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Review article

A Review on Colorectal Cancer and the Role of Traditional Chinese Herbal Medicine as Complementary Therapy

Jie Ji[1], Hiu Ching Phang[1], Xian Gu[2], Riyanto Teguh Widodo[3], Bey Hing Goh[4,5], Phei Er Kee[6], Siew-Keah Lee[7], Ashok Kumar Janakiraman[8], Long Chiau Ming[9*], Kai Bin Liew[1*]

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[1]Faculty of Pharmacy, University of Cyberjaya. Persiaran Bestari, 63000 Cyberjaya, Selangor, Malaysia ; 2112-4733@st.cyberjaya.edu.my (JJ) ; phanghiuching@gmail.com (HCP)

[2]Department of Oncology 5, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 200032 Xuhui District, Shanghai, China; 13761347124@163.com (XG)

[3]Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur 50603, Malaysia; riyanto@um.edu.my (RTW)

[4]Sunway Biofunctional Molecules Discovery Centre, School of Medical and Life Sciences, Sunway University, Bandar Sunway, 47500, Darul Ehsan, Selangor, Malaysia; beyhingg@sunway.edu.my (BHG)

[5]Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW, Australia

[6]Biorefinery and Bioprocessing Engineering Laboratory, Department of Chemical Engineering and Materials Science, Yuan Ze University, Chungli, Taoyuan 320, Taiwan; pheier.kee@saturn.yzu.edu.tw (PEK)

[7]M. Kandiah Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Selangor, Malaysia; leesiewkeah@utar.edu.my (SKL)

[8]Faculty of Pharmaceutical Sciences, UCSI University, No 1, Jalan Menara Gading, UCSI Heights, 56000 Cheras, Kuala Lumpur, Malaysia; ashok@ucsiuniversity.edu.my (AKJ)

[9]School of Medical and Life Sciences, Sunway University, Sunway City, 47500 Subang Jaya, Selangor, Malaysia

*Corresponding authors: School of Medical and Life Sciences, Sunway University, Sunway City, 47500 Subang Jaya, Selangor, Malaysia; chiaumingl@sunway.edu.my (LCM), Faculty of Pharmacy, University of Cyberjaya. Persiaran Bestari, 63000 Cyberjaya, Selangor, Malaysia; liewkaibin@cyberjaya.edu.my (KBL)

Abstract: Colorectal cancer (CRC), encompassing cancers of the colon and rectum area, is the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths globally, posing a significant health challenge. In 2020, CRC contributed to 9.4% of all cancer fatalities. With the significant rise in cases among the elderly, it is projected that

the figure will double by 2035 globally, particularly in less developed countries. For many years, surgery and chemotherapy have been the mainstay treatments for cancer, but patients with metastatic disease have generally faced poor outcomes. Currently, there is a renewal of interest to explore the potential of natural products to treat cancers. Nature provides many effective treatments for severe diseases, with around 75–80% of the global population relying on conventional medical practices due to limited access to healthcare and concerns about synthetic medicine safety. Natural products are crucial for treating infectious diseases, cancer, and neurological disorders, and references in religious texts have spurred scientific validation of traditional claims. These products are excellent sources for CRC treatments, with nearly 50% of current cancer therapies derived from natural ingredients. This review focuses on the discussion of colorectal cancer and the potential of Chinese traditional herbs used in treating colorectal cancers. Furthermore, various signalling pathways of CRC and the possible mechanism of TCM intervening in these pathways are also discussed.

Keywords: colorectal cancer; traditional Chinese medicine; herbal; natural products; cancer treatment; SDG 3 Good health and well-being

1. Introduction

Cancer is a class of diseases marked by uncontrolled cell growth and division, encompassing over 100 diseases that develop over time and involve abnormal cell behaviour[1]. Cancer can develop in any body tissue, and each type has unique characteristics. The disease starts when a cell breaks free from normal growth controls and begins to multiply on its own. The human body has about 30 trillion cells that normally regulate each other's growth. Healthy cells only reproduce when instructed by other cells, ensuring that each tissue maintains proper size and function. Cancer cells ignore these controls, leading to unchecked growth and the formation of tumours, eventually spreading to other body sites. Over time, these malignant cells become more aggressive and can be fatal when they disrupt vital tissues and organs[2,3].

Scientists have identified key principles in cancer development. Tumor cells descend from a common ancestral cell that began to multiply inappropriately due to mutations in specific genes[4]. These genes, found in the DNA of cell chromosomes, control the production of proteins that regulate cell behaviour[5]. Mutations can alter these proteins, leading to cancer. Tumour development occurs in three main stages: initiation, where a normal cell acquires a genetic mutation and increases its tendency to proliferate; hyperplasia, in which the altered cell and its descendants reproduce excessively while still appearing normal; and dysplasia, where the cells become abnormal in shape and orientation, leading to uncontrolled growth[6,7].

If a tumour has not invaded surrounding tissues, it is called "in-situ cancer." Some cells may eventually acquire additional mutations, allowing the tumour to invade other

tissues and spread through the blood or lymphatic system. This stage is considered malignant and can lead to new tumours (metastases) that disrupt vital organs[4].

Recently, there has been a renewed interest and discussion on using natural products and their extracts to treat cancer. Traditional Chinese Medicine (TCM) has often been used by the Chinese community since ancient times as an adjunct and complementary therapy to treat colorectal cancer (CRC) aiming to enhance the patient's life quality and minimize side effects from conventional treatments like chemotherapy[3]. TCM plays an important role in post-operative care by helping to speed up recovery, reduce inflammation, and prevent recurrence. As a result, a detailed discussion on the roles of various TCMs as complementary medicine and their possible mechanisms intervening in the signalling pathways of CRC would be interesting and beneficial for the healthcare community to further explore the use of these products in clinical settings[4].

This review aims to provide a comprehensive overview of CRC including its development, risk factors, and current treatment strategies, while also evaluating the potential of TCM as an alternative or complementary therapy for CRC. The efficacy, mechanisms of action, and current state of research on the use of TCM in CRC treatment are thoroughly discussed. Additionally, the paper explores potential future directions for TCM in CRC treatment, encouraging further research into the integration of TCM as a complementary approach in modern oncology.

2. Colorectal Cancer

Colorectal cancer (CRC), encompassing cancers of the colon and rectum area, poses a major global health challenge as the third most commonly diagnosed and second deadliest cancer worldwide[8,9]. With the significant rise in cases among the elderly, it is projected that the figure will double by 2035 globally, particularly in less developed countries[10]. The two major contributing factors to the rise of the global incidence of CRC are environmental and genetic factors. Additionally, the risk of CRC heightens with age in patients with long-term ulcerative colitis and Crohn's disease. Various studies have identified risk factors for CRC, including diet, lifestyle, family history, and chronic inflammation[8,11].

The current screening process is effective in diagnosing CRC because the cancer is common and develops gradually from adenomas to carcinomas[12,13,14]. Evidence indicates that the development of early adenoma to CRC may take at least ten years, although the exact timeline for this development remains uncertain. This period is long enough and provides ample opportunity for detection and treatment. Removing colorectal adenomas can prevent CRC, and early detection significantly reduces mortality rates[15]. Effective strategies also involve identifying and monitoring high-risk populations, including families with hereditary CRC syndromes, individuals with inflammatory bowel disease, those with a family history suggesting a genetic predisposition to CRC but without detectable genetic markers and individuals whose phenotypic traits indicate a high-risk[16]. The metabolome has proven valuable in identifying key biological activities affected by genetic variation, with faecal

occult blood tests (FOBTs) and lower endoscopy being commonly used for CRC screening[16].

2.1. Colorectal Cancer Development

Colorectal cancer (CRC) is genetically diverse and develops through various mechanisms, often characterized by numerous somatic mutations due to distinct gene expression profiles[16,17,18]. It is classified into hypermutated and non-hypermutated types based on mutation rates. CRC progression begins when there is a change in genetic or epigenetic changes of epithelial cells, leading to hyperproliferation and the development of benign adenomas, which can eventually progress to cancer and metastasize through pathways like chromosomal instability (CIN) and microsatellite instability (MSI)[19,20]. The adenoma-carcinoma sequence is a common pathway for sporadic CRC cases, typically associated with the CIN-positive subtype and inflammation-related cancer development[21]. Benign precursor lesions, present in all CRC pathways, offer a significant window for secondary prevention since they can take years to develop into invasive cancer[22]. Most CRCs are adenocarcinomas, with a polyp potentially taking up to 18 years to become invasive, and metastasizing within nine years on average. CRC staging, from 0 (carcinoma in situ) to IV, determines the severity and treatment options, with surgery being the primary treatment for early stages and a combination of surgery, chemotherapy, and targeted therapy for advanced stages. However, no definitive cure exists for stage IV or recurrent CRC[23,24,25].

2.2. Global Epidemiology

Based on the data from GLOBOCAN, it was estimated that 19.3 million new cases of various cancers and 10 million cancer deaths worldwide in the year 2020. Out of this figure, 1.93 million were CRC cases and CRC caused 0.94 million deaths. Incidence and mortality of CRC cases are not distributed fairly across different regions worldwide. It is reported that CRC-detected incidence and mortality rates are generally higher in higher income areas than areas with lower income. Studies showed that the highest incidences (45.94%) and death (49.37%) rate are reported in the upper-middle income countries. Collectively, these two groups have contributed more than 88% and 85% of the incidence and mortality of CRC[26,27].

2.3. Signalling Pathway Involved in CRC

Several signalling pathways have been identified to be involved in CRC, including P13K/Akt, NF-κB, MAPK, Wnt/β-catenin, vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), Hedgedog signalling pathways. The mechanisms of each pathway are discussed in detail in the following subsections.

2.3.1. P13K-Akt

The PI3K/Akt signalling pathway is essential for regulating various biological functions, including cell survival, death, migration, protein synthesis, and metabolism. Its abnormal activation provides a growth advantage to tumour cells, and mutations in PI3K are among the most common alterations observed in CCRC[28], greatly influencing disease progression and clinical outcomes. The main components of this pathway include Phosphatase and Tensin Homologue Deleted on Chromosome Ten (PTEN), PI3K, Akt, and their downstream effectors[29].

PTEN and PI3K form a critical axis that regulates several proto-oncogenic signals, often disrupted in tumorigenesis and exploited by cancer cells for survival[30]. PTEN acts as a tumour suppressor and is frequently mutated in various cancers, playing a vital role in maintaining phosphatidylinositol levels[31]. PI3Ks are classified into three types, with Type I being the most extensively studied. Type I PI3K phosphorylates PIP2 to produce PIP3, which binds to proteins with a PH domain, facilitating the translocation of Akt to the cell membrane. Hence, Akt undergoes self-phosphorylation and activation at Ser124 and Thr450[32]. Akt, a serine/threonine kinase, has three isoforms: Akt1, Akt2, and Akt3. Each isoform features three functional domains: the N-terminal PH domain for protein-lipid interactions, the central kinase domain (CAT) containing an ATP-binding site (Thr308) crucial for activation, and the C-terminal EXT domain with a regulatory hydrophobic motif and a critical phosphorylation site (Ser473). Activated PI3K collaborates with 3-phosphoinositide-dependent protein kinase 1 (PDK1) to phosphorylate Akt at Ser473 and Thr308, leading to its activation. Once activated, Akt translocates to the nucleus, where it regulates various downstream proteins, including mTOR, Bad, caspase-9, NF-κB, and forkhead box O transcription factors, which are integral to the regulation of cell survival, proliferation, apoptosis, and angiogenesis[33,34,35].

2.3.2. NF-κB,

NF-κB, a nuclear transcription factor initially identified in B lymphocytes, typically exists as an NF-κBp50/NF-κBp65 dimer. This dimer dissociates when stimulated by tumour necrosis factor, interleukins, or chemical agents, allowing it to translocate into the nucleus. NF-κB plays a key role in linking inflammation and cancer and contributes to CRC development and progression[36]. Abnormal NF-κB activation is observed in around 50% of CRC patients and is linked to colitis-associated cancer (CAC). Elevated expression of NF-κB p65 is seen in CRC tumour tissues compared to normal mucosa. Activation of NF-κB creates a pro-inflammatory tumour microenvironment, regulating genes involved in cell proliferation, apoptosis, metastasis, angiogenesis, drug resistance, and inflammation. NF-κB also induces the transcription of various genes, such as tumour necrosis factor, interleukins, matrix metalloproteinase, and Bcl3, thereby promoting inflammatory responses, cancer cell proliferation, and migration[37].

2.3.3. MAPK

The MAPK family consists of three key categories: MAPKKKs, MAPKKs, and MAPKs, which play vital roles in cellular processes like inflammation, gene expression, cell division, survival, and apoptosis by amplifying and transmitting extracellular signals to the nucleus. Activation of the MAPK signalling pathway begins with the activation of MAPKKKs (e.g., Raf, TAK) by growth factors, cytokines, oxidative stress, and GTP-binding proteins. This triggers the phosphorylation of MKK, leading to the activation of MAPK through double phosphorylation at threonine/tyrosine sites[38].

The MAPK family includes four subunits: ERK1/2, JNK/SAPK, p38MAPK, and BMK1/ERK5. ERK1/2 regulates cell growth and differentiation but can promote tumorigenesis in ovarian, colon, and breast cancers when excessively activated. JNK is involved in stress-induced tumour proliferation, apoptosis, and metastasis, with links to diseases like arthritis and asthma. The p38MAPK family, with subunits such as p38α, p38β, p38γ, and p38δ, influences numerous physiological and pathological processes, including inflammation and apoptosis. ERK5 promotes cell cycle progression, endothelial cell proliferation, and vascular growth and is associated with cancers like liver, breast, and prostate cancers when highly activated. The MAPK pathway also interconnects with other signalling pathways, such as NF-κB and STATs, playing a regulatory role in inflammatory responses and cancer progression[39,40].

2.3.4. Wnt/β-catenin

The Wnt gene family, comprising homologous genes Int and Wingless, encodes 19 Wnt secreted glycoproteins and is a central part of the Wnt signalling pathway[41], which is divided into two main types: canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. The canonical pathway is involved in cell proliferation and migration[42,43]. The Wnt/β-catenin signalling pathway starts with interactions between cell surface receptors from the Frizzled (FZD) family and involves several key proteins, including adenomatous polyposis coli (APC), Axin, low-density lipoprotein receptor-related protein 5 (LRP5), LRP6, dishevelled (Dsh), glycogen synthase kinase 3 (GSK3), casein kinase 1 (CK1), and T cell factor (TCF)/lymphoid enhancer factor (LEF)[44]. β-catenin plays a crucial role in this pathway by binding to transcription factors like c-Myc, cyclin D1, and matrix metalloproteinases (MMPs) to regulate target gene expression[45].

Activation of the Wnt/β-catenin pathway promotes cancer stem cell proliferation and differentiation, and in most colorectal cancer (CRC) cases, overexpression of pathway target genes leads to cell cycle dysregulation, enhancing invasion and metastasis[46,47,48]. Therefore, controlling the Wnt/β-catenin signalling pathway is crucial in inhibiting CRC growth and metastasis[49].

2.3.5. Vascular endothelial growth factor (VEGF)

Tumor angiogenesis is a key factor in colon cancer invasion and metastasis, with research primarily focusing on VEGF and associated pathways. VEGF, initially identified as a cytokine that increases vascular permeability, is critical in promoting the formation of new blood vessels in tumours. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (PLGF), all of which play roles in colon cancer angiogenesis by stimulating endothelial cell proliferation and enhancing capillary permeability[50]. This allows for the extravasation of proteins, which aids in new capillary formation. Hypoxia-inducible factor (HIF) and transforming growth factor beta (TGF-β1) regulate VEGF expression, offering potential targets for anti-angiogenesis therapies in cancer treatment[51].

2.3.6. Transforming growth factor-β (TGF-β)

TGF-β is a multifunctional cytokine involved in numerous cellular processes, including embryonic development, tissue homeostasis, and immune regulation[52]. It belongs to the TGF-β superfamily, which consists of over 35 proteins such as activins and bone morphogenetic proteins[53]. These proteins signal through a heterotetrameric complex composed of type 1 and type 2 serine-threonine kinase receptors, transmitting extracellular signals to the cell nucleus to influence gene expression[54]. TGF-β signalling can either inhibit or promote cell proliferation and regulate immune responses. In cancers like CRC, alterations in downstream proteins, particularly Smad proteins, play a key role[53]. For example, Smad4 mutations are linked to compromised intestinal barrier integrity, altered gut microbiota, and weakened immune responses, contributing to colon cancer development[55].

2.3.7. Hedgedog

The Hedgehog signalling pathway is composed of ligands, receptors, and transcription factors. While Drosophila has a single Hedgehog ligand, mammals have three: Sonic Hedgehog (Shh), Indian Hedgehog, and Desert Hedgehog[56]. In this pathway, the patched (Ptch) receptor (with Ptch1 and Ptch2 subtypes) and Smoothened (Smo) protein are key components. Without Hedgehog ligands, Smo remains inhibited by Ptch. The glioma-associated oncogene homolog (Gli) family of transcription factors (Gli1, Gli2, and Gli3) regulates the transcription of target genes, with Gli1 as an activator, Gli2 as mainly an activator, and Gli3 as primarily inhibitory[57,58].

In CRC, the Hedgehog signalling pathway predominantly functions through the Shh-Ptch-Gli axis. In this context, Shh is frequently overexpressed, and abnormal activation of this pathway—often due to mutations in other associated genes—plays a crucial role in CRC development. Moreover, the Hedgehog signalling pathway affects the invasive potential of colorectal tumours and can facilitate tumour metastasis[59,60]. Activation of this pathway is associated with negative clinicopathological characteristics and poor survival rates among

CRC patients[61]. Thus, thoroughly investigating the Hedgehog signalling pathway is essential for its clinical implications in CRC prevention, treatment, and prognostic evaluation.

3. Current Treatment Strategies for Colorectal Cancer

Surgery and chemotherapy have long been the primary treatments for cancer patients. However, individuals with metastatic disease have traditionally faced a poor prognosis. Advances in primary and adjuvant therapies have extended survival times for CRC patients. Surgery, one of the most frequent treatments, is typically necessary to remove the tumour completely[62]. Around 25% of CRC cases are identified at an advanced stage, and an additional 20% of earlier-stage cases later develop metachronous metastases, complicating the possibility of curative surgery and frequently contributing to cancer-related deaths. To manage the tumour, radiotherapy or chemotherapy may be used pre- or post-surgery to reduce its size or halt its progression[63].

3.1. Targeted Therapy

Targeted therapy has become a groundbreaking strategy that greatly enhances overall survival rates in CRC patients. Treatments such as bevacizumab, an anti-angiogenesis agent and cetuximab, an anti-EGFR (epidermal growth factor receptor) agent have demonstrated significant success, spurring the swift development of new drugs designed to block various immunological pathway checkpoints[64]. Several key molecular checkpoints have been identified as potential targets for CRC treatment, including mesenchymal-epithelial transition factor (c-MET), hepatocyte growth factor (HGF), epidermal growth factor/epidermal growth factor receptor (EGF/EGFR), vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR), immune checkpoints (T cells), insulin-like growth factor/insulin-like growth factor 1 receptor (IGF/IGF-1R), transforming growth factor (TGF), Wnt/β-catenin, Notch, and Hedgehog pathways. In response to these targets, the U.S. Food and Drug Administration (FDA) has approved several targeted therapies for CRC. Cetuximab, the first of these agents, received FDA approval in 2004, and since then, many more targeted therapies have been approved, with others currently under development. Extensive preclinical and clinical research has been carried out on these drugs[16].

3.2. Gene Therapy

Gene therapy utilizes genetic material, like DNA or RNA, to treat a range of diseases, including cancer. This approach can involve replacing or repairing defective genes, and in some cases, it may trigger an immune response or be applied as an independent treatment. In CRC, mutations and genetic abnormalities play a significant role in driving the progression of the disease[65]. The potential to combat CRC lies in the modification and correction of these defective genes, as well as in preventing the overexpression of certain genes. The progression of colon cancer involves alterations in numerous genes, which may stem from point mutations, the formation of oncogenes, deregulation or deletion of proto-oncogenes, and the inactivation of tumour suppressor genes[49].

Approximately 2,600 clinical studies had been conducted in 38 countries as of November 2017, with over half of them classified as phase I trials[66]. Of the 1,309 gene therapy studies, only 45 advanced to phase III. A total number of 11 gene treatments for CRC are currently undergoing testing in the United Kingdom[67]. Of the estimated 50,000 to 100,000 genes in the human body, only a small fraction are involved in regulating the cell cycle. Defective genes are recognized as one of the major contributors to CRC, with around 30% of colon cancers being linked to gene mutations, some of which have hereditary connections. The main advantage of gene therapy lies in its ability to deliver specific genes directly to tumour cells, targeting and suppressing the malfunctioning gene, which in turn helps to slow down tumour growth[68].

3.3. Immunotherapy

Tumor immunotherapy has caught the attention of researchers because it shows great promise for treating CRC. Many clinical studies are currently testing immunotherapies in people with CRC[69]. Some of these immunotherapy methods include cytokine treatment, complement inhibition, adoptive cell therapy, cancer vaccines, immune checkpoint inhibitors and monoclonal antibody (mAb) therapy. Most of these studies are in phase I or II, and the results so far are promising. To date, more than 24 immunotherapy-based clinical trials for CRC have been conducted, with over 40 trials currently enrolling or set to begin enrolling patients soon[70].

3.4. Monoclonal Antibody Therapy

In this treatment approach, humanized antibodies inclusive of Cetuximab and Panitumumab are employed to manage metastatic CRC by specifically targeting the epidermal growth factor receptor (EGFR)[71]. Additionally, ongoing clinical trials are exploring other monoclonal antibodies (MAbs) for CRC, including adecatumumab, which targets the epithelial cell adhesion molecule (EpCAM), labetuzumab, which targets carcinoembryonic antigen (CEA), and pemtumomab, which is directed against mucins.

3.5. Cancer Vaccines

Cancer vaccines are made to boost the activity of T-cells or B-cells against cancer by delivering antigens to antigen-presenting cells (APCs) like dendritic cells (DCs). These vaccines also have elements that activate the DCs loaded with antigens and guide them to nearby lymph nodes. Examples include the DC vaccination and OncoVAX[72].

Since most CRCs express the tumor-associated carcinoembryonic antigen (CEA), DCs can be loaded with CEA mRNA or CEA peptides. Many CRC patients who received DC vaccinations showed CEA-specific T-cell immune responses, especially in advanced cases[73]. Oncovax treatment uses the patient's cancer cells mixed with an immune-boosting substance to trigger an immune response against the tumour and prevent colon cancer from returning after surgery. Combining this targeted immunotherapy with surgery greatly improves patient survival rates[74].

3.6. Natural Products and Traditional Chinese Medicine as Therapy

Nature provides many effective treatments for severe diseases, with approximately 75-80% of the global population relying on traditional medical systems due to limited access to healthcare and concerns about synthetic medicine safety[75]. Natural products are crucial for treating infectious diseases, cancer, and neurological disorders, and references in religious texts have spurred scientific validation of traditional claims. These products are excellent sources for CRC treatments, with nearly 50% of current cancer therapies derived from natural ingredients[76]. Types of natural products include alkaloids, polysaccharides, polyphenols, diterpenoids, and unsaturated fatty acids, each offering unique benefits. New natural products have advanced cancer prevention and treatment, with compounds like andrographolide, berberine, curcumin, and resveratrol undergoing clinical trials for CRC[77].

These compounds work by disrupting cancer pathways such as metastasis, invasion, apoptosis, and angiogenesis. Despite their benefits, drug resistance and side effects remain challenges in CRC treatment. Combining natural compounds with traditional chemotherapy, like 5-FU, can enhance cancer cell susceptibility to treatment. In China, injections like Ai-Di, Shen-Qi-Fu-Zheng, and Matrine, approved by the Chinese FDA, have improved response rates and quality of life for advanced CRC patients while reducing side effects[78].

Additionally, herbs and spices, used for centuries, offer preventive and therapeutic benefits against CRC. When used in large doses, they can protect against CRC or serve as adjuvant therapy with chemotherapy. Herbs and spices contain bioactive chemicals that benefit health by modulating pathways like BCL-2, K-ras, and MMP, activating caspases, and influencing ER-stress-induced apoptosis[79].

Traditional Chinese Medicine (TCM) is often used by the Chinese community as an adjunct therapy to treat CRC aiming to enhance the patient's life quality, minimize side effects from conventional treatments like chemotherapy, and sometimes slow tumor growth. TCM approaches include the use of herbal formulas, acupuncture, dietary therapies, and qi gong exercises[78].

A variety of herbal combinations are reported to be used traditionally to target CRC, focusing on enhancing immune function, reducing inflammation, and preventing cancer metastasis. Common herbs include *Astragalus membranaceus* (Huang Qi), *Ginseng* (Ren Shen), and *Scutellaria barbata* (Ban Zhi Lian). These herbs are believed to help tonify the body's qi (vital energy), reduce tumour size, and support recovery after surgery or chemotherapy[80,81].

On the other hand, TCM is used as chemotherapy side-effect mitigation. TCM herbs are commonly employed to alleviate the side effects of chemotherapy and radiation, such as fatigue, nausea, and weakened immunity. For example, *Ginseng* and *Astragalus* are often prescribed to boost energy levels and support immune function, while other herbs like *Licorice* (Gan Cao) may help reduce inflammation and improve digestion[78].

Some TCM herbs, such as *Curcuma* (Yu Jin), *Oldenlandia* (Bai Hua She She Cao), and *Scutellaria barbata* (Ban Zhi Lian), are believed to have direct anti-cancer effects. These herbs are used to inhibit cancer cell proliferation, induce apoptosis (programmed cell death), and reduce angiogenesis (the formation of new blood vessels that supply tumours). Some other TCMs are used as immune modulation to boost the body's immune system. Herbs like *Cordyceps* (Dong Chong Xia Cao) and *Lingzhi* (Reishi mushroom) are commonly used for their immune-boosting and anti-tumor properties. They help to enhance the body's natural ability to fight cancer cells and maintain overall health during CRC treatment[78,79].

TCM plays an important role in post-operative care by helping to speed up recovery, reduce inflammation, and prevent recurrence. Specific herbs are used to nourish the body, improve digestive health, and increase the strength of the digestive system following surgical treatment for CRC.TCM emphasizes detoxification of the body and balancing internal organ functions. By reducing toxins and controlling inflammation, TCM may reduce the risk of CRC recurrence. *Poria* (Fu Ling) and *Dandelion* (Pu Gong Ying) are used for detoxification purposes[78,79]. Figure 1 illustrates the actions of active compounds of TCM on various signalling pathways.

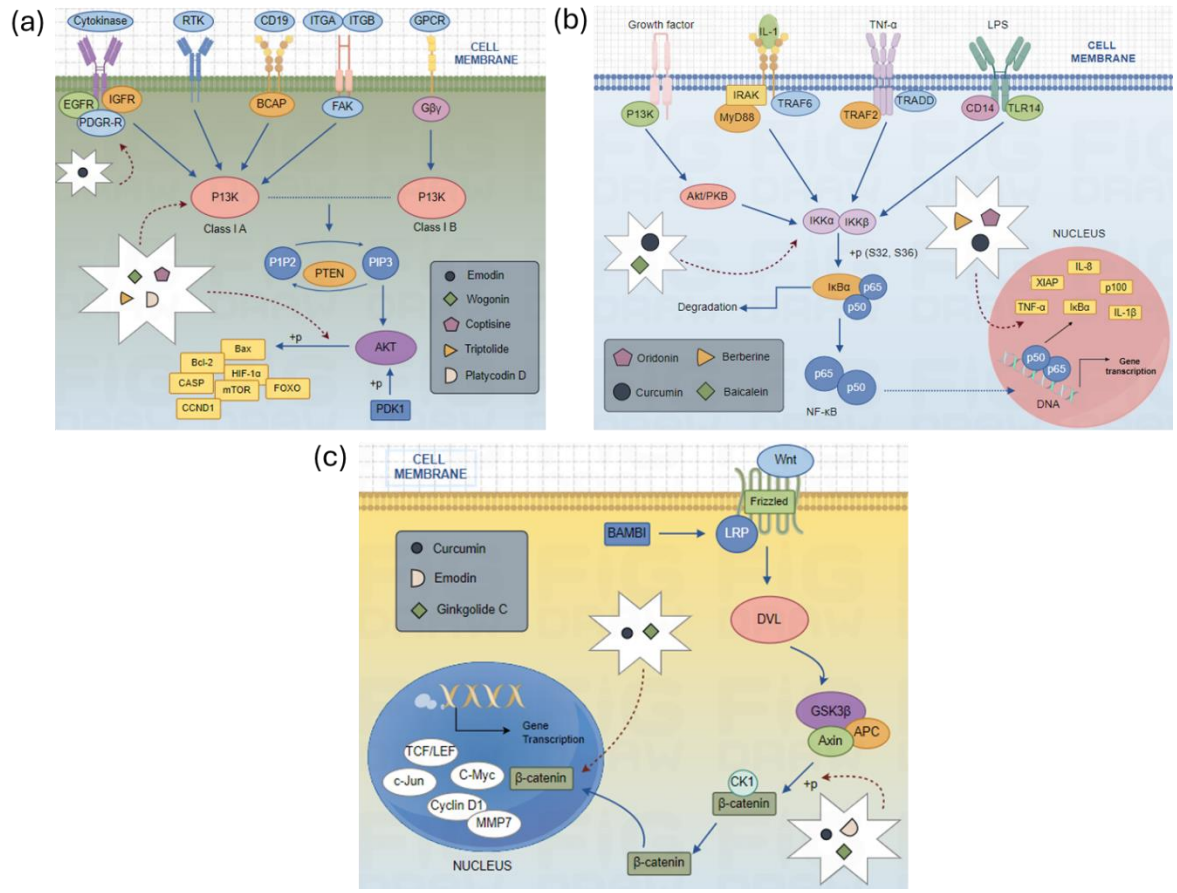

Figure 1. Active compounds of TCM on (a) PI3K/Akt, (b) NF-κB and (c) Wnt/β-catenin signalling pathways. Adapted from *Chen et al.* [82] and created with Figdraw.

4. Traditional Chinese Medicine and Herbs

TCM, along with various herbs and their extracts, has been extensively studied for their remarkable therapeutic effects in treating CRC. These substances exert their effects by inducing apoptosis, inhibiting cell proliferation, migration, invasion, and adhesion, and modulating gut microbiota[80]. Various types of TCM The following subsections provide an overview of the therapeutic effects of different types of TCM and herbs, as well as their applications in previous studies.

4.1. PI3K/Akt Pathway

4.1.1. Huang Qin

Huang Qin is a root that is derived from *Scutellaria baicalensis*[81]. It consists of flavonoids such as wogonin which has anti-inflammatory, immunomodulatory and analgesic effects[83]. In a study by Ma *et al*.[84], the Huang Qin was administered to the colitis-associated colorectal cancer mice and it showed a significant reduction of inflammatory factors such as interleukin-6 in those mice model. In another study Zhu *et al*.[85], it showed that the administration of Huang Qin into colorectal cancer mice can improve gut dysbiosis, reduce tumour burden and promote cell apoptosis through suppression of PI3K/Akt pathway. Hence, the plant is evidently exhibiting significant anti-colorectal cancer activity.

4.1.2. Jie Geng

Jie Geng is a kind of *Platycodon grandiflorum* that is rich in Platycodin D[86]. Research conducted by Liu *et al*.[87], showed that platycodin D functions to regulate the Akt pathway in different cells. In combination with cetuximab, the platycodin D may inhibit the growth, migration and invasion via the downregulation of PI3K and Akt phosphorylation thus increasing the cytotoxic effect of cetuximab. A meta-analysis done by Chen *et al*.[88] showed that a combination of Jie Geng and Huang Qi can reduce postoperative wound infection following a colorectal cancer surgery. The study was performed with 1256 patients and observed for 30 days post-surgery. The outcome of the study showed a combination of both Chinese herbs could reduce hospitalization and the use of antibiotics.

4.1.3. Tounong powder extracts

Tounong powder extract is a Chinese medicinal formula which initially was used to treat skin ulcers and later to treat ulcerative colitis[89]. Fang *et al*.[90] reported that the Tounong powder extract induced LoVo cell growth inhibition through PI3K/Akt pathway, downregulated the expression of cytokine signalling and upregulated the expression of caspase-3 and caspase-9. These mechanisms proposed were found to induce cancer cell apoptosis and help in the condition of colorectal cancer cell patients.

4.1.4. Jiedu Sangen decoction

Jiedu Sangen decoction is a TCM shown promising effects in the treatment of colorectal cancer. It contains *Geujaponieum Thumnb, Polygonum Cuspidatum* and *Radix Actinidiae Chinesis* which showed suppressive effects against migration and invasion of colon cancer cells[91]. Research by Yuan *et al*.[92], showed that Jiedu Sangen decoction can inhibit the invasion and metastasis of colon cancer cells by reversing epithelial-to-mesenchymal transition. The action is primarily mediated through the Akt/GSK-3β signalling pathway by increasing the expression of E-cadherin and decreasing the expression of N-cadherin and other cytokines. Besides that, Sun *et al*.[93] revealed that Jiedu Sangen decoction in combination with 5-fluorouracil can reverse the potency of 5-fluorouracil resistance in vitro and anti-tumour efficiency in vivo by inhibiting the signalling pathway of PI3K/Akt/HIF-1α. It helps to regulate the glycolysis proteins and induces apoptosis of colorectal cancer cells.

4.1.5. Teng Huang

Teng Huang contains gambogic acid which has been proven to have anti-tumour effects in many tumours. Research by Zhou and Ma[94] studied the mechanism of gambogic acid in human colon cancer SW620 cells and gambogic acid demonstrated that it could inhibit the SW620 cell proliferation, invasion and migration. The expression of PI3K, Akt, P21 and MMP-2 were significantly altered in a dose-dependent manner followed by the gambogic acid treatment. Wei *et al*.[95] reported that gambogic acid significantly reduced the tumour sphere formulation, percentage of side population and percentage of CD133CD44 cells. The result is most likely due to the decrease in the expression of stemness and EMT-associated markers in colorectal cancer cells and an increase in the ZFP36 expression leading to the inhibition of EGFR/ ERK/ ZFP36 signalling pathway to inhibit the tumour growth.

4.2. p21 Expression

4.2.1. Lei Gong Teng

Lei Gong Teng is a plant extracted from *Tripterygium wilfordii* which contains triptolide that has anti-inflammatory and immunosuppressive activities[86]. A study reported that triptolide enhanced the p21 expression and reduced cyclin A1 expression which can inhibit DNA replication by blocking the G1 phase[96]. Therefore, it inhibits the colon cancer cell proliferation. Wang *et al*.[97] showed that triptolide treatment in mice can decrease the incidence of colon cancer formation, decreased the secretion of interleukin 6, IL6R and phosphorylated STAT3, and arrested the G1 phase of tumour cells. Therefore, triptolide exhibits the anti-tumour effects.

4.3. PD-1 Blockade

4.3.1. Gegen Qinlian Decoction

Gegen Qinlian Decoction is well-known for the relief of diarrhoea and ulcerative colitis[98]. Lv *et al*.[98] reported that taking Gegen Qinlian Decoction with PD-1 immunotherapy could enhance the effects of PD-1 blockade in colorectal cancer. The study found that a combination of these could increase the proportion of CD8+ T cells in peripheral blood and tumour tissues, improve gut microflora, and increase the expression of IFN-γ for cancer killing.

4.4. Caspase Dependant Pathway

4.4.1. Dong Ling Cao

Dong Ling Cao also known as *Rabdosia rubescens*, contains active components such as oridonin that show significant anticancer properties[99]. A study by Ji *et al*.[100] showed that oridonin can inhibit the growth of colon cancer cells which is the SW620 cell line through induced apoptosis by activation of caspase-3. In another study by Kang *et al*.[101], it was reported that oridonin can inhibit caspase-9 to induce apoptosis in human laryngeal cancer HEp-2 cells. They also suggested that oridonin can reduce the autophagy programme therefore increasing the apoptotic ratio of cancer cells.

4.4.2. Huang Lian

Huang Lian is a Chinese herb that is derived from the dried roots of *Coptis chinensis*, *Coptis teeta* and *Coptis deltoidei*[102]. It is used to alleviate heat, astringe extra fluids and resolve toxins in the body. In a pharmacology synergistic study done by Gong *et al*.[102], Huang Lian was studied together with Gan Jiang to investigate the synergism and mechanism against colorectal cancer. There are 65 constituent compounds of both ingredients found that can inhibit colorectal cancer cell growth by restraining the proliferation of cancer cells and inducing apoptosis. Furthermore, Huang Lian contains berberine, a kind of isoquinoline alkaloids, that has anti-tumour properties. Berberine demonstrated anti-tumour properties by inducing caspase-dependent and caspase-independent programmed cell death and modification of miRNA. Mi-429 has higher expression level in colorectal cancer and inhibition of E-cadherin with berberine showed reduction in mi-429 levels in tumour cells[103,104].

4.4.3. Huang Bai

Extraction from *Phellodendron chinense* called Huang Bai is rich in berberine[82]. It shares the same chemical components as Huang Lian and Xiao Bo. Berberine as discussed showed anti-inflammatory and anti-tumour properties. A study by Chen *et al*.[105] concluded that berberine reversed the upregulation protein expression of Ki-67 and β-catenin and possessed downregulation in multiple cytokine expressions including interleukin-1β, matric

metallopeptidase 9 and such in an AMO/DSS model mice. Such a process could regulate cell proliferation, angiogenesis and invasion through the NF-κB signalling pathway. As a consequence, it exerts anti-tumour effects on colorectal cancer cells. In another study by Gong *et al*.[106], berberine can inhibit the proliferation and migration of colorectal cancer cells by downregulating the GRP78 protein. The study was conducted on SW480 cells and berberine downregulates the expression of GRP78 to inhibit the proliferation of the cancer cell.

4.4.4. Xiao Bo

Xiao Bo is a Chinese herb extracted from *Berberis silva-taroucana* Schneid that contains berberine as the main component for anti-tumour properties. Berberine exerts anti-cancer effects by affecting the cell cycle and stimulating the cell apoptosis. Mechanisms of berberine in anti-cancer activities include regulation of gene expression like E-cadherin, induction of G1/G0 cell cycle arrest, inhibition of oxidative stress through regulating AMPK pathway and improvement in gut microflora. In summary, berberine exerts antitumor effects in colorectal cancer cells which could be used in colorectal cancer patients in future[106].

4.4.5. Gui Jiu

Gui Jiu is from the *Podophyllum peltatum* species and contains a large amount of podophyllotoxin and deoxypodophyllotoxin as the chemical component. The podophyllotoxin is highly cytotoxic to various cancer cells. In research by Lee *et al*.[107], the podophyllotoxin was administered to the HCT116 cell. The result showed podophyllotoxin can inhibit cell proliferation and induce cell apoptosis in HCT116 cells. As the concentration of podophyllotoxin increases, the percentage of apoptotic cells also increases. The study also suggested that podophyllotoxin can arrest the G2 and M phase of HCT116 cells, activate caspases and induce apoptosis of HCT116 cells. Hence, the podophyllotoxin exhibits anticancer effects.

Besides that, deoxypodophyllotoxin was also found to have an anticancer effect as it was highly cytotoxic. The mechanisms were proposed by Gamage *et al*.[108] showing that deoxy-podophyllotoxin could induce apoptosis by activating the mitochondrial pathway via regulation of BCL-6 proteins. Deoxypodophyllotoxin can also cause depolymerisation of tubulin leading to cancer cell apoptosis.

4.4.6. Ban Mao

Ban Mao, commonly known as Mylabris contains norcantharidin which is crucial for the anti-tumour effect. Yang *et al*.[109] reported that norcantharidin causes colorectal cancer cell apoptosis by nuclear fragmentation and chromatin condensation. The activation of caspase-3, caspase-8 and caspase-9 occurs due to the release of cytochrome C. Besides that, Qiu *et al*.[110] found that norcantharidin has anti-tumour activities through inhibition of EGFR and c-MET factor in HCT-116 and HT-29 cells. In the study, they also measure the degree

of apoptosis of the colorectal cancer cells by norcantharidin. The study also showed apoptosis percentage increased in a concentration-dependent manner.

4.5 NK-κB Pathway

4.5.1. Jiang Huang

Jiang Huang, also known as Curcumin, is the major component of *Curcuma longa*. It is widely used to reduce inflammation. Many journals and studies have been conducted to show the anti-inflammatory properties and anti-tumour mechanisms of Huang Jiang. In research by Park and Chris[111], curcumin was found to inhibit cell proliferation and cytokine production via inhibition of NK-κB target genes. Evidence suggests that NK-κB plays a crucial role in initiating and promoting the growth of cancer cells when it binds to DNA. Curcumin can regulate NK-κB through blocking the signalling pathway of caspase 3 and caspase 9. Other than that, Huang Jiang possesses antioxidant effects which can scavenge free radicals including reactive oxygen species and nitrogen species through the inhibition of lipoxygenase, cyclooxygenase and superoxide dismutase[112]. These antioxidant properties suggest Huang Jiang to be a candidate for chemo-preventive agents.

4.5.2. Wu Mei Wan

Wu Mei Wan is generally applied to treat chronic digestive diseases such as diarrhoea and colitis ulcerative[82]. In a study by Lu *et al*.[113], they administered Wu Mei Han at different stages of colorectal cancer model mice. The result showed a significant effect on inhibiting inflammatory responses and tumours during the early stage of colorectal cancer by reducing the cytokines such as interleukin-6, interleukin-1β and TNF-α in colon tissues. The administration of Wu Mei Han also can alter the PI3K/Akt signalling pathway which exhibits anti-tumour properties. In another research by Jiang *et al*.[114], Wu Mei Han investigated the downregulation of the NK-κB/IL-6/STAT3 signalling pathway on C57BL/6 model mice. The results showed Wu Mei Han can prevent colorectal cancer cells by regulating the microbial flora in the gut and decreasing the carcinogenic proteins to inhibit the NK-κB/IL-6/STAT3 signalling pathway. As a result, Wu Mei Han exhibits anti-tumour properties and inhibits the proliferation of cancer cells.

4.6. Others

4.6.1. Ren Shen

Ren Shen also known as Ginseng has been reported for many health benefits including anti-cancer effects[115]. It contains ginsenosides that could kill cancer cells through a few mechanisms including reduction in mitochondrial damage and reactive oxygen species in colorectal cancer cells. The mechanisms were supported by research from Li *et al*.[116] by introducing ginsenosides to human colorectal cancer cells HCT116 and SW480. The study showed that Ren Shen can reduce the reactive oxygen species and inhibit the NK-κB signalling pathway in colorectal cancer cells, steamed Ren Shen could confer stronger anti-

oxidant effects when compared to raw Ren Shen. Meanwhile, another study by Shao *et al*.[117] reported that ginsenoside compound K provides anti-colorectal cancer effects. The research was conducted with AOM/DSS model mice. The result showed disruption of gut microbiota in AOM/DSS model mice could recover by administering ginsenoside compound K. It resulted in increase in *A. muciniphila* count in the gut and reduced the colorectal cancer cells through modulating CD8 T cells.

4.6.2. Yin Xing Ye

Yin Xing Ye is the leaf from *Ginkgo biloba* that contains a kind of diterpenoid lactone called ginkgolide C. Yang *et al*.[118] reported that ginkgolide C possessed an anti-cancer effect through modulating the Wnt/β-catenin signalling pathway. The study was conducted in colorectal cancer cell models HT-29, SW480 and KM12SM. The ginkgolide C inhibits the expression of Wnt3a and β-catenin proteins to downregulate the Wnt/β-catenin signalling pathway. Overall, the colorectal cancer cells were reduced as the mechanism of ginkgolide C reduced proliferation and promoted apoptosis. Moreover, Yin Xing Ye also contains ginkgolic acid that demonstrated anti-tumour activity. Qiao *et al*.[119] reported that ginkgolic acid can reduce the expression of invasion-associated proteins like MMP-2, CXCR4 and uPA in SW480 cancer cells. The reduction in those proteins induced the AMPK signalling pathway, leading to a reduction in cell proliferation and induced apoptosis in cancer cells.

4.6.3. Sheng Jiang

Sheng Jiang is a species of *Zingiber officinale* which contains gingerol as its active ingredient that has anti-cancer properties. Hu *et al*.[120] observed that treatment with 8-gingerol resulted in reduced phosphorylation levels of EGFR and its downstream effectors, STAT3 and ERK, in HCT-166 and DLD1 cells. This reduction led to decreased expression of key target genes, including cyclin D1, c-Myc, and MMP2. However, the addition of EGF was able to restore the phosphorylation levels and protein expression, indicating that 8-gingerol inhibits the proliferation and migration of CRC cells by targeting the EGFR/STAT/ERK signalling pathway. Furthermore, Yusof *et al*.[121] reported that a combination of γ-tocotrienol and 6-gingerol could provide a synergistic effect to induce cytotoxicity and apoptosis in HT-29 and SW837 human colorectal cancer cells. Other than that, more mechanisms of anti-tumour effects of 6-gingerol were studied by Lee *et al*.[122], the 6-gingerol suppresses the β-catenin expression, activates the NAG-1 expression and suppresses the cyclin D1 expression at the transcriptional and translational levels. In summary, those mechanisms allow Sheng Jiang to give anti-inflammatory and anti-cancer effects.

4.6.4. Bai Hua She She Cao

Bai Hua She She Cao is a Chinese herb from *Hedyotic diffusa* which contains ursolic acid as an active chemical component. A study by Kuo *et al*.[123] indicated that Bai Hua She She Cao could suppress tumour angiogenesis through inhibition of Sonic hedgehog signalling

in colorectal cancer. Cai *et al*.[124] reported that Bai Hua She She Cao administered to colorectal cancer mouse xenograft model can reduce the tumour volume and tumour weight. The result suggested that Bai Hua She She Cao can modulate the STAT3 phosphorylation, which eventually induces cancer cell apoptosis and inhibits cancer cell proliferation.

4.6.5. Mi Hou Tao

Ursolic acid was also found in Mi Hou Tao which exerts anti-proliferative and pro-apoptotic effects on colorectal cancer cells. Shan *et al*.[125] conducted research on HT-29 colon cancer cells to examine the influences of ursolic acid. The result showed that HT-29 colon cancer cell growth was inhibited by ursolic acid in a dose and time-dependent manner. The research suggested that the mechanism of ursolic acid to suppress cancer cell growth is through the downregulation of phosphorylation of EGFR, ERK, MAPK and JNK, downregulation of Bcl-2 and Bcl-xL expression as well as activation of caspase-3 and caspase-9. Moreover, Zhao *et al*.[126] conducted research on ursolic acid against colorectal cancer SW620 cells. The result demonstrated suppression of proliferation, migration and induction of apoptosis on SW620 cells. The mechanisms are mainly due to the G0/G1 phase arrest and downregulation of Wnt/β-catenin signalling pathway.

4.6.6. Yin Yang Huo

Yin Yang Huo, refers to as horny goat weed, is from the epimedium genus in the family *Berberidaceae.* It contains icariin that shows anti-tumour effects against cancer cells, mainly through induction of apoptosis and arrest of the tumour cell cycle, while suppression of adhesion and migration of tumour cells, angiogenesis and proliferation of tumour cells[127]. Tian *et al*.[128] demonstrated that icariin can enhance p53 activity to reduce colorectal cancer cell growth. The study was conducted on colorectal cancer HCT116 cells. The HCT116 cells are reduced by icariin through enhancing p53 expression and damaging the DNA. Zhang *et al*.[129] also reported that icariin significantly improved the disease activity and reduced inflammatory damage of colon tissue in the DSS-induced colitis model mice. The icariin can inhibit the interleukin-6 and TNF-α expression and remarkably increase the p65 expression in DSS model mice. Other than that, the study also found out that icariin can improve the gut microflora such as *Lactobacillus* to protect the colon tissues.

4.6.7. Chuan Xiong

Chuan Xiong rhizome contains the alkaloid ligustrazine, which has been reported to exhibit tumour-suppressive activity by inhibiting the growth, metastasis and epithelial-mesenchymal transition of cancer cells[130]. Bian *et al*.[131] found that ligustrazine demonstrated inhibitory effects on the proliferation of colorectal cancer SW480 and CT26 cells through a few mechanisms. Those mechanisms are the upregulation of pro-apoptotic protein, downregulation of anti-apoptotic protein, arrest of the G0/G1 phase and regulation of p53-dependent mitochondrial pathway. As a result, the cancer cells will undergo apoptosis. Besides that, Chen *et al*.[132] studied the effect of different concentrations of ligustrazine on

colorectal cancer SW480 cells. The SW480 cells that underwent ligustrazine treatment were reduced mainly due to the inhibition of PI3K, Akt and mTOR phosphorylation and inhibition of the EMT process.

4.6.8. Ling Zhi

Ling Zhi is a kind of fungus from the *Ganoderma lucidum*[133]. Ling Zhi contains *Ganoderma lucidum* polysaccharide (GLP), which exhibits anti-tumour effects through mechanisms such as apoptosis induction, anti-proliferation, reactive oxygen species (ROS) generation and antioxidative properties[134]. Liu *et al*.[135] reported that GLP could alleviate colorectal cancer by modifying the gut microflora. The study showed that administration of GLP into the colorectal cancer mice could reduce mortality by 30% mainly through the reduction in cancer-related genes and regulation of gut microflora. In addition, Jiang *et al*.[136] showed that GLP can reactivate the mutant p53 in colorectal cancer cells leading to induced apoptosis.

4.6.9. Dang Gui

Dang Gui (*Angelica sinensis*) has been traditionally used in Chinese medicine for various health benefits, attributed to its rich content of bioactive compounds including terpenoids, lignans, coumarins, and phthalides[137]. Both coumarins and phthalides are known for their anti-metastasis and anti-tumour properties, as they can form non-covalent interactions with active sites in organisms[138]. A study by Hao *et al*.[139] demonstrated that the supercritical fluid extract of Angelica sinensis could serve as an adjuvant to oxaliplatin for treating colorectal cancer (CRC), showing inhibition of viability, metastasis, and invasion in HCT116 cells. Zhao *et al*.[140] investigated the effect of *Angelica sinensis* root extract on AOM/DSS model mice. The result demonstrated that the extract has a cancer-preventive effect with a decrease in tumour incidence.

A summary of the above discussion is presented in Table 1, along with their corresponding images.

Table 1. CRC inhibition signalling pathway of various TCM.

Signaling pathway	Chinese Herbal Medicine	Appearances	Effects	References
PI3K/Akt Signaling Pathway	Huang Qin		- Reduced inflammatory factors - Improved gut microbiome - Promote cell apoptosis	[84,85]
	Jie Geng		- Inhibit growth, migration and invasion of tumour	[87,88]
	Tounong powder extracts		- Downregulate the expression of cytokine signalling - Upregulate the expression of caspase-3 and caspase-9 - Promote apoptosis	[89,90]

	Jiedu Sangen decoction		- Increasing the expression of E-cadherin - Decreasing the expression of N-cadherin and other cytokines.	[92,93]
	Teng Huang		- Inhibit growth, migration and invasion of tumour	[94,95]
p21 Expression	Lei Gong Teng		- Increased the p21 expression - Decreased cyclin A1 expression - Inhibit DNA replication	[96,97]
PD-1 blockade	Gegen Qinlian Decoction		- Increase the proportion of CD8+ T cells - Improve gut microflora - Increase the expression of IFN-γ	[98]

Caspase dependant pathway	Dong Ling Cao		- Induced apoptosis activity	[99,100]
	Huang Lian		- Induced apoptosis activity - Inhibit cancer cell proliferation	[102]
	Huang Bai		- Upregulation protein expression of Ki-67 and β-catenin - Downregulate cytokines	[82,105]
	Xiao Bo		- Regulation of gene expression - Induction of G1/G0 cell cycle arrest - Inhibition of oxidative stress - Improved in gut microflora	[106]

	Gui Jiu		- Induced apoptosis activity	[107]
	Ban Mao		- Induced apoptosis activity	[109]
NK-κB signaling pathway	Jiang Huang		- Inhibit cell proliferation and cytokine production	[110,111]
	Wu Mei Wan		- Decrease cytokine production - Improved in gut microflora - Inhibit cell proliferation	[113]
	Ren Shen		- Reduction in mitochondrial damage and reactive oxygen species	[115]

Others	Yin Xing Ye		- Induced apoptosis activity - Inhibit cancer cell proliferation	[118]
	Bai Hua She She Cao		- Induced apoptosis activity - Inhibit cancer cell proliferation	[123]
	Mi Hou Tao		- Induced apoptosis activity - Inhibit cancer cell proliferation	[125]
	Yin Yang Huo		- Inhibit cytokine production. - Improved gut microflora	[127]

Chuan Xiong		- Induced apoptosis activity - Inhibit cancer cell proliferation	[130]
Ling Zhi		- Induced apoptosis activity - Inhibit cancer cell proliferation - Reduced reactive oxygen species - Improved gut microflora	[131]
Dang Gui		- Induced apoptosis activity - Inhibit cancer cell proliferation	[139]

5. Potential future directions of TCM in CRC

Over the past decades, TCM has been widely used in the treatment of CRC as an adjuvant therapy corresponding to Western medicine. One particularly progressive trend is the concomitant use of TCM with chemotherapy, radiation therapy, and surgery to enhance patient survival rates whilst decreasing side effects from the treatments themselves[78]. Herbal mixtures such as Huang Qi, Bai Hua She She Cao, and Ban Zhi Lian have been demonstrated to exhibit their own preventable, anti-inflammatory, and antitumor features. These herbs not only have immunomodulatory effects but also inhibit cancer cell growth and induce apoptosis in colorectal cancer cells. Meanwhile, the emphasis of TCM on syndrome differentiation and personalized therapy is being merged with modern precision medicine. The researchers are also investigating how the genetic mutations and gut microbiome profiles unique to colorectal cancer patients coincide with personalized TCM therapy plans designed for more precise, targeted therapies[65].

In the future, a variety of TCM treatments have the potential for CRC treatment. Eras to elucidate processes by which TCM herbs and such pathways might be used in cancer-fighting. Moreover, there is a continued need for large-scale RCTs to confirm the beneficial approach in TCM treatment and to further determine appropriate doses. One of the most important ways is to investigate TCM in combination with targeted therapy, such as immune checkpoint inhibitors and monoclonal antibodies. This synergy could broach novel means of addressing drug resistance and enhancing clinical outcomes in patients. Further research into the influence of TCM on the gut microbiome, as well as genomic and epigenetic regulation, may offer insights that strengthen the integration of TCM into modern colorectal cancer treatment, enhancing its potential as a personalized and precision-based therapy[21].

6. Conclusions

In conclusion, colorectal cancer (CRC) remains a significant global health challenge due to its high incidence and mortality rates, particularly in developed countries. Traditional treatments, including surgery and chemotherapy, have been the mainstay for CRC management, yet their limitations highlight the urgent need for alternative therapies. This review underscores the potential of TCM as a complementary approach, offering promising therapeutic benefits through various mechanisms, such as anti-inflammatory, anti-proliferative, and immune-modulatory effects. By integrating TCM with conventional treatments, there is potential for improved patient outcomes and reduced adverse effects, paving the way for more holistic and personalized cancer care. Continued research and clinical trials are essential to fully understand the efficacy and safety of TCM in CRC treatment, which could ultimately contribute to more effective and accessible cancer therapies worldwide.

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