



Pharmacological insights into antioxidants against colorectal cancer: A detailed review of the possible mechanisms



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ABSTRACT

Colorectal cancer (CRC) is ranked as the fourth most lethal and commonly diagnosed cancer in the world according to the National Cancer Institute's latest report. Treatment methods for CRC are constantly being studied for advancement, which leads to more clinically effective cancer curing strategy. Patients with prolonged chronic inflammation caused by ulcerative colitis or similar inflammatory bowel disease are known to have high risks of developing CRC. But at a molecular level, oxidative stress due to reactive oxygen species (ROS) is an important trigger for cancer. Hence, in recent years, exogenous antioxidants have been immensely experimented in pre-clinical and clinical trials, considering it as a potential cure for CRC. Significantly, potential antioxidant compounds especially derivatives of medicinal plants have received great attention in the current research trend for CRC treatment. Though antioxidant compounds seem to have beneficial properties for the treatment of CRC, there are also limitations for pure compounds to be tested clinically. Therefore, this review aims to delineate the pharmacological awareness among researchers on using antioxidant compounds to treat CRC and the measures taken to prove the effectiveness of such compounds as impending drug candidates for CRC treatment in modern medication.

1. Introduction

In recent years, colorectal cancer (CRC) has been listed as the third most fatal cancer in the world [1,2]. The etiology of CRC varies among tumor formation but most findings address the cellular signaling and cycle regulations [3]. CRC can be caused by environmental and physiological factors such as microbial infections, radiations, smoking habits, excessive alcohol consumption and red meat intake, and fundamentally gene mutations [4,5,2]. Majority of CRC cases are sporadic but studies have shown up to 30% of cases as a component of heredity and

is equally vulnerable in both male and female patients [6]. CRC develops from prevailing severe ulcerative colitis at the inner lining of colon or rectum, or inflammatory bowel diseases that involve any section of the gastrointestinal tract. Ulcerative colitis was not considered as a detrimental condition since patients who have undergone colectomy were normally cured [7,2]. Chronic inflammation due to severe ulcerative colitis leads to CRC, which occurs at multiple sites and are often poorly distinguished from general CRC. Therefore patients who are at risk of developing CRC caused by ulcerative colitis need to be diagnosed earlier at the stage of dysplasia or cancer precursors,

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allowing surgery to be performed [1]. The risk of ulcerative colitis related CRC has decreased at recent times with development of surgical techniques but long-standing colitis in general population retains the high risk of having CRC. Although surgery is the main tool for the possible cure of CRC, radiotherapy or chemotherapy is applied at times to patients upon surgery, subjected to the stage of disease [8]. It was reported however that these treatment protocols were unable to cure CRC, as 30% of stage I-III patients and approximately 65% of stage IV patients experience recurrent ailment [9,2,5].

Chemoprevention studies using plant-derived compounds, vitamins and nutritional supplements were considered old-fashioned for cancer prevention but in recent years, it has been extensively explored after considering the role of inflammation in various tumor formations. Carcinogenesis of a common epithelial tumor of CRC which takes almost 20 years before the initial symptom occurrence therefore chemoprevention is functional to inhibit the metastasis of CRC during this long period of time [4,5]. It is likely to attribute the inflammatory reaction and metastasis of CRC to the cell signaling pathways regulated by free radicals or reactive oxygen species (ROS) [10,11,8]. Oxidative stress is known as the etiological factor of CRC, via DNA damage and mutation in oncogenes and activation of cancer cell proliferation pathways [12–14,4]. It is noted that oxidative stress causes fibrosis and tissue injury in CRC progression through immune-activated inflammatory response. This situation causes antioxidant deficiency in patients diagnosed with ulcerative colitis. Therefore, recent reviews suggest the supplementation of exogenous natural antioxidants with potent anti-inflammatory and cell signaling prevention effects for chemoprevention of CRC [2,4,5,8,10,11].

Exogenous antioxidants are diverse in their biological properties and chemical structures, consisting of large groups of molecules [10,11]. Due to their diversity and abundance, these compounds are classified into three major groups namely; vitamins and derivatives, minerals, and polyphenols. Polyphenols are the largest group of antioxidants, which can be divided further into flavonoids and phenolic acids. Flavonoids are known to constitute the major portion of polyphenols which are commonly found in all plants [15]. Flavonoids are mostly present in fruits, vegetables, tea, wine and other medicinal plant products. It is well observed that plant derived antioxidant compounds are vastly studied for various cancer treatments including therapeutic potentials for CRC [10,11]. Consuming flavonoid rich diet lowers the risk of CRC and helps to mitigate the severity of cancer [8]. Knowledge on potential antioxidant compounds to be used for the treatment of CRC is still expanding [16,2,5,10,11]. Therefore, this review aims to delineate the pharmacological awareness among researchers on using antioxidant compounds to treat CRC and the measures taken to prove the effectiveness of such compounds as impending drug candidates for CRC treatment in modern.

2. Conventional and modern types of treatment for CRC

Being the foundation of cancer care, conventional treatment is the most extensively accepted and practiced treatment, compared to the modern and alternative treatments. Conventional treatments for CRC includes surgery, radiation, and systemic chemotherapy which are given selectively to help the patients based on the location, type, size, stage and spreading tendency of cancer [17]. Modern treatment includes the devised method from conventional therapy mainly to reduce side effects and to increase compliance and specificity. An example of modern treatment is the stem cell therapy that involves transplant of blood-producing stem cells to restore lost blood components during the course of treatment [18]. Another example of modern treatment is the individualized treatment to cater for different patients' susceptibility as each and every one of us varies by different sets of the genome [19]. Recently, an advanced diagnostic tool known as the genomic tumor assessment helps to identify the genetic mechanism of tumor to provide treatment based on the genetic changes, promising high specificity of

treatment [20]. Molecular pathologic epidemiology (MPE) is a current research combining molecular pathology with epidemiology of cancer. The knowledge in using MPE to diagnose the precise etiology of CRC is growing lately with the accumulation of scientific databases from multiple fields includingpharmaco-MPE, immune-MPE, microbial-MPE, and so on [21]. These biomedical databases from various CRC patients of diverse environmental conditions and factors helps to identify the underlying genetic conditions related to the external factors causing CRC. Research through integration of these databases could provide a suitable tailored method with specifications to each CRC patient [22]. Besides that, there are ongoing trials on altering drug designs by cooperating nanoparticles with cancer medicine as an appealing drug delivery platform [23]. Meanwhile, alternative treatments are the unconventional therapies with the lack of scientific or medical evidence about its therapeutic activities [24]. This mostly may involve the marketing strategies that could influence the decision-making psychology in persuading the patients. Some alternative therapies may overlap with the conventional therapy given leading to unwanted detrimental side effects [25]. Improving overall wellbeing by promoting body and mind healing is also a part of alternative therapy practice for CRC. These therapies often focus on the prevention rather than cure.

Chemotherapy remains the most prominent type of treatment in practice among conventional approaches. It may be used alone or in conjunction with other treatment options. Since it works systematically into the system, it has the potential to control metastasis of cancer [26]. There is also another form of chemotherapy known as the regional chemotherapy whereby the injected drug is transported directly to the tumor, preventing unnecessary drugs reaching other healthy parts of the body [27,8]. An example of chemotherapy agent is the fluoropyrimidine 5-fluorouracil (5-FU), which is used in the first line of chemotherapy not exclusive to CRC but also to neck and breast cancers [28,29]. The response rates of 5-FU among advanced stage of CRC patients is only 10–15%, therefore approaches in combining 5-FU with other chemo drugs such as irinotecan and oxaliplatin has enhanced its efficacy up to 40–50% [30,31]. However, chemotherapy encounters some drawbacks such as the limitation in solubility of drugs, lack of anti-cancer selectivity, and the development of multidrug resistance in patients. To overcome these problems, increasing the dosage level is a risky deed as most of the drugs are listed under the narrow therapeutic index (NTI), which means they are prescribed near or at the maximum tolerated dose level [32]. During the course of chemotherapy, treatment using a combination of few drugs are common to enhance the efficacy, but the cytotoxic effects of these anti-cancer drugs towards the normal healthy cells becomes an issue which needs critical attention. Table 1 shows the common choices of treatments, the advantages and disadvantages for the treatment of CRC.

Nature of chemotherapy is to interfere with the events involved in cell proliferation, growth as well as its survival. Besides killing the cancer cells, it may disrupt the normal healthy cells when they are in contact with the chemo drugs and this phenomenon is known as the 'contact inhibition' [33]. This results in the occurrence of side effects such as loss of hair, nausea and digestive problems due to damages made in the rapidly growing normal cells [34]. To reduce the likelihood of unintended effects, the selectivity of the drug is vital. A drug should only be therapeutically active on the targeted cell line; therefore, its mechanism of action should precisely target the key difference occurring in the cancer cells alone. Multidrug resistance is a significant challenge faced in cancer treatment when the tumor acquires resistance against the chemotherapy drugs that were supposed to suppress or kill them. This is mainly due to the active removal of the drug from the therapeutic site, reducing the drug's bioavailability for its best therapeutic activity. Thereby, the remaining active cancer cells, which were not affected by the drug, tend to evolve resistance towards the particular drug [35]. Fig. 1 shows the difference in the mechanism between the conventional and the modern drugs on CRC therapy. Modern therapy involves the identification of an important feature in the

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