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Review

Colorectal cancer and medicinal plants: Principle findings from recent studies

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ABSTRACT

Colorectal cancer is one of the most frequent malignancies in the world. Although recent advances in chemotherapy have improved management and survival of colorectal cancer patients, side effects and resistance to chemotherapy have shown the limitations of current chemotherapy and led to the search for alternative treatments. In this context, medicinal plants provide a large number of molecules with proven cytotoxic and apoptogenic activities against several types of cancers including colorectal cancer. These molecules belong to various phytochemical families and trigger different signaling pathways. Here, we review the recent findings regarding the anti-colorectal cancer activities of several plants, both *in vitro* and *in vivo*, and the phytochemical molecules possibly responsible for these activities. Besides, their effects on several cancer signaling pathways are discussed. This review highlights the importance of medicinal plants as promising sources of lead anti-colorectal molecules.

1. Introduction

Colorectal cancer is the 3rd most common cancer worldwide. In recent years, a rapid rise in colorectal cancer incidence and mortality has been observed in several developing countries [1]. An increase of 60% of this malignancy incidence is expected by 2030 [2]. Colorectal cancer is the result of a progressive accumulation of genetic and epigenetic alterations, leading to a marked genomic instability. Indeed, colorectal cancer has been associated with multiple mutations: mutational inactivation of tumor-suppressor genes such as P53, APC and TGF-β, and activation of oncogene pathways (RAS, BRAF, and PI3K) [3]. Genetically, colorectal cancer is classified into three categories: sporadic (60%) referring to patients with no family history, familial (30%) comprising patients with at least one blood relative with colorectal cancer or an adenoma and hereditary colorectal cancer (10%) resulting from germline inheritance of mutations [4].

Medicinal plants used by about 70% of the world population are a promising source of anticancer bioactive molecules [5]. Searching for anticancer drugs from plants started in the 1950's when vinca alkaloids were discovered [6]. Several anticancer drugs currently in clinical use are plant-derived products and include taxol, vinblastine or vincristine, irinotecan, camptothecin and their derivatives or analogs [7]. In the present paper, we have reviewed the most recent studies on cytotoxic and apoptogenic activities of medicinal plants against colorectal cancer. Furthermore, risk factors and therapeutic approaches for treating colorectal cancer have been discussed.

2. Risk factors

Besides the hereditary predisposition, most cases of colorectal cancer are sporadic and develop slowly over years [8]. Several risk factors for colorectal cancer have been reported such as obesity, smoking, alcohol intake and consumption of processed and red meat [9].

2.1. Obesity

Epidemiological studies have shown that obesity contributed to the increase in both incidence and mortality from colorectal cancer [10]. It has been demonstrated that the colorectal cancer risk increased by 7%

Abbreviations: AMPK-GLUT1, AMP-activated protein kinase-glucose transporter 1; Bax, bcl-2 associated X protein; Bcl-2, B-cell lymphoma gene 2; Bim, bcl-2-like 4; BRAF, v-raf murine sarcoma viral oncogene homolog B1; Cdk, cyclin-dependent kinase; CIMP, CpG island methylator phenotype; COX-2, Cyclooxygenase-2; DLEC1, deleted in lung and esophageal cancer 1; IC_{50}, inhibitory concentration of 50%; JNK, c-Jun NH2-terminal kinase; MSI, microsatellite instability; MMPs, metalloproteinases; NF-κB, nuclear factor κB; PARP, poly(ADP-ribose) polymerase; PGE_2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma viral oncogene homologue; ROS, reactive oxygen species; VEGF-A, vascular endothelial growth factor-A

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for each 2 kg/m^2 rise in body mass index [11]. Recently, Lee et al. (2015) [12] reviewed 16 cohort-studies carried out between 1970 and 2014 and concluded that obesity prior to the diagnosis of colorectal cancer was associated with increased colorectal cancer-specific mortality. It has been suggested that disturbing of the dynamic role of the adipocyte in energy homeostasis by obesity, resulted in alteration of adipokine (leptin and adiponectin) signalling. In addition, insulin resistance caused by obesity has been shown to contribute to colorectal cancer development [13]. In fact, hyperinsulinemia caused by insulin resistance through β-cells compensation, increased hepatic growth hormone–mediated synthesis of IGF-1, and high levels of C-peptide are thought to be the linking mechanism between obesity and colorectal cancer [14].

2.2. Smoking

Tobacco smoke exposure has been associated with 20% of colorectal cancer cases in USA [15]. Zhao et al. (2010) [16] studied the effect of cigarette smoking in Canadian non-smokers, former and current smokers. They showed a strong association between colorectal cancer risk and cigarette smoking years, the amount of cigarettes smoked daily, and cigarette pack years. Heineman *et al.* (1994) [17] found in a 26-years follow-up of American smokers that earlier age at smoking initiation was a risk factor for colorectal cancer.

The association cigarette smoking-colorectal cancer may be explained by the epigenetic modifications. Indeed, CIMP (CpG island methylator phenotype) and BRAF mutations have been shown to be associated with cigarette smoking [18,19]. Similar findings are also reported by Curtin et al. (2009) [20] and Rozek et al. (2010) [21]. Recently, Tillmans et al. (2015) gave evidence supporting the serrated pathway in colorectal carcinogenesis. According to this hypothesis, *BRAF* mutation initiates the serrated pathway which progresses through a serrated precursor (sessile serrated adenoma) to cancers characterized by mutant *BRAF*, high CIMP and, often, high MSI [22].

Cigarette smoking induces prostaglandin E2 (PGE_2) synthesis, which in high concentrations is considered a high-risk factor for colon cancer [[23]]. This may be due to the activation of the arachidonic cascade. Cyclooxygenase-2 (COX-2), a major enzyme in inflammation, converts arachidonic acid to PGE_2. Effects of COX-2 in colorectal carcinogenesis are mainly mediated through PGE2 which inhibits apoptosis and stimulates angiogenesis [24]. It has been demonstrated that nicotine, a major compound of tobacco smoke promoted *in vivo* colon tumor growth and angiogenesis by increasing COX-2 and PGE_2 [25].

2.3. Red and processed meat

Epidemiological studies from around the world established a marked association between increased colorectal cancer and high intake of red or processed meat.

A positive association has been demonstrated between processed red meat intake and distal colon cancer risk in two large cohorts: the Nurses'Health Study (n = 87,108 women, 1980–2010) and Health Professionals Follow-up Study (n = 47,389 men, 1986–2010) [26]. In a large systematic review of fifteen cohort studies, Norat *et al.* (2010) [27] found that each 100 g/day increase in red and processed meat intake resulted in a summary relative risk of 1.16 for colorectal cancer. Similar findings were previously reported showing a summary relative risk of 1.28 for each 120 g/day increase in red and processed meat intake [28].

Bastide et al. (2011) [29] reviewed prospective cohort studies of colon cancer reporting heme intake. They found that dietary heme was associated with increased risk of colon cancer.

Several hypotheses may explain the carcinogenic potential of red and processed meat involved in colorectal cancer: (a) high saturated fat- and cholesterol- content promoting carcinogenesis via genotoxicity mechanisms promoted by lipid peroxidation and inflammation, or via insulin resistance or fecal bile acids, (b) iron and heme-iron involved in carcinogenesis promotion (lipoperoxidation), (c) carcinogenic compounds (polycyclic aromatic hydrocarbons, heterocyclic aromatic amines) resulted after cooking meat at high temperatures, (d) N-nitroso carcinogenic compounds formed by adding sodium nitrite to processed meats [30]

3. Therapeutic approaches

Treatment of colorectal cancer consists of surgery (early-stage disease), chemotherapy, radiotherapy and more recently targeted therapies. Although the outcome in metastatic colorectal cancer has been improved by the use of the targeted therapies, several limitations and side effects have been observed [31].

Several side-effects have been reported to be associated with chemotherapeutic agents use such as fluorouracil (neutropenia, stomatitis, diarrhea), irinotecan (bone marrow suppression, nausea and alopecia) or oxaliplatin (dysesthesias and renal dysfunction) [32].

Even when therapies allow long survival, long-term effects of treatment such as sensory neuropathy, urinary incontinence, gastrointestinal problems and sexual dysfunction can persist for several years [33]. Furthermore, resistance to chemotherapy is considered one of the greatest challenges in colorectal metastases management, contributing to higher mortality rates [34].

4. Medicinal plants and colorectal cancer

4.1. Artemisia sieversiana Ehrh.

Artemisia sieversiana Ehrh (Asteraceae) growing in the temperate zones of Asia, Europe, and North America, is used to treat infections, cold, diarrhea, jaundice, fever and hysteria [35,36]. The genus Artemisia has gained more attention owing to its richness of bioactive molecules and its ethnomedicinal uses in traditional medicine.

Several phytochemicals have been found in different parts of the plant such as flavonoids, sterols, coumarins and terpenoids including 21 guaiane-type sesquiterpenes, 3 germacrane-type sesquiterpenes, 1 muurolane-type sesquiterpene, and 1 diterpenoid [37,38]. The major compounds reported in the essential oils of the aerial parts were: 1,8-cineole, geranyl butyrate, borneol and camphor [39].

Different biological activities of *A. sieversiana* have been reported. Earliest studies reported antitumor, nematicidal and anti-inflammatory effects of the plant and/or its phytochemicals [40–42]. The alcoholic extract of the *A. sieversiana* was shown to possess an important antioxidant activity, comparable to that of the ascorbic acid [43]. Furthermore, antibacterial and antifungal activities of several polar and apolar extracts of *A. sieversiana* were demonstrated in different microbial strains [44,45].

The plant has been shown to possess therapeutic effects on diseases affecting the gastrointestinal tract. In fact, ethnobotanical studies documented the use of the plant to treat gastrointestinal disorders and pains [46]. The methanolic extract of this plant demonstrated promising anthelmintic activity against the gastrointestinal nematode *Haemonchus contortus* [47]. Moreover, two metabolites extracted from the metanolic extract of *A. sieversiana* aerial parts inhibited SMMC-7721 hepatocarcinoma cells growth [48]. Similarly, two sesquiterpenes namely 2*α*,9*α*-dihydroxymuurol-3(4)-en-12-oic acid (**1**) and 13*α*-methyl-(5*α*H,6*α*H,7*α*H,8*α*H)-austricin 8-*O*-*β*-D-glucopyranoside have been identified in the plant. These molecules were able to inhibit Hep-G2 cells growth [49].

Ethanol extract of the aerial parts of *A. sieversiana* exhibited marked cytotoxic effects against three colorectal cancer cell lines: HT-29, HCT-15 and COLO 205. The growth inhibition of COLO 205 was attributed to apoptosis induction, DNA damage and loss of mitochondrial membrane potential [50].

The aerial parts (leaves and flowers) of the plant contain important