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Scutellaria Baicalensis Georgi in the Suppression of Colorectal Cancer Through Modulation of the Intestinal Flora

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Abstract: Colorectal cancer (CRC) is a common malignant tumor worldwide, and its incidence and mortality are growing year by year. In recent years, the beginning and course of CRC are directly linked to intestinal flora imbalance, according to an increasing number of research.Therefore, finding a unique treatment approach and direction that can regulate the intestinal flora is therefore urgently needed. Traditional Chinese medicine as an adjuvant therapy for CRC has the characteristics of multi-targets, multi-levels, multi-links, and overall regulation, and it has significant advantages in the prevention and management of CRC.Scutellaria baicalensis Georgi (SBG), as one of the main drugs in the utilisation of traditional Chinese medicine as an adjuvant therapy for CRC, has been widely studied and recognised. Studies have shown that SBG and its active ingredients can aid in the prevention and management of CRC by regulating the intestinal flora, improving the imbalance of the flora, inhibiting the proliferation of harmful microorganisms, and enhancing the function of advantageous microorganisms. In addition, scutellaria can also inhibit the incidence and development of CRC by inhibiting inflammatory response, inducing apoptosis of cancer cells and blocking signaling pathways

Keywords: Scutellaria baicalensis Georgi, Intestinal flora, Colorectal cancer, Anti-tumour mechanism of action.

1. Introduction

Colorectal Cancer (CRC) is one of the most common malignant tumors with high morbidity and mortality worldwide. With about 1.9 million new cases and around 930,000 fatalities worldwide in 2020, CRC is expected to rank third in terms of cancer incidence and second in terms of cancer-related mortality. With the changes in people's living environment and dietary habits, the incidence rate of CRC has been on the rise, particularly in the more urbanised countries and regions, and has become an important disease that threatens human life and health [1]. Thus, CRC has become one of the key diseases that need urgent attention and solution in the global medical community. In recent years, as the scientific fields of systems biology, microecology, and molecular biology continue to advance, the function of intestinal flora in the development and incidence of CRC has gradually received widespread attention. In typical circumstances, the intestinal flora keeps the host in a dynamic equilibrium, helps to keep the intestinal barrier’s integrity intact, and regulates the

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immunological system of the body [2]. However, in CRC patients, specific damage to the gut may lead to dysbiosis. This dysbiosis could be a factor in the onset and spread of CRC by triggering chronic inflammation, production of oncogenic metabolites, abnormalities in the immune system and disruption of the intestinal barrier, among other mechanisms [3]. Therefore, the search for novel preventive and therapeutic strategies that can regulate intestinal flora has become a popular subject in contemporary medical research.

Traditional Chinese medicine (TCM) has the characteristics of holistic concept and individualised treatment, which can comprehensively regulate the balance of the body's internal environment through a multi-component and multi-targeted mechanism of action. At the same time, studies have shown that TCM has unique advantages in regulating intestinal flora to prevent and treat CRC. Scutellaria baicalensis Georgi (SBG), as a specific representative TCM, has anti-inflammatory, antioxidant and anti-tumor pharmacological effects [4]. A growing number of studies in recent years has shown that SBG could assist with both prevent and treat CRC by regulating the composition and metabolism of intestinal flora and restoring flora homeostasis. However, studies on SBG inhibiting CRC by regulating intestinal flora are still limited, especially its specific mechanism has not been fully elucidated. This paper aims to explore the possible mechanisms by which SBG inhibits the development of CRC by regulating the intestinal flora and to provide a new scientific foundation for both the prevention and management of CRC.

2. Relationship between intestinal flora and colorectal cancer

Given that the human body is its greatest micro-ecosystem, the intestinal flora is often regarded as the "forgotten organ" in human health and diseaseand plays a vital part in keeping host health and regulating a variety of physiological functions. Under normal conditions, a dynamic balance between the intestinal flora and the host is maintained to maintain intestinal homeostasis, and this balance is essential for normal physiological functions of the body [5]. Under homeostatic conditions, the intestinal flora constitutes a natural shield against infection, and its metabolic activity not only protects the intestinal mucosal barrier to defend against pathogen invasion and colonisation, thus reducing the risk of infection, but also produces short-chain fatty acids (SCFAs), including acetic, butyric and propionic acid via metabolism, which supply cells of the intestinal epithelium with energy, encourage the differentiation and repair of the intestinal epithelial cells, enhance the intestinal mucosal barrier integrity and prevent highly hazardous substances from penetrating through the intestinal wall integrity, and prevent highly hazardous substances from entering the body’s flow via the intestinal wall [2]. On the other hand, intestinal flora can facilitate the release of anti-inflammatory factors by participating in and regulating the immunological system of the body, which plays a role in suppressing inflammatory responses [2]. Therefore, intestinal flora dysbiosis can aid in the advancement of and incidence of CRC through the following mechanisms:

2.1. Generation and enhancement of chronic inflammatio

Dysbiosis of intestinal flora leads to disturbances in the intestinal internal environment and triggers a sustained inflammatory response. It induces intestinal epithelial cells to over-secrete pro-inflammatory factors which include tumor necrosis factor- α(TNF-α) and interleukin-6 (IL-6), which in turn further activates inflammation-related signalling pathways such as NF-κB, PI3K/AKT and other inflammation-related signaling pathways, forming a pro-inflammatory-cancer-causing vicious circle, exacerbating inflammatory responses and thereby accelerating the development of CRC [2]. Meanwhile, under the continuous stimulation of chronic inflammation, inflammatory cells (e.g., macrophages and neutrophils) can generate reactive nitrogen species (RNS) and reactive oxygen species (ROS), which are free radicals with strong oxidative capacity, and will interact with biological

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constituents such lipids, proteins, and DNA, resulting in DNA damage, which therefore triggers the development of CRC [5].

2.2. Production of carcinogenic metabolites

Altered metabolites of the flora are also important factors in tumorigenesis. Certain intestinal flora metabolise secondary bile acids, for example, deoxycholic acid (DCA), which could promote colon cancer cell proliferation and contribute to CRC carcinogenesis and progression by inducing oxidative stress leading to DNA damage, thereby increasing genomic instability [2]. In addition, the imbalance of SCFAs, such as acetic, propionic and butyric acid, further promotes CRC, e.g., butyric acid possesses antiproliferative and anticancer properties, inhibits cancer cell growth, and induces apoptosis. Whereas, dysbiosis can lead to reduced levels of butyric acid, thus weakening the inhibitory effect on colorectal cancer cells [2].

2.3. Disruption of intestinal barrier function

Dysbiosis also leads to disruption of the tight junction structure seen in intestinal epithelial cells. It has been found that intestinal dysbiosis can lead to down-regulation of expression or structural damage of tight junction proteins, such as ZO-1 and Occludin, which can disrupt the integrity of the intestinal barrier, increase intestinal permeability, and make it easier for harmful substances (e.g., pathogenic bacteria, bacterial products, and metabolites) to penetrate into the body, triggering chronic inflammation, which can then promote the development of CRC [6].

2.4. Production of genotoxins of bacterial origin

Some pathogenic bacteria can also directly induce carcinogenesis in host cells through the production of genotoxins. For example, E. coli produces colibactin, which induces DNA double-strand breaks, leading to cell cycle disruption and genomic instability, which therefore promotes the evolution of CRC [2]. Furthermore, fusobacterium nucleatum produces FadA adhesin, which adheres to colonic epithelial cells and stimulates the β-catenin signalling pathway, enhancing the value-added capacity of cancer cells, thereby increasing the risk of CRC carcinogenesis [2].

In a word, intestinal flora plays a multidimensional, complex and far-reaching role in the pathogenesis of CRC. Dysbiosis collectively drives CRC development and progression by promoting chronic inflammation, production of oncogenic metabolites, impairment of intestinal barrier function, and production of genotoxins, among other aspects. Therefore, restoring the balance of intestinal flora could be a possible target for the therapy of CRC.

3. Pharmacological mechanism of SBG

SBG, also known as camellia root, is a perennial herbaceous root plant of the genus Scutellaria in the family Labiatae, and its root is the main medicinal part. As a traditional Chinese medicine, the first recorded reference to SBG may be found in Shennong Ben Cao Jing, which is Classic of the Materia Medica of the Divine Husbandman and SBG was classified as a "superior" drug [4]. Its pharmacological efficacy has been recorded in Shennong Ben Cao Jing: "SBG, bitter and cold, is the main treatment for jaundice with all kinds of fever, coughing and reversal of the upper qi, and dysentery with dampness-heat [7]. For a long time, it is used to treat lung heat cough, dampness-heat diarrhea, jaundice fever, blood heat and other diseases, with the efficacy of eliminating heat, drying out moisture, diarrhoea and detoxifying. With the development of modern pharmacological research, a variety of bioactive components of SBG and their potential roles in the prevention and management of a variety of diseases have been gradually revealed. SBG is rich in a variety of bioactive components,

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the most important of which are flavonoids (such as baicalin, baicalein, baicalein and baicalin), terpenoids and polysaccharides, etc. It is also rich in many trace elements, such as iron, copper and zinc, etc. These components give SBG a remarkable anti-inflammatory effect. These components endow SBG with significant anti-inflammatory, antioxidant, anticancer, and many other pharmacological effects, which makes it occupy an important position in both Chinese medicine clinics and modern medical research [4]. The database search revealed that heat-clearing and detoxifying Chinese medicines including SBG have shown good anti-colorectal cancer activity in the last 20 years [8]. Meanwhile, based on bioinformatic analysis prediction, 58 herbal medicines including SBG were found to be effective against inflammatory bowel disease-colorectal cancer [9]. In addition, by observing that SBG extract significantly improved the makeup of rats' the intestinal flora in the absence of the spleen and dampness-heat model, it was found that SBG had an important role in intestinal flora homeostasis, which established a crucial foundation for the use of SBG intervention in intestinal flora for the treatment of CRC strategy [10].

4. SBG inhibits colorectal cancer by regulating intestinal flora

SBG has received extensive attention in both TCM and modern medicine for its wide range of anti-inflammatory, antioxidant and antitumor pharmacological properties [4]. An increasing number of research conducted in recent years have revealed that SBG can improve the intestinal microenvironment by regulating the composition and metabolic activity of intestinal flora, thus effectively inhibiting the incidence and development of CRC.

4.1. Reducing the inflammatory response

4.1.1. Reduction of pro-inflammatory factors/inhibition of signalling pathways

Making advantage of rat models of chemotherapy-induced intestinal mucositis (CIM), the results demonstrated that baicalein greatly decreased the serum concentrations of TNF-α and IL-6 and slowed down the inflammatory response in mice [11]. Meanwhile, the anti-inflammatory effect of baicalein was explored using a TNBS (2,4,6-trinitrobenzene sulfonic acid)-induced colitis model in mice. It was found that baicalein greatly decreased level of the activation of PI3K/AKT/NF-κB and down-regulated the expression levels of TNF-α and IL- 6 in contrast to the control group [12]. These studies demonstrated that baicalein had the ability to lower the levels of pro-inflammatory factors (IL-6, TNF-α) by down-regulating the activation status of the PI3K/AKT/NF-κB pathway, thereby attenuating chronic inflammatory responses and effectively inhibiting the development of CRC.

4.1.2. Regulating the balance of intestinal flora and restoring intestinal microenvironmental homeostasis

Experimental studies were conducted to analyze the regulatory effects of baicalein on the intestinal flora through a mouse model of chemotherapy-induced intestinal mucositis (CIM). It showed that the richness and diversity of intestinal probiotics (Lactobacillus and Bifidobacterium) significantly increased, while the richness and diversity of harmful microorganisms (Anabaena spp. and Clostridium spp.) significantly decreased after baicalein intervention [11]. It was further verified that baicalein prevented the occurrence of CRC to a certain extent by encouraging the spread of advantageous microorganisms (e.g., Lactobacillus and Bifidobacterium), inhibiting the growth of pathogenic bacteria (Bacteroidetes and Clostridium), regulating intestinal pH and restoring the equilibrium of the intestinal flora to inhibit the occurrence of chronic inflammation, reducing the generation of ROS and RNS, and decreasing the DNA damage induced by oxidative stress.

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4.2. Regulation of colorectal cancer metabolite production

By utilising an anti-PD-1 resistant melanoma mouse model, baicalein increased the richness and diversity of advantageous microorganisms (e.g. Lactobacillus, Bifidobacterium) and decreased the richness and diversity of harmful microorganisms (e.g. Bacteroidetes, Clostridium spp.) in the gut, which led to a substantial elevation in the concentrations of SCFAs (e.g. butyric acid) and an improvement in the PD-1 (CD8+ T cells/Treg) balance in the immune microenvironment, which in turn enhanced CD8+ T cell-mediated tumor suppression [13]. This demonstrated that baicalein could inhibit CRC growth by raising the number of advantageous microorganisms, boosting the synthesis of advantageous metabolites, such as SCFAs, improving the colorectal microenvironment, and inhibiting the proliferation of colorectal cancer cells. Meanwhile, in rat models of ulcerative colitis brought on by dextran sulphate sodium (DSS), baicalein magnesium was found to significantly improve the bile acid metabolic process and regulate the composition and level of bile acids in serum and colonic tissues. It showed that baicalein magnesium increased the levels of beneficial bile acids (e.g., taurocholic acid) and decreased the levels of harmful bile acids (e.g., deoxycholic acid), which improved metabolism of bile acids and inhibited inflammatory responses [14]. This further authenticates that baicalein may lower the risk of developing CRC by modulating the metabolism of the flora and decreasing the levels of harmful metabolites (e.g., secondary bile acids), thereby reducing the pro-inflammatory response.

4.3. Repair/enhancement of intestinal mucosal barrier immune function

Using the dextran sulphate sodium (DSS)-induced colitis animal model, it was found that the protein expression levels of ZO-1 and Occludin in the colon tissue of experimental mice decreased significantly, and the intestinal permeability increased, whereas after baicalein administration, the expression of these proteins showed a significant increase, and intestinal permeability was also significantly improved, and the structure of tight junction protein was repaired, thus enhancing the intestinal barrier's integrity [15]. This suggests that via elevating the expression levels of tight junction proteins, such as ZO-1 and Occludin, and improving the intestinal barrier integrity, baicalein can restore the intestinal barrier function thus reducing the penetration and inflammatory response of pathogenic bacteria and toxins and lowering the risk of CRC.

Regarding the production of genotoxins of bacterial origin, although there are no relevant mouse experiments demonstrating that SBG inhibits the production of genotoxins of bacterial origin (e.g., colibactin and FadA adhesin) and its oncogenic mechanism through the regulation of the intestinal flora, it is reasonable to speculate about the potential role of SBG and its active constituents (e.g., baicalein and baicalein) based on their known mechanisms of action. SBG and its active ingredients (e.g. baicalin and baicalein) have been shown to have anti-inflammatory, antioxidant, and intestinal flora-regulating effects, inhibiting the growth of harmful microorganisms (e.g. Escherichia coli and Clostridium nucleatum) and promoting an increase in the richness and diversity of advantageous microorganisms (e.g. Lactobacillus and Bifidobacterium). The anti-inflammatory effects of SBG inhibit the generation of pro-inflammatory cytokines in the gut, such as TNF-α and IL-6, to reduce inflammatory responses, while the antioxidant effects of SBG attenuate DNA damage induced by oxidative stress. These effects may indirectly reduce the genotoxins synthesis and prevent DNA damage and activation of oncogenic signalling pathways. Future studies may further validate the inhibitory effect of SBG on genotoxin-mediated CRC and its specific mechanism through mouse models.

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5. Conclusion

Scutellaria baicalensis Georgi, as a TCM with anti-inflammatory, antioxidant and intestinal flora regulating properties, can inhibit inflammation and tumor growth via controlling the intestinal flora and improving the dysbiosis, which has a great potential application value in the prevention and management of CRC, while there are still some limitations and challenges in the research of its practical application. Studies have shown that baicalin and baicalein in SBG can improve the microenvironment of CRC, inhibit inflammatory responses and induce apoptosis of cancer cells by affecting the metabolites produced by the intestinal flora (e.g., SCFAs), but the specific types of target flora and the mechanism of action are still unclear, and inter-individual heterogeneity of the intestinal flora may lead to a large discrepancy of the therapeutic efficacy of baicalein in different individuals. In particular, the metabolism of baicalein into baicalein under the action of intestinal flora is affected by the composition of the flora, which further increases the instability of the efficacy. In addition, most of the current studies are still at the stage of models of animals and experiments conducted in vitro and lack the support of long-term clinical follow-up and randomized controlled trials (RCTs) to comprehensively evaluate the clinical effectiveness and safety of baicalin in intervening with the intestinal flora. Meanwhile, external factors such as the use of antibiotics and dietary practices may also interfere with the regulatory effects of baicalin on intestinal flora, further increasing the uncertainty of its clinical application.

Despite its limitations, SBG has a promising application in both prevention and therapy of CRC by regulating the intestinal flora. In the future, the molecular mechanism of SBG in regulating intestinal flora can be explored by macro-genomics and metabolomics technologies, and key target bacteria with specific regulatory effects can be screened out by single-strain co-culture technology. Meanwhile, the effectiveness and safety of SBG in interfering with intestinal flora can be systematically evaluated by conducting multi-center, RCTs to establish a standard dosing model. In addition, the combined application of SBG with other treatments, such as combined probiotic supplement or intestinal microecological therapy, can be further explored to further enhance the regulatory ability of SBG on intestinal flora, expand its application range in CRC prevention and adjuvant therapy, and provide a more accurate and safe natural medicine strategy for CRC prevention and management.

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