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## Review article

## Chemoprevention of colorectal cancer



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## ARTICLE INFO

## Article history:

Received 5 September 2015

Received in revised form

1 December 2015

Accepted 7 December 2015

Available online 27 January 2016

## Keywords:

Chemoprevention

Colorectal cancer

Colon

Cancer

## ABSTRACT

**Introduction:** There are many studies which suggest that the occurrence of colorectal cancer is closely related to the dietary habits. It is known that a number of substances occurring in food can protect against the development of colon cancer. A procedure consisting of using natural or synthetic materials to prevent the progression of cancer is called chemoprevention. **Aim:** The aim of the paper is to present a number of substances having a chemopreventive effect in colorectal cancer.

**Material and methods:** A method that was used for the creation of this article was to review the literature.

**Discussion:** There are many substances having chemopreventive effect in colorectal cancer. During the many years of research, more than 200 potentially active ingredients have been detected, whose clinical relevance is constantly tested. These include epigallocatechin gallate, dietary fiber, probiotics, vitamin D, selenium, folic acid, methionine, anthocyanins, procyanidins, curcumin, resveratrol, antioxidant as vitamins A, C, E and  $\beta$ -carotene, genistein, allicin and others. These substances act by maintaining the balance between cell proliferation, differentiation and apoptosis of epithelial cells of the colon. Additionally, they have an ability to bind and degrade the potential carcinogens. What is more, they have a predisposition to slow down the cycle of colon cancer cells and to limit their ability of metastasis.

**Conclusions:** There are many substances that have a potentially chemopreventive effect in colorectal cancer but currently chemoprevention is of limited use in the prevention of colon cancer. This is mainly due to the fact that there is a lack of clear evidence of preventive and therapeutic effects of chemopreventive substances.

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## 1. Introduction

There are many studies which suggest that the occurrence of colorectal cancer is closely related to dietary habits. It is known

that a number of substances occurring in food can protect against development of colon cancer (Fig. 1).

A procedure consisting of using natural or synthetic materials to prevent the progression of cancer is called chemoprevention.<sup>1</sup> During the many years of research more

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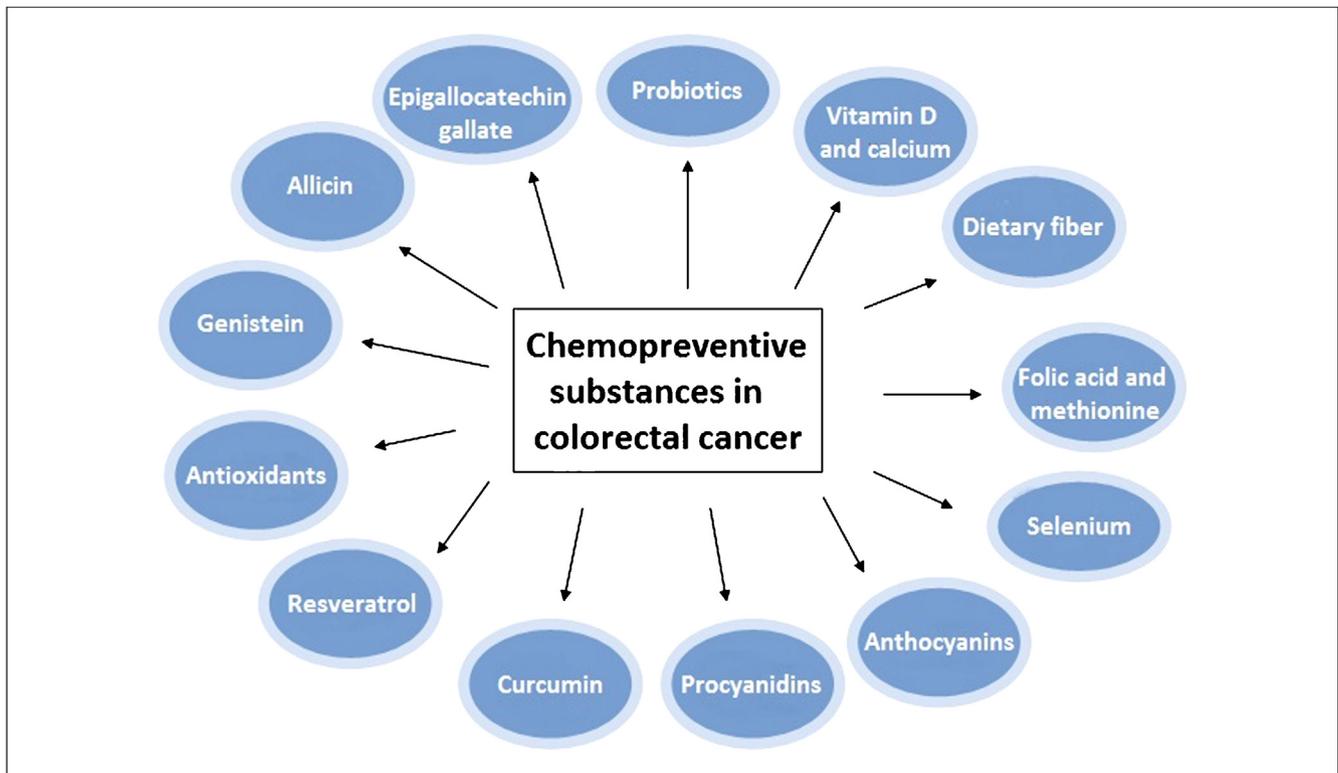


Fig. 1 – Chemopreventive substances in colorectal cancer.

than 200 potentially active ingredients,<sup>2</sup> whose clinical relevance is constantly tested, have been detected.

## 2. Aim

The aim of the paper is to present a number of substances having a chemopreventive effect in colorectal cancer.

## 3. Material and methods

A method that was used for the creation of this article was to review the literature.

## 4. Discussion

Epigallocatechin gallate is a biologically active compound contained in green tea. It belongs to a group of catechins, whose content in tea leaves is 30%–42% of dry weight.<sup>3</sup> The chemopreventive action of epigallocatechin gallate is inhibition, reversal or delay of the process of carcinogenesis in its early stages. It has been proven that this compound has a protective effect against a number of substances inducing cancer in many organs, including colon.<sup>4</sup> Studies conducted in China and Japan have proved reduction of colorectal cancer risk among people who consume green tea.<sup>5</sup> The preventive effect was demonstrated with ingestion of green tea in an amount of more than 10 cups per day.<sup>6,7</sup>

In the human body, dietary fiber carries a variety of health-related functions: it increases excrement weight, shortens intestinal transit, lowers the pH of the intestinal contents, binding potential carcinogens in the gastrointestinal tract and affects the growth of beneficial intestinal microflora.<sup>8</sup> In addition, it has been proven that the metabolites of fiber play an important role in maintaining the balance between cell proliferation, differentiation and apoptosis of epithelial cells of the colon.<sup>9</sup> By itself it is not considered to be a chemopreventive substance, but considering its above-described indirect action, dietary fiber may reduce the risk of colorectal cancer.<sup>8</sup> Based on the analysis it was found that the incidence of colorectal cancer is reduced in the group of people who consume 31 g of dietary fiber daily, compared with the group in which the consumption of this component is less than 10 g per day.<sup>10</sup> Other studies have not confirmed the above hypothesis. This may be due to the fact that the effect of a diet rich in fiber depends on the type of fiber consumed – for example, in fruits pectin is dominant, cereals are rich in hemicellulose, and each fraction of fiber is characterized by different properties, and different effects in the gastrointestinal tract.<sup>9</sup>

Probiotics are living organisms that, when ingested, have a beneficial effect on the host.<sup>11</sup> Prebiotics are compounds non-digestible by human and can enhance the effects of probiotics.<sup>12</sup> The specimen containing both a probiotic and a prebiotic is called symbiotic.<sup>9</sup> In the scientific literature there have been more and more reports which indicate the role of prebiotics, probiotics and synbiotics in the prevention of colon cancer.<sup>9</sup> Mechanisms of their activity in relation to colorectal cancer are not fully understood yet. It is known, that the lactic

acid bacteria are characterized by their ability to bind and degrade the potential carcinogens and for the induction of enzymes which are involved in metabolism of carcinogens.<sup>13</sup> In animal experiments it has also been demonstrated that bacteria *Lactobacillus acidophilus* and *Bifidobacterium longum* inhibit the process of carcinogenesis. Furthermore, it was found that under the experimental conditions prebiotics reduced tumor growth.<sup>14</sup> Another advantageous effect of probiotics and prebiotics is to synthesize short chain fatty acids, particularly butyric acid and butyrate. They have an ability to act on the genes that regulate cell proliferation, thereby inhibiting the proliferation of tumor cells.<sup>15</sup> Thus, studies in animal models show that the probiotics, prebiotics and synbiotics play an important role in the fight against colorectal cancer.<sup>9</sup>

It has been shown that vitamin D has a preventive effect against colon cancer. Peters et al.<sup>16</sup> conducted a study which reported a reduction in the risk of colorectal cancer by 26% with increasing concentrations of vitamin D3 in serum by 10 ng/mL. Calcium, whose good source is milk,<sup>17,18</sup> is also considered as a chemopreventive component – analysis of the tests performed on 135 000 of patients shows significant reduction in the risk of colorectal cancer in the application of a minimum daily dose of 1.25 g of calcium.<sup>19</sup> Furthermore, epidemiological studies indicate that calcium and vitamin D are interacting factors limiting risk of some cancers, including colon cancer.<sup>9</sup> This hypothesis has been confirmed by studies carried out by Peterlik et al.<sup>20</sup> – they provide evidence that vitamin D and calcium act synergistically, which is why in chemoprevention it is necessary to supplement both compounds.

There has also been a study focused on finding the correlation between intake of selenium and the incidence of prostate cancer. It was observed that consumption of this element in a dose of 200 µg per day reduces the risk of not only prostate cancer but also colorectal cancer.<sup>20</sup> Nelson et al. presented a summary of the research results on chemopreventive effects of selenium – according to them, this element is significant for the incidence of colorectal cancer.<sup>21</sup>

Folic acid and methionine play an important role in maintaining the stability of DNA.<sup>9</sup> Their deficiency in diet can cause a breach of the proper synthesis, repair, and transcription of DNA. It may also lead to increased DNA damage, which is a risk factor of carcinogenesis.<sup>22</sup> In the review study, results of several studies relating to the importance of folate as a chemopreventive substance were summarized, and it was determined that supplementing diet with folic acid reduces the risk of colorectal cancer.<sup>23</sup> In cohort studies reduced risk of colon cancer in men and rectal cancer in women, due to dietary supplementation of significant amounts of methionine,<sup>24</sup> was also shown.

Anthocyanins are biologically active compounds which have a relatively low absorption and penetration into the bloodstream.<sup>9</sup> The subject of the research on anthocyanins was extracts or aqueous solutions derived from red grapes, blueberries, chokeberry, cherry, blackberry, black currants, cranberries, raspberries or strawberries. Authors of numerous studies have found the antitumor effect of an anthocyanin, which consisted of reducing lipid peroxidation and inhibiting cell proliferation.<sup>9</sup> These properties were confirmed by Wang et al.<sup>25</sup> in the study related to consumption of black raspberry

powder at a dose of 60 g per day for 2–4 weeks by a group of 25 patients diagnosed with colorectal cancer or a precancerous condition.

Procyanidins, as described above anthocyanins are minimally absorbed by the digestive tract, and therefore their concentration in the colon may be high – up to several hundred micromoles per liter of the intestinal contents.<sup>26</sup> This creates potential opportunities for local antitumor effect. High content of procyanidin can be found in berry and chokeberry.<sup>9</sup> These compounds are also present in the peel and flesh of apples, which indicates the chemopreventive effect of this fruit in relation to colorectal cancer.<sup>27</sup> The antitumor effect of procyanidins from apples was also confirmed in animal model studies. It was found that they inhibit promotion and progression of carcinogenesis and constitute a preventive agent on the stage of initiation of cancer.<sup>27</sup>

Curcumin is a polyphenol. It exhibits high antioxidant activity. It was found that its anti-tumor activities against colon cancer are limiting the survival of cancer cells, inhibiting their proliferation, invasiveness and angiogenesis blocking, and limiting the ability of metastasis.<sup>9</sup>

Literature data indicate potential use of resveratrol in the chemoprevention of colorectal cancer. In in vitro studies it has been shown that resveratrol has a predisposition to slow down the cycle of colon cancer cells.<sup>28</sup> There are reports indicating a synergistic effect of resveratrol and curcumin.<sup>29</sup>

Vitamins A, C, E and β-carotene are antioxidants. Antioxidants occurring in plant material are important for protecting the body against cancer.<sup>30</sup> Their chemopreventive properties are also supported by the low toxicity and lack of side effects.<sup>31</sup> It should be noted, that the effect of antioxidants depends on the ingested quantity – at too high doses, their role is changing and substances with protective effects become severe.<sup>30</sup>

Another potential chemopreventive agent occurs in soybeans – it is genistein.<sup>31</sup> It belongs to the group of flavonoids. In animal models studies it has been shown that soy diet has an inhibitory effect on the carcinogenesis process.<sup>32</sup> The effect of genistein is inhibition of cell growth and induction of their apoptotic death.<sup>31</sup>

In recent years there have been suggestions that a balanced diet combined with regular consumption of adequate amounts of fresh garlic reduces the risk of colorectal cancer.<sup>33</sup> Antitumor agents are contained in garlic sulfur compounds.<sup>34</sup> An antitumor effect of substances such as: diallyl sulfide (DAS), diallyl disulfide (DADS), as well as diallyl trisulfide (DATS) has been experimentally confirmed.<sup>33</sup> It has also been shown that allicin, which is the biologically active component of fresh crushed garlic extract, induces apoptosis of colon cancer cells.<sup>35</sup> Many studies do not confirm the anticancer activity of garlic.<sup>36,37</sup> Nevertheless, the World Cancer Research Fund (WCRF) recommends regular consumption of garlic in the prevention of colorectal cancer.<sup>33</sup>

In chemoprevention, where natural compounds are implemented, interactions between various components of a product or the entire diet are important, because the ultimate effect of their mutual action may be different from what is achieved with the administration of each substance. This is due to the fact that a specific substance may have a synergistic, additive, or even antagonistic effect.<sup>9</sup>

## 5. Conclusions

There are many substances that have a potentially chemopreventive effect in colorectal cancer but currently chemoprevention is of limited use in prevention of colon cancer. This is mainly due to the fact that there is lack of clear evidence of preventive and therapeutic effects of chemopreventive substances.

On the basis of current knowledge the following dietary recommendations for the prevention of colorectal cancer can be drawn:

- consume a well-balanced and varied diet,
- eat vegetables and fruits that are a unique source of antioxidants, dietary fiber, allicin, genistein, resveratrol, anthocyanins, procyanidins and folic acid,
- eat cereal products which are a good source of dietary fiber, methionine and selenium,
- eat dairy products that provide large amounts of calcium and contain probiotics,
- replace the consumption of red meat with marine fish rich in vitamin D,
- regularly drink green tea.

## Conflict of interest

None declared.

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