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Mini Review

Current Assessment of Phytochemicals in Anticancer Treatment

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Abstract

Phytochemicals are bioactive compounds for cancer treatment, serving as vital sources for novel drugs. Vinca alkaloids, taxanes, colchicine, podophyllotoxin, camptothecin, irinotecan and roscovitine stand out as the most used potential phytochemicals in cancer treatment. These phytochemicals act by affecting various molecular pathways. The primary aim of this study is to discuss the potential of phytochemicals, which are active compounds in natural products, and to explain their effects on molecular targets. At the same time, the derivatives of these phytochemicals and their effects on various cancer cells are the subject of discussion in this study. The information obtained about anticancer phytochemicals evaluated at preclinical and clinical levels may shed light on new studies to be conducted in the future.

Keywords: Phytochemicals; Cancer; Irinotecan

Introduction

Phytochemicals and derivatives available in herbs are encouraging choices to enhance treatment efficacy in cancer patients and to minimize adverse effects. The mainly present chemotherapeutic agents, such as antimetabolites (e.g., methotrexate), DNA-interactive agents (e.g., cisplatin, doxorubicin), anti-tubulin agents (taxanes), hormones, and molecular targeting agents, have caused recurrencing of cancer, drug resistance and toxic effects on non-targeted tissues. Therefore, the development of effective and side-effect-free phytochemical-based anti-cancer treatment has attracted attention by all researchers worlwide. Some of the remarkable anticancer phytochemicals are 6-Shogaol, Allicin, Alpinumisoflavone, Andrographolide, Apigenin (APG), Baicalein and baicalin, Curcumin, Decursin and decursinol, Dicumarol (DIC), Epigallocatechin (EGCG), Emodin, Genistein, Gingerol, Glycyrrhizin, Hispidulin, HS-1793, Licochalcone A (LicA), Nimbolide, Physapubescin B, Pterostilbene, Resveratrol, Sulforaphane (SFN), Thymol, Thymoquinone (2-isopropyl-5-methyl-1,4-benzo-quinone, TQ), Ursolic acid (UA) and Withaferin A (WA). These phytochemicals have been evaluated on preclinical efficacy in various animal models [1]. Phytochemicals currently used in cancer treatment: Vinca alkaloids, taxanes, camptothecin derivatives, podophyllotoxin and derivatives and roscovitine are the most used in clinical studies [2] (Figure 1). Phytochemicals exert antitumor effects through different mechanisms. The anticancer mechanisms of action of phytochemicals are still a topic of research [3]. Colchicine, paclitaxel, and vinca alkaloids are the earliest plant-derived microtubule-targeting agents, and paclitaxel and vinca alkaloids are currently important drugs used in the treatment of cancer. Microtubule-targeting agents inhibit the proliferation of cancer cells by disrupting interphase cell signaling events and/or preventing the precise functioning of spindle microtubules, both of which ultimately induce cell death via apoptosis on many different cancers, such as ovarian, breast, bladder, prostate, and lung cancers,

and lymphoma. Taccalonolides, persin, curcumin, combretastatins, noscapine, maytansine, chalcones, and quercetin, have been shown as most studied microtubule targeting agents after the taxanes and vinca alkaloids. Conspicuously, curcumin, combretastatins, noscapine, maytansine, and quercetin have already undergone clinical trials evaluating their efficacy against various cancers [4]. Vinblastine, vincristine, vindesine and vinorelbine have shown antitumor activity by binding to tubulin. Vinblastine and vincristine especially arrest the metaphase of the cell cycle due to cell interaction and disruption of microtubule function and tubulin comprising of mitotic spindle apparatus [5]. Irinotecan causes cell death by trapping the enzyme on DNA, manufacturing cytotoxic protein-linked DNA breaks as Topoisomerase I primary target (Figure 1). Although irinotecan continues to be used despite its various side effects (such as diarrhea, neutropenia), this camptothecin derivative targeting topoisomerase 1 is currently used in combination regimens such as FOLFIRI and FOLFIRINOX, continues to be used extensively to treat metastatic or advanced solid tumors such as colon, stomach and pancreatic cancers and others [6].

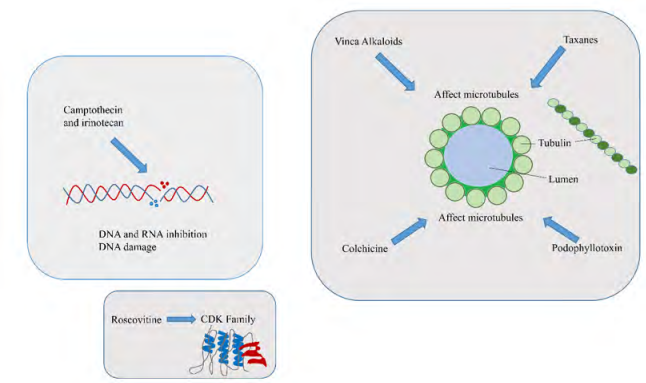

Figure 1: Phytochemicals currently used in cancer treatment and their effect mechanisms.

Camptothecin derivatives have been evaluated anti-tumor activity against small-cell lung cancer (NCI–H446, H69, drug-resistant H69AR cells, drug-resistant NCI–H446/Irinotecan cells and drug-resistant NCI–H446/EP cells) *in vitro*. The findings have indicated that outstanding antitumor activity and drug-resistance in small-cell lung cancer both *in vivo* and *in vitro* [7]. Camptothecin derivative YCJ100 has shown high cytotoxic activity compared to Topotecan in SW480, SW1990, Hep3B, HepG2, A549, A2780, HeLa, and QBC cells via similar to the mechanism of topotecan. At the same time, YCJ100 has been more potent than topotecan in primary HCC and ICC mouse models, as well as a xenograft mouse model [8]. Roscovitine, a cyclin-dependent kinase (Cdk) inhibitor, has been shown to inhibit Cdk family 1, 2, 5, 7 and 9 by arresting the proliferation of various tumor cells (Figure 1). Several preclinical and clinical studies indicate that roscovitine is a well tolerated oral agent with therapeutic potential against a number of tumor types. Even though, roscovitine monotherapy in cancer clinical trials have not been very promising, knowledge regarding its synergistic cytotoxicity with several anticancer agents in multiple cancer types is prominent. Accordingly, roscovitine in combination with sapacitabine is currently undergoing clinical trials in advanced solid tumors (clinicaltrials.gov.in; NCT00999401) [9]. Taxanes are one of the most effective drug kinds used for the cure of breast and ovarian cancers, and are also used to treat squamous cell carcinoma of the neck and head. Taxanes bind to microtubules with higher affinity than vinca alkaloids. Podophyllotoxins interact with DNA topoisomerase II leading to break down of DNA strands resulting cell-cycle arrest at G2-phase. Podophyllotoxin is used for the semisynthesis of anticancer drugs, such as azatoxin, etoposide, etopophos, and teniposide, as well as GL331, NK611, tafluposide, Pand TOP-53. Etoposide has been observed to be affect on brain tumor in combination therapy with cyclophosphamide, cisplatin, vincristine, and carboplatin. Due to toxicity of podophyllotoxin, etoposide and teniposide, have been used in treatment for testicular cancer, lung cancer, gliomas, and lymphomas. Podophyllotoxins have also been used in combination with cisplatin within the first-line chemotherapy for extensive-stage SCLC or small-cell lung cancer. Colchicine has affected on the depolymerization of the microtubules at high concentrations and the regulation of the microtubules at low concentrations. Colchicine inhibits cell migration, adhesion, and invasion in hypopharyngeal cancer cells, causing in prominent anticancer effects. The anti-proliferative effect of colchicine on hepatocellular carcinoma cells is approximately 200-fold less than that of epirubicin. A small amount of colchicine has been confirmed as clinically appropriate within the palliative treatment of hepatocellular carcinoma. Except for these, combretastatin, geniposide and their derivatives,

artesunate, homoharringtonine, salvicine, ellipticine, maytansin, thapsigargin, bruceantin phytochemicals have been investigated on many cancer cells *in vitro* and *in vivo* models [10].

Conclusion

Many phytochemicals have been verified safe, therapeutically effective and biocompatible in clinical trials and have therefore used in cancer treatments. Potent therapeutic chemicals such as colchicine, camptothecin and podophyllotoxin have shown serious side effects that restrict their use. Phytochemicals such as vinca alkaloids, taxane, ellipticin, camptothecin, combretastatin, curcumin, podophyllotoxin, homoharringtonine and others have been recognized for their potential anticancer effects on a variety of neoplastic diseases. Researchs show that bioactive phytochemicals have multiple effects on many molecular targets of cancer cells. These phytochemicals could be developed as non-toxic and therapeutically effective drug products to combat various malignancies.

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