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Review Article

Evidence for Edible Chinese Herbal Medicine as an Alternative Approach for the Treatment of Colorectal Cancer

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ABSTRACT

Colorectal cancer (CRC) is the leading cause of cancer lethality worldwide, inflicting a heavy burden on society. Unfortunately, the complex nature of CRC pathogenesis renders current chemotherapies and targeted therapies unsatisfactory. Conventional medicine generally concentrates on the killing of tumor cells by inducing cell death or activation of the immune system, which often leads to adverse effects or relapsed chemoresistance. On the contrary, Chinese medicine theory pays attention to the patients' whole inner system and helps to shrink the tumor with consideration of overall body condition. Since numerous Chinese herbal medicines (CHM) are used as food, the edible CHMs as diet resources therapy represent a promising alternative for the treatment of CRC. Recent research has made remarkable progress toward the therapeutic effects of edible CHM for CRC. In this review, experimental CRC models, the holistic characteristic of edible CHM, and recent research on the efficacy and mechanisms of edible CHM as anti-CRC agents are discussed, as well as the safety aspect of edible CHM.

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Introduction

Colorectal cancer (CRC) is a carcinoma, generally an adenocarcinoma, in the colon or rectum [1]. It is amongst the most common cancers worldwide, affecting approximately 3.5 million people with 1.4 million incidences and 694,000 mortalities in 2012 [2]. The treatment of CRC relies on several factors including the size, location, and the stage of the tumor, whether or not it is recurrent, and the overall health status of the patient. During recent decades, various novel therapeutic approaches for CRC have been developed, which led to a steady improvement in the results of treatment. In general, the three most common approaches to treatment are surgery, chemotherapy, and radiotherapy.

A majority of CRC can be cured by removal (endoscopic or surgical approach) of the primary tumor if the disease is in early stages (stages 0 to III according to Tumor-node-metastasis (TNM) classifications [3]. However, for patients at an advanced stage of disease (stage IV), apart from the removal of the tumor, both primary and metastasized if applicable, chemotherapy such as 5-fluorouracil (5-FU), leucovorin, and oxaliplatin combining with targeted therapy are the most commonly used. Initially, some patients (40-50%) respond to the chemotherapy, but eventually, drug resistance (intrinsic or acquired) follows, thereby limiting the clinical efficacy.

Under this situation, many researchers have focused their attention on natural products with anti-CRC activities. As a holistic and

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combinational approach, the application of Chinese herbal medicines (CHM) in the management of CRC has its unique advantages. Over the past few years, the use of CHM has become increasingly popular among cancer patients worldwide. Correspondingly, there are increasing numbers of pre-clinical and clinical studies conducted to provide evidence for the use of CHM as adjuvant CRC treatment or to provide meaningful information for the development of more effective anti-CRC drugs. Interestingly, many CHMs are consumed for both medicinal and food purposes in the form of traditional food dishes and herbal products. The line between the medicinal and food characteristics of these herbal medicines is often blurred due to the dual uses. Moreover, many Chinese traditional dishes and cuisines may contain one or more types of herbal medicines. Additionally, the concept of diet therapy is widely accepted. Therefore, the introduction of herbal food products that contain CHM as diet therapy would be a promising alternative for CRC management. The present review herein aims to summarize the role of edible CHMs as functional food for diet therapy in CRC management with an emphasis on their underlying mechanisms.

Mechanism of CRC Development

Accumulating evidence shows that CRC is a complex and heterogeneous disease. Three known major molecular groups accounting for the development of CRC have been identified. First, the chromosomal instable group which most commonly features an increase of mutations in specific oncogenes and tumor suppressor genes. Second, the microsatellite instable group, which results from genetic hypermutability caused by DNA mismatch repair genes abnormality. The third group is the CpG island methylation phenotype.

Transformation of normal colon epithelial cells into invasive and metastatic CRC cells requires multiple mutations on the genes. The chromosomal instability pathway accounts for around 70% of sporadic CRC and is prototypical for CRC molecular evolution [4]. In the beginning, a pre-malignant precursor lesion (an adenoma) appear after the loss of function mutation of genes in the Wnt pathway APC or CTNNB [5]. Subsequently, mutations of KRAS, TP53, and SMAD4 occur and speed conversion into an invasive and metastatic phenotype (Figure 1) (Cancer Genome Atlas, 2012) [6].

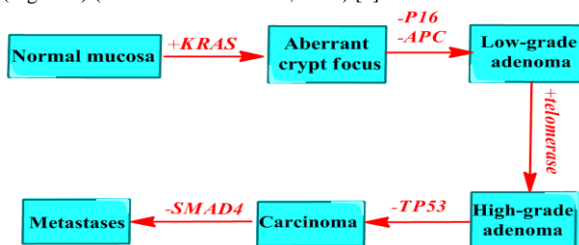


Figure 1: Chromosomal instability pathway in CRC development. The sequence starts from aberrant crypt focus formation often with *KRAS* activation mutations featuring slight disturbances of crypt structure and in some cases, epithelial dysplasia. Thereafter, adenoma, which is small and generally tubular and has confined cytonuclear and characteristics of dysplasia, follows with frequent inactivation mutations of APC. In the next stage, telomerase is stimulated, and the lesions generally display large, villous architecture and cytonuclear properties of advanced dysplasia. The development of invasive carcinoma is commonly

followed by TP53 mutations. Finally, further mutations such as *SMAD4* inactivation promote progression towards metastasis.

Edible CHM for CRC Treatment

I Traditional Chinese Medicine Perspective of CRC

Through the perspective of traditional Chinese medicine (TCM) theory, a tumor is not only the morphological changes but also, and more importantly, the functional changes of specific tissues or organs [7]. In TCM, the tumor results from the stagnation of toxin and heat, obstruction of phlegm/dampness, Qi stagnation and blood stasis, and imbalanced yin and yang in viscera and bowels. CRC is caused by the accumulation of toxins. It results from an imbalance of the body with deficient of 'qi' and extra toxic fluids and 'heat'. This situation is further exasperated by a weakened spleen and kidneys, leading to the flow and accumulation of toxins into the intestine. 'Qi' deficiency is regarded as the major driving force leading to CRC. TCM discriminate malignant bowel blockage from that of benign. In malignant blockage, there exists both mechanical blockage of the bowel and hindrance of 'qi', blood stasis and aggregation of toxins. These issues are thought to have a serious influence on surgical outcomes and needed to be fixed to obtain uncomplicated surgery [8].

In China, CHM has been used for treating cancers for several thousand years. The rationale for using herbal medicine in the treatment of CRC is based upon specific properties of the herbal medicine. Therefore, herbs with properties to accelerate circulation, eradicate blood stasis, clear toxins and heat, energize the spleen and kidneys and most importantly, replenish 'qi' are becoming popular as major remedies [8]. The herbal preparation often consists of many ingredients, which, based upon the clinical experiences, can act synergistically to exert its effects in various ways. Firstly, it can alleviate the damage caused by chemo/radiotherapy against the normal cells and tissues in the body. Secondly, it can strengthen the efficacy of chemo/radiotherapy. Thirdly, it can ameliorate inflammatory and infectious complications in normal tissues adjoining the tumor. Fourth, it can boost immunity and body resistance. Fifth, it can make better the patients' overall condition and quality of life. Last but not least, it can extend the life expectancy of the patients in an advanced stage of cancer [9].

II In Vitro Evidence of Edible CHM for CRC

CHM and their active components have been shown to exhibit cytotoxic activities in various human CRC cell lines with HT-29, LoVo, CaCo-2, SW-480 and -620, HCT-8 and -116, and colo-205 being the most common ones (Table 1).

Among the CHM used for both the medicinal and food purposes, *Coptis chinensis* (Huanglian), *Curcuma longa* (Jianghuang), *Hedyotis diffusa* (Baihuasheshecao), *Panax notoginseng* (Sanqi), *Panax quinquefolius*, *Salvia miltiorrhiza* (Danshen), *Scutellaria baicalensis* (Huangqin), and *Zingiber officinale* (Shengjiang) are the most intensely studied (Table 1). The images of these CHMs were shown in (Figure 2), and some of their anti-CRC active compounds are shown in (Figure 3). It has been reported that extracts from *C. chinensis* could inhibit the proliferation of HCT-116 cells by suppressing cyclin B1 expression and inhibiting CDC2 kinase activity and induce apoptosis in SUN-C4 cells [10, 11].

Berberine, an isoquinoline alkaloid, isolated from *C. chinensis* has been reported to stimulate apoptosis through inducing ROS stress and activation of JNK/p38 MAPK and FasL in SW-620 cells, and to inhibit invasion and metastasis of SW-620 and LoVo cells via cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) mediated JAK2/STAT3 signaling

pathway [11, 12]. Moreover, curcumin, a polyphenol, isolated from *C. longa* has been reported to induce apoptosis in HT-29, colo-205, and LoVo cells, and to inhibit migration and invasion in colo-205 cells by inhibiting NF- κ B/p65 and down-regulating COX-2 [13, 14, 15].

Table 1: *In vitro* study of edible CHM for CRC treatment.

Species/ Formulation	Extract/ compound	Cell lines	Pharmacodynamic indicators	Refs
<i>C. chinensis</i>	Methanol extracts	SNU-C4	↓Viabilities; ↑apoptosis populations; ↑Bax; ↑caspase3; ↓Bcl-2;	(Kim <i>et al.</i> 2004) [56]
	Water extracts	HCT-116	↓Viabilities; ↓colony formation; ↑G2 phase population; ↓cyclin B1; ↓cdc2 kinase activity;	(Li <i>et al.</i> 2000) [10]
	Berberine	SW-620	↓Viabilities; ↑caspase 3 and 8 activation; ↑PARP cleavage; ↓Bid, c-IAP1, Bcl-2, Bcl-XL; ↑p-JNK, p-p38; ↑ROS; ↑p-c-jun, FasL, t-Bid;	(Hsu, Hsieh, <i>et al.</i> 2007) [20]
<i>C. longa</i>	Curcuminoids	5 primary cells	↓Viabilities; ↑apoptosis population; ↓mitochondrial membrane potential (MMP);	(Hsu, Weng, <i>et al.</i> 2007) [21]
	Curcumin	HT-29	↓Viabilities; ↓COX-2;	(Du <i>et al.</i> 2006) [57]
	Curcumin	Colo-205	↓Viabilities; ↓NF- κ B p65, COX-2; ↑COX-1; ↓MMP2/9; ↓invasion ability;	(Su, Chen, <i>et al.</i> 2006) [58]
	Curcumin	Caco-2, HT-29	↓EGFR expression; ↓ERK and Elk-1 activity; ↓Egr-1 expression and activity;	(Chen, Xu, and Johnson 2006) [59]
	Curcumin	LoVo	↓Viabilities; ↑LDH release; ↑apoptosis population; ↑caspase-3 and 9 activation; ↓MMP; ↑cytochrome c release, ↑Bax, p53; ↓Bcl-2, survivin;	(Guo <i>et al.</i> 2013) [15]
	Curcumin	Colo-205	↓Viabilities; ↑apoptosis population; ↑ROS, Ca ²⁺ ; ↓MMP; ↑caspase 3 activity; ↑Bax, cytochrome C, p53, p21; ↓Bcl-2;	(Su, Lin, <i>et al.</i> 2006) [14]
	Curcumin	HT-29	↓Viabilities; ↓COX-2;	(Goel, Boland, and Chauhan 2001) [60]
<i>G. lucidum</i>	Curcumin	HT-29	↓Viabilities; ↓apoptosis population; ↓pAkt, COX-2; ↑p-AMPK; ↑G1 population;	(Lee <i>et al.</i> 2009) [13]
	Ganoderic acid Me	HCT-116	↓Viabilities; ↑apoptosis population; ↑p53, Bax; ↓MMP; ↑cytochrome c release; ↑caspase 3 activity;	(Zhou <i>et al.</i> 2011) [46]
<i>H. diffusa</i>	Triterpenoids	SW-480	↓Cell number; ↓DNA synthesis;	(Xie <i>et al.</i> 2006) [30]
	Ethanol extracts	HT-29	↓Viabilities; ↑apoptosis population; ↑DNA fragmentation; ↓MMP; ↑Bax/Bcl-2; ↑caspase 9 and 3 activation;	(Lin <i>et al.</i> 2010) [61]
	Ethanol extracts	HCT-8	↓Viabilities; ↓P-glycoprotein, ABC subfamily G member 2;	(Li, Wang, <i>et al.</i> 2015) [16]
	Ethanol extracts	HT-29	↓Viabilities; ↑apoptosis population; ↓p-Stat3; ↓Cyclin D1, CDK4, Bcl-2; ↑p21, Bax;	(Lin <i>et al.</i> 2015) [17]
	Ursolic acid	HT29	↓Viabilities; ↑apoptosis population; ↓p-EGFR, p-ERK1/2, p-p38, and p-JNK; ↓Bcl-2, Bcl-xl; ↑caspase 3 and 9 activity;	(Shan <i>et al.</i> 2009) [62]
<i>P. notoginseng</i>	Ursolic acid	SW-480, LoVo	↓Viabilities; ↓clone formation; ↓migration ability; ↓MMP9; CDH1 expression; ↓p-Akt, p-ERK; ↓COX-2, PGE2; ↑NF- κ B and p300 translocation; ↑apoptosis population; ↑PARP; ↑caspase 3 and 9 cleavage; ↑cytochrome c release;	(Wang, Liu, <i>et al.</i> 2013) [36]
	Panaxadiol	HCT-116	↓Viabilities; ↑apoptosis population; ↑G1 population;	(Li <i>et al.</i> 2009) [20]
	N-butanol fraction- N-butanol fraction	HCT-116 SW-480	↓Viabilities; ↑apoptosis population; ↓Viabilities; ↓DNA synthesis; ↑apoptosis population; ↑S, G2 phase population;	(Wang <i>et al.</i> 2007) [25] (Wang, Xie, <i>et al.</i> 2009) [18]

<i>P. quinquefolius</i>	Steamed extracts	HCT-116, SW-480	↑Apoptosis population; ↓MMP; ROS; ↑NF-κB activation;	(Li <i>et al.</i> 2010) [63]
	Ginseng extracts	HCT-116	↓Viabilities; affect ephrin receptor pathway;	(Luo <i>et al.</i> 2008) [64]
	Ginsenoside Rh2	HCT-116, SW-480	↓Viabilities; ↑apoptosis population; ↑ROS; NF-κB activation; ↑Bax, Bad; ↓Bcl-2, Bcl-XL; ↑cytoplasmic vacuoles;	(Li <i>et al.</i> 2011) [65]
	Ginsenoside Rg3	SW-480	↓Migration ability; ↓NF-κB activity; ↓MMP-9, COX-2;	(Song <i>et al.</i> 2015) [66]
	Ginsenoside Rg3	HCT-116	↓Viabilities; ↓colony formation; ↓β-catenin nuclear translocation; ↓PNCA;	(He <i>et al.</i> 2011) [22]
<i>S. miltiorrhiza</i>	Cryptotanshinone	SW-480, HCT-116, LoVo	↓Viabilities; ↑apoptosis population; ↓anchorage independent growth; ↑caspase cleavage; ↓Bcl-2; ↓p-Stat3; ↓pEGFR; ↑p21 levels; ↓CyclinD1, survivin;	(Li, Saud, <i>et al.</i> 2015) [24]
	Tanshinone IIA	Colo-205	↓Viabilities, ↑apoptosis population; ↑p53, p21; ↑cytochrome c release; ↑Fas; ↑caspase 8 and 3 cleavage;	(Su <i>et al.</i> 2008) [58]
<i>Z. officinale</i>	Ethanol extracts	HCT-116, HT-29	↓Cell viability; ↑apoptosis population; ↑G1 phase population;	(Abdullah <i>et al.</i> 2010) [27]
	6-gingerol	LoVo	↓Viabilities; ↓cyclin A, B1, CDK1; ↑p27, p21; ↑ROS, p-p53; ↑G2 phase population;	(Lin, Lin, and Tsay 2012) [29]
	6-Gingerol	HCT-116, HT-29	↓Viabilities; ↑apoptosis population; ↑G1 phase population; ↓cyclin D1; ↑nonsteroidal anti-inflammatory drug-activated gene-1; ↓β-catenin translocation; ↑PKCε, GSK-3β activation;	(Lee, Cekanova, and Baek 2008) [28]



Figure 2: Images of the medicinal parts of the Chinese herbal medicine used for both medicinal and food purposes.

Clinically, *H. diffusa* has been used as a main component in some Chinese medicine formulas for CRC treatment. Ethanol extracts of *H. diffusa* have been shown to inhibit the proliferation of 5-FU resistant HCT-8 cells via downregulation of the expression of p-glycoprotein and ATP-binding cassette subfamily G member 2, and to inhibit proliferation and induce apoptosis in HT-29 cells through inactivation of IL-6-inducible Stat3 pathway [16, 17]. Furthermore, the n-butanol fraction of *P. notoginseng* has been shown to inhibit proliferation and induce apoptosis in SW-480 cells, while potentiates the cytotoxic effects of 5-FU against HCT-116 cells [18, 19]. Interestingly, panaxadiol from *P. notoginseng* potentiated the cytotoxic effects of 5-FU against HCT-116 cells [20]. Moreover, ginsenoside Rg3 from *P. quinquefolius* or *P. ginseng* inhibited SW-480 cell migration via inhibition of NF-κB, and

exerted antiproliferative effects on HCT-116 cells by down-regulating Wnt/β-catenin signaling [21, 22].

Tanshinone IIA, a diterpene quinone, isolated from *S. miltiorrhiza* could inhibit the growth and induce apoptosis in colo-205 cells [23]. Cryptotanshinone, another compound from *S. miltiorrhiza*, could suppress the growth and induce apoptosis in SW-480, HCT-116, and LoVo cells via the inhibition of Stat3 [24]. With regard to *S. baicalensis*, an aglycone-rich fraction from this herb has been shown to stimulate apoptosis in HCT-116 and HT-29 cells through the mitochondrial pathway [25]. Wogonin, a mono-flavonoid from *S. baicalensis*, could retard the proliferation in HCT-116 cells by Wnt/catenin signaling pathway and inactivation of CDK8 [26].

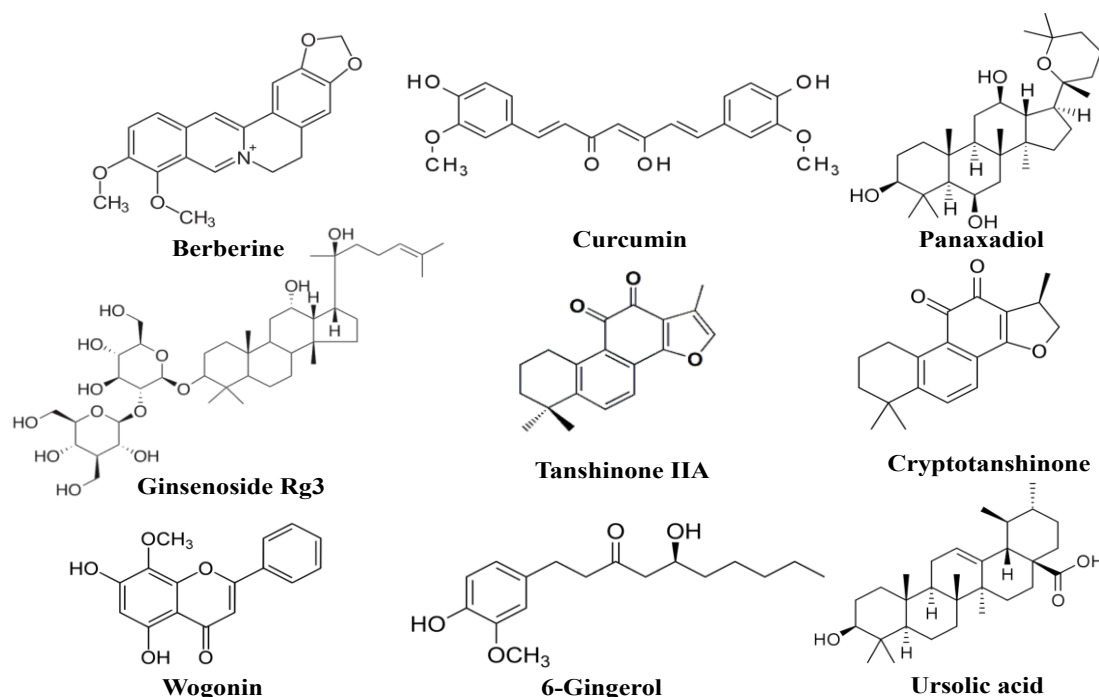


Figure 3: Chemical structures of the representative anti-CRC compounds from edible Chinese herbal medicine.

The other Chinese herb *Z. officinale* has been used as a TCM for centuries. The ethanol extracts of *Z. officinale* have been reported to trigger apoptosis and G1-phase arrest in both HCT-116 and HT-29 cells [27]. As a major pharmacologically active component of *Z. officinale*, 6-gingerol has also been reported to induce apoptosis and G1-phase arrest against HCT-116 as well as HT-29 cells [28]. Interestingly, in LoVo cells, 6-gingerol inhibited the proliferation of the cells via G2-phase arrest [29]. These results indicated that 6-gingerol could inhibit the proliferation of different human CRC cells through different mechanisms.

III *In Vivo* Evidence of Edible CHM for CRC

Carcinogenesis models are useful to understand the nature of cancer development and explore different approaches to impede the process under *in vivo* conditions. In this context, 1,2-dimethylhydrazine (DMH)- or azoxymethane (AOM)-initiated and dextran sulfate sodium (DSS)-induced mice/rat experimental colon carcinogenesis models are excellent models of CRC and have been widely used in herbal medicine studies. Moreover, genetic models of intestinal carcinogenesis (APC min) and xenograft models have also been extensively used to determine the chemo preventive and chemotherapeutic effects of herbal medicines or their active compounds (Table 2).

Table 2: *In vivo* study of Chinese herbal medicine for CRC treatment.

Species	Extract/compound	<i>In vivo</i> model	Pharmacodynamic indicators	Refs
<i>C. chinensis</i>	Berberine	SW-620 and LoVo xenograft and lung metastasis	↓Tumor volume; ↓tumor foci number;	(Liu <i>et al.</i> 2015) [12]
	Berberine	DMH and DSS-induced tumor	↓Tumor number; ↓tumor incidence;	(Wu <i>et al.</i> 2012) [67]
	Berberine	APC Min/+ mice;	↓Polyps number and size; ↓cyclin D1, c-Myc;	(Zhang <i>et al.</i> 2013) [34]
	Berberine	AOM and DSS-induced tumor	↓Tumor number and size; ↓Ki-67, COX-2; ↑AMPK; ↓p-mTOR, p-p65; ↑caspase 3 cleavage;	(Li, Hua, <i>et al.</i> 2015) [68]
<i>C. longa</i>	Curcumin	C-26 xenograft; zebrafish;	↓Vascular formation; ↓tumor volume;	(Gou <i>et al.</i> 2011) [69]
<i>G. lucidum</i>	Triterpenes	HT-29 xenograft	↓Tumor volume; ↓Ki-67; ↑Beclin-1, LC-3;	(Thyagarajan <i>et al.</i> 2010) [70]
<i>H. diffusa</i>	Ethanol extract	HT-29 xenograft	↓Tumor volume; ↓intratumoral microvessel density; ↓SHH, PTCH-1, SMO, Gli-1; ↓VEGF-A, VEGFR2;	(Lin <i>et al.</i> 2013) [71]
	Ethanol extract	HT-29 xenograft	↓Tumor volume and weight; ↑apoptosis population; ↓PCNA; ↓p-Stat3; ↑Bax, p21; ↓Bcl-2, cyclin D1, CDK4;	(Cai <i>et al.</i> 2012) [72]

	Aqueous extract	HCT-116 xenograft	↓Tumor volume and weight; ↑p-AMPK ;↓mTORC1; ↑p53 activation;	(Lu <i>et al.</i> 2016) [38]
<i>P. quinquefolius</i>	protopanaxadiol	HCT-116 xenograft	↓Tumor size; ↓PCNA;	(Gao <i>et al.</i> 2013) [12]
<i>R. Astragalii</i>	Astragalus saponins	HT-29 xenograft	↓Tumor volume; ↓p-Akt, p-mTOR, VEGF, VEGFR1, VEGFR2; ↓COX-2;	(Law <i>et al.</i> 2012) [73]
	Astragalus saponins	HT-29 xenograft	↓Tumor volume and weight; ↓PCNA;	(Tin <i>et al.</i> [39] 2007)
	Astragalus saponins	HCT-116 xenograft	↓Tumor volume and weight; ↓PCNA; ↓VEGF;	(Auyeung, Law, and Ko 2014) [41]
<i>S. miltiorrhiza</i>	Tanshinone IIA	Colo-205 xenograft;	↓Tumor volume; ↓P-glycoprotein, LC-3 II; ↓VEGF, NF-κB p65, and MMP 7;	(Su 2012) [74]
<i>S. baicalensis</i>	Baicalein	AOM and DSS-induced tumor	↓Tumor number;	(Kim <i>et al.</i> 2013) [32]
	Baicalein	HCT-116 xenograft	↓Tumor volume;	(Wang <i>et al.</i> 2015)
	Baicalin	HCT-116 xenograft	↓Tumor volume; ↑survival rate;	(Yang <i>et al.</i> 2013) [75]
<i>Z. officinale</i>	6-gingerol	HCT-116 xenograft	↓ tumor volume; ↓ leukotriene B4; ↓leukotriene A4 hydrolase;	(Jeong <i>et al.</i> 2009) [76]

Using the DMH or AOM and DSS-induced CRC model, berberine from *C. chinensis* has been shown to inhibit colon tumorigenesis by AMP-activated protein kinase signaling pathways [30, 31]. Moreover, baicalein (derived from *S. baicalensis*) has also been reported to inhibit CRC progression in DMH/AOM-DSS-induced model [32, 33]. It has also been shown that berberine could attenuate intestinal polyps' growth in APC Min mice [34].

The human CRC cell xenograft model is probably the most popular for the study of the therapeutic effects of CHM. In particular, baicalin has been shown to inhibit HCT-116 xenograft tumor growth [35]. Additionally, baicalein inhibited the growth of orthotopic xenograft tumors derived from HCT-116 cells deficient in a mismatch repair gene [36]. Furthermore, it is illustrated that *H. diffusa* ethanol extracts could inhibit HT-29 xenograft tumor growth via the inhibition of Stat3 signaling pathway, while inhibiting HCT-116 xenograft tumor growth via the activation of AMP-activated protein kinase signaling pathway [37, 38]. Moreover, Astragalus saponins have been reported to inhibit the growth and angiogenesis of HT-29 xenograft tumors [39, 40]. Furthermore, in HCT-116 xenograft tumor, Astragalus saponins have also been shown to inhibit tumor growth and proangiogenic factors generation [41].

IV Clinical Evidence of Edible CHM for CRC

It has been reported that compared with conventional therapy alone, CRC patients receiving herbal medicine and vitamins combined with conventional therapy could decrease the risk of death in stage I by 95%, stage II by 64%, stage III by 29%, and stage IV by 75% [42]. Oral administration of berberine (300 mg, thrice per day) for 6 months significantly decreased the polyp size of familial adenomatous polyposis patients, together with the cyclin D1 expression in the polyp [34]. A cohort study showed that the combined treatment of TCM and western medicine had significant clinical value and potential for reducing the relapse or metastasis rate in stage II and III of CRC after a conventional radical operation [43]. Moreover, a preliminary double-blind, randomized clinical trial indicated that the administration of aged garlic extracts for 12 months significantly decreased the size and number of colonic adenomas in CRC patients [44].

Furthermore, PHY906, a four-herb Chinese medicine formula consists mainly of edible CHM described 1800 years ago, enhanced the anti-tumor effects of the chemotherapy in patients with advanced CRC, as shown in a phase I/II clinical trial (Farrell and Kummar, 2003) [9]. Recently, a systematic review suggested that compared with chemotherapy treatment alone, CHM as adjunctive therapy with chemotherapy had a significant efficacy in terms of prolonging survival, enhancing tumor response, improving quality of life, strengthening the immune system, and alleviating acute adverse effects [45].

V Safety Concerns of Edible CHM

It is generally believed that edible plants, such as crops and vegetables are definitely safe. In reality, it is not always as expected. Toxins may inherently be present in edible plants, for instance, potatoes (*Solanum tuberosum*) contain steroids alkaloids which are toxic and even teratogenic for humans, *Lupinus albus* contains up to 5% quinolizidine alkaloids which are also toxic [46]. Although bioactive agents or extracts from edible plants are relatively safe, attention should be paid to the safety of some edible plants when taken frequently. In general, the active constituents in herbal supplements should be isolated before consumption. This procedure ensures the separation of the plant's products with desired therapeutic benefits from those which are not and even toxic. A case in point is *Cinnamomum aromaticum*, which is widely used to obtain the spice 'cinnamon' [47]. Cinnamon possessed many beneficial health effects, including anti-inflammation, anti-microbial, blood glucose control, reducing cardiovascular disease, boosting cognitive function and reducing risk of colonic cancer [48]. Moreover, *C. aromaticum* also exhibited an anti-diabetic effect [49]. However, *C. aromaticum* contains large amounts of coumarins that exert strong anticoagulant, carcinogenic and hepato-toxic properties [50]. Consequently, regular consumption of *C. aromaticum* in large quantities may be harmful [51]. In addition, the lack of strict quality control over the consumption of herbal supplements also draws our attention to the safe use of edible plants. Strict quality control procedures are imposed during the manufacture of conventional drugs to guarantee the consistency of active ingredients in all samples. However, rigorous quality control procedures are not well followed in the preparation of herbal supplements. Moreover, in some extreme occasions, poisonous plants were regarded as genuine herbs. For example, Kelp (seaweed)

tablets, a widely available dietary supplement in health food stores rich in vitamins and minerals, contain varied content of iodine and some seaweed dishes may exceed daily tolerable intake of 1100 mg [52].

Another safety concern when consuming edible CHM is herb-drug pharmacokinetic interaction. In most cases, DN patients are simultaneously using conventional medicine and traditional herbal medicine with the latter as an adjuvant. Comparatively, modern drugs have their merits in specifically targeting disease-related molecules through definite pathways; whereas TCM edible plants have the superiority that their multi-components may exert a synergetic effect and benefit the whole internal milieu of patients, raising the possibility that the combinational administration of TCM edible plants and modern drugs may provide better therapeutic effects on diseases, especially chronic and comprehensive diseases like DN. However, after co-administration, edible plants may reduce the permeability of the conventional drug in the intestinal tract and may also affect its metabolism in the liver and cause hypoglycemia. Research by Puranik and colleagues (2011) found that the technology-based supercritical extract of *Cassia auriculata* caused a significant reduction in absorption of metformin, indicating the need to include pharmacokinetic herb-drug interaction studies to avoid unexpected side effects [53]. Another case is the commonly used herb St. John's wort. Hyperforin and hypericin, the active component of St. John's wort, induce CYP3A4 and P-glycoprotein, respectively. Thus, it is likely that drugs that are metabolized by CYP3A4 and P-glycoprotein will interact with St. John's wort [54, 55]. Therefore, physicians and the patients need to pay crucial attention to potential adverse herb-drug interactions when TCM edible plants are used as an adjuvant in disease management.

Conclusion

The above described *in vitro*, *in vivo*, and clinical results strengthen the fact that edible CHM can interfere with numerous molecular pathways related to cancer initiation and progression. These pieces of evidence undoubtedly highlight the application of edible CHM as novel chemo preventive and chemotherapeutic agents for CRC intervention. In future studies of edible CHM, various molecular mechanisms and targets for tumor growth inhibition, apoptosis, anti-angiogenesis, and particularly metastasis still remain to be resolved. Currently, clinical trials with edible CHM conducted for CRC treatment are very limited. Therefore, in order to take full advantage of edible CHM, much more well-designed clinical trials are necessary for further evaluation of the safety and efficacy of edible CHM against CRC.

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