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Medicinal plants of the genuses *Salvia* and *Hypericum* are sources of anticolon cancer compounds: Effects on PI3K/Akt and MAP kinases pathways

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ABSTRACT

Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the incidence is highly influenced by diet. Epidemiological studies have supported the idea that some medicinal plants may influence the risk of CRC through modulation of several biological processes, including proliferation, survival and cell death. The PI3K/Akt and MAP Kinases pathways are frequently constitutively activated in CRC and components of these pathways are important molecular targets for CRC treatment.

This review describes the effects of Mediterranean species of medicinal plants of the genuses *Salvia* and *Hypericum* and some of their main phytochemical constituents (quercetin, luteolin, rosmarinic acid and ursolic acid) in their ability to control CRC progression by modulating molecular targets of the PI3K/Akt and MAP Kinases signaling pathways. These plants and their bioactive constituents have been shown by our group and by several others to have the ability to control CRC progression. The significance of the effects strongly suggests the applicability of these plants' extracts or individual constituents in cancer therapy as well as in functional foods or nutraceuticals.

Contents

1. Introduction

Colorectal cancer (CRC) has a complex etiology and pathogenesis [1,2]. Contributory factors include diet and lifestyle as well as

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inherited and somatic mutations [2,3]. It is estimated that only 15–30% of CRCs have a clear hereditary component (including the Familial Adenomatous Polyposis, FAP, and the Hereditary Non-polyposis Colorectal Cancer, HNPCC), the remaining majority being sporadic [3].

CRC is the third most common type of cancer worldwide being mainly a disease of industrialized countries, such as North American, parts of Europe, Australia, New Zealand and Japan [4]. Although the overall 5-year survival rate of CRC patients has increased during the past 2 decades from 51% to 65%, its incidence and mortality are continually increasing. Approximately 1 in 3 people who develop CRC die of this disease [4,5]. Chemotherapeutic agents currently available as clinical options include 5-fluorouracil (5-FU), oxaliplatin, irinotecan, capecitabine, bevacizumab, cetuximab and panitumumab, which are used alone or in combinations [5]. However, due to severity of side effects and resistance mechanisms new drugs are needed against CRC [5]. Plants constitute a good source of active molecules and medicinal plants are particularly interesting in the search for new leads. It is, therefore, not surprising that about 50% of all existing drugs used in the clinic stem from natural source [6], such as Vincristine, Vinblastine, Camptothecin, Paclitaxel, Etoposide, and many more FDA (Food and Drug Administration) approved agents [6–8].

Although there is much to be learned about diet and CRC, many studies have reported a relationship between nutritional factors and CRC, supporting the idea that dietary constituents may affect CRC by either reducing or enhancing its risk [9,10]. An appropriate diet may minimize CRC risk, suggesting the possible benefit of preventive strategies based on diet. There are evidences that the Mediterranean diet is associated with lower risk of overall cancer incidence and mortality including of CRC [11]. Diet and dietary supplements may also have a potential therapeutic role either alone or when used in combination with conventional pharmaceuticals through enhancement of their effects overcoming resistance or decreasing side effects [10].

The National Cancer Institute (NCI) has identified a large number of plant-based foods with anticancer properties with beneficial effects in a single or multiple molecular targets [6–8,12]. With respect to green tea (from the plant *Camellia sinensis*), although some studies have not found positive effects, many epidemiological and laboratory studies have found a positive correlation between tea consumption and reduction of human cancer risk, including CRC [13,14]. Further studies have demonstrated that epigallocatechin gallate (EGCG), particularly abundant in green tea is responsible for many antioxidant and anticancer properties with effects in many signal transduction pathways [15]. The use of EGCG alone or in combination with chemotherapeutic drugs has been suggested for the prevention and treatment of cancer [15]. Many other plant extracts have also been shown to constitute rich sources of bioactive food compounds especially of phenolic compounds, which are considered to play an important role as anticarcinogenic agents due to their antioxidant properties [7,16–18]. Reactive oxygen species (ROS) and free radicals, produced by cancer cells, activate a number of genes and signal transduction pathways that mediate cancer cell proliferation and survival. Therefore, the radical scavenging activity of phenolic compounds present in plant foods by reducing ROS levels contribute to a decrease in the activity of redox-sensitive pathways, thus decreasing cancer progression [18–20]. Under some conditions, pro-oxidant effects of natural compounds may also be beneficial decreasing cancer progression [21,22]. In addition, direct interactions between plant food constituents and multiple key elements in signaling transduction pathways have been reported [12,18,23,24].

Several clinical studies have also reported the beneficial effects of some herbal medicines and phytochemicals on the survival, immune modulation and quality of life of cancer patients, when used alone or in combination with conventional therapy [25–29]. However, the number of these clinical trials is still small to establish their clinical effectiveness [27,28]. Thus, although information derived from clinical trials is still insufficient, the number of significant *in vitro* and *in vivo* studies has increased providing evidences of the great promise of natural products and plants extracts for clinical use [29].

2. Oncogenic mutations and signaling pathways in CRC

The small GTP-binding protein Ras transduces signals from membrane growth factor tyrosine kinase receptors (RTKs) and is a common upstream molecule of several signaling pathways, including the PI3K (phosphotidylinositol-3 kinase)/Akt and the mitogen-activated protein kinsase (MAPK/ERK) pathways [3]. Mutations of *RAS* are found in 25–30% of cancers and *KRAS* is the most frequently mutated *RAS* isoform in human cancers, accounting for 40% of *KRAS* mutation in CRC [2,3,30–32].

The upregulated PI3K/Akt and Raf/MAP/ERK pathways by the oncogene *RAS* regulate tumor progression, invasion, angiogenesis and resistance to CRC therapy [1,33,34]. The gene for *BRAF*, a kinase directly activated by Ras in the MAPK pathway, may also be constitutively activated by mutation. CRC patients that display either *KRAS* or *BRAF* mutations have showed worse prognosis and shorter survival than those with wild-type *KRAS* and *BRAF* genotype [35].

2.1. PI3K/Akt pathway

The phosphotidylinositol-3 kinases (PI3Ks) are a family of lipid kinases and the class I PI3K is a major regulator of cell growth, proliferation and apoptosis evasion [36]. This class of PI3Ks can be activated by RTKs, such as PDGF-R (platelet-derived growth factor receptor), EGF-R (epidermal growth factor receptor) or IGF-R (insulin-like growth factor receptor) and by G protein-coupled receptors (GPCRs) [37,38]. The activation of PI3K leads to Akt/PKB recruitment *via* its pleckstrin homology (PH) domain and, once at the membrane, Akt is phosphorylated at threonine (T308) and serine (S473) residues by the activated protein serine/treonine kinase 3′-phosphoinositide-dependent kinase-1 (PDK-1) and the target of rapamycin complex 2 (TORC2) [37,38]. Subsequently, Akt modulates the function of numerous substrates such as mammalian target of rapamycin complex 1 (mTORC1), glycogen synthase kinase-3 (GSK-3), cyclin-dependent kinase inhibitors p27 and p21, MDM2, BAD, procaspase-9 and transcription factor Forkhead box (FOXO) [37,39]. Nearly 40% of CRC tumors have been demonstrated to have alterations in one of the genes related with PI3K signaling [40].

Cancer associated mutations of PI3K have been found only in class I PI3K. Somatic mutations of the catalytic subunit *PI3KCA* gene are found in approximately 15–20% of CRCs, showing some degree of overlap with *KRAS* mutations [3]. *PIK3CA* mutations have been demonstrated to occur as a primary genetic event in CRC, having a relevant importance in the carcinogenic process [41]. CRC cell lines with *PIK3CA* mutations have increased proliferative capacity and survive under environmental stresses [42], are more resistant to apoptosis and have higher metastatic potential [43]. Moreover, mutations in the *PIK3CA* gene occur more frequently in combination with other mutations, such as *KRAS* or *BRAF*, than in isolation, suggesting a possible synergistic effect for an efficient malignant transformation [44,45]. Mutations in the *AKT* gene are not common in humans, however, some studies have reported an up-regulation of phosphorylated Akt in about 50% of CRC carcinomas [46–48]. The fact that alterations in components of the PI3K/Akt pathway occur with high frequency in CRC tumors makes them attractive targets for the development of novel anticancer agents to treat CRC.