

DOI 10.36074/grail-of-science.26.08.2022.62

A REVIEW OF THE ANTICANCER NATURAL PRODUCTS: ALKALOIDS, FLAVONOIDS

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According to the international agency for research on cancer 1 in 5 people develop cancer during their lifetime, suggesting that more than 50 million people are living within five years of a past cancer diagnosis (World Health Organization (WHO, 2020, para. 1). Despite novel approaches like nanomedicine, targeted therapy, and immunotherapy in cancer treatments during the last decades, chemoresistance has remained the chief hurdle in eliminating cancerous cells (Elgendy , Alyammahi & Alhamad, 2020, p. 103095). About 9 out of 10 cancer deaths are due to spreading of cancer cells from the primary tumor mass towards close and far tissues (a process called metastasis). Treatment failure followed by consequent recurrence of cancer cells and metastasis is the leading cause of death. Many survivors suffer from serious acute or chronic complications after cancer therapy (Qian, Mei, & Zhang, 2017, p.38). Furthermore, chemotherapy commonly induces a variety of side-effects in patients as a result of nonspecific action against both normal cells and cancerous cells. For instance, chemotherapeutic drugs result in alopecia by affecting not only fast dividing cancer cells, but hair follicles as well. Nausea and vomiting are the most common symptoms induced by chemotherapy, with gastrointestinal symptoms including diarrhea (and in some cases constipation) being another common side effect. Chemotherapy is also known to impair immune function and bone marrow activity (Li et al., 2020, p.599073). The identification of approved doses of anticancer drugs is another point to be given careful attention, especially those with higher cost and administered for a longer duration. Larger doses of chemotherapeutic drugs may increase the risk and severity of the aforementioned side effects, and are not cost-saving. 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 (Meriggi & Zaniboni, 2020, pp.1–11).

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. Although vincristine has been used in combination with chemotherapy regimens as an anticancer agent for about 50 years in the treatment of acute lymphoblastic leukemia (ALL) and other lymphoid malignancies, its clinical use is limited because of its involuntary pharmacokinetic features, specifically its high degree of neurotoxicity. According to a vast body of *in vivo* research, Captopotecin CPT nanoformulation is used to treat bladder, liver, brain, breast, cervix, colon, lung, ovaries, pancreas, prostate and skin cancers (Ghanbari-Movahed, Kaceli, Mondal, Farzaei, & Bishayee, 2021, p.480). Yen et al. (2014) revealed that CPT-loaded micelles dramatically suppress tumor growth, enhancing tumor elimination of urothelial carcinoma in rat populations (Yen et al., 2014, pp.11591–11602). 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.

Flavonoids are suggested to have a broad spectrum of biological benefits, including anti-inflammatory, antiallergic, antioxidant, antimicrobial, antiviral and anticancer effects. Epidemiological analysis in different countries indicates an association between dietary intake of flavonoids and cancer of breast, gastrointestinal tract, skin, prostate and hematological malignancies. Although there is little knowledge about the correlation between the chemical structure of flavonoids and anticancer activity, results of some studies confirmed the role of structural properties of flavonoids and cytotoxic activity (Khan et al., 2021, p.100010).

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. 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, & Hu, 2019, pp. 1517-1535).

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