantageous effects of TA-paclitaxel nanoparticles over paclitaxel alone in breast cancer therapy was confirmed (Chowdhury et al., 2019, p. 133–148). Another study by Ren et al. reported intraperitoneal injections of oxaliplatin and tannic acid polymeric nanoparticles into a thermo-sensitive hydrogel (OXA/TA NPs-H) reduced the growth of CT26 peritoneal colon cancer in model mice (*in vivo*) (Ren et al., 2019, p. 279–289).

The antimutagenic qualities of *essential oils* (EOs), responsible for their chemopreventive characteristics, has been shown by Toscano-Garibay and coworkers (Toscano-Garibay et al., 2017, p. 11479). Importantly, EOs such as farnezol and nerolidol suppress hepatic drug metabolizing enzymes, which leads to increased plasma concentration of drugs or toxic substances (xenobiotics) on one hand. On the other hand, inhibition of these enzymes may result in a reduced conversion of xenobiotics to more active metabolites and thus lower cellular toxicity, contributing in chemoprevention (Špičáková et al., 2017, p. 509). It has been documented that EOs synergistically enhance the anticancer efficacy of conventional therapeutic agents. d-Limonene, obtained from citrus fruits, when used in combination

with docetaxel in human prostate carcinoma DU-145, enhanced chemosensitivity, diminishing the amount of toxic docetaxel. This combination resulted in higher reactive oxygen species (ROS) production, as well as glutathione reduction and increased cytochrome C release. β-Caryophyllene, a sesquiterpene produced by various plants, markedly potentiated cytotoxic activity of paclitaxel relatively 10 times in MCF-7 (human breast cells), DLD-1 (human colon cells) and L-929 (mouse fibroblasts) tumor cell lines. This synergistic effect is probably due to the increased plasma membrane permeability for paclitaxel passage (Pezzani et al., 2019, p. 110). Haibo Cheng et al. (2018, p. 1413) revealed that combined treatment of elemene and gefitinib suppressed viability and proliferation of lung cancer cells, markedly reversed epithelial-mesenchymal transition, decreasing invasive capacity and cellular migration, impairing the self-renewal ability of lung cancer cells.

Conclusions. In this article we reviewed several investigations which testify to various promising anticancer activities of phytochemicals. It is becoming evident that phytomedicines play an important role in cancer treatment when combined with classical chemotherapeutic agents. It is of great importance to identify molecular signaling pathways of cytotoxicity in phytochemicals. Moreover, further clinical trials are necessary in order to observe to what extent phytochemicals influence the metabolism of chemotherapeutic agents and their anti-tumor effects.

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