Adjuvant effects of Chinese medicinal tonics on gastric, liver, and colorectal cancers—OMICs-based contributions to understanding their mechanism of action

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Gastric, liver, and colorectal cancers belong to gastrointestinal (GI) cancers, one of the most threatening diseases in the world. The tonics class in Chinese medicines plays a critical role in antigastrointestinal cancer as adjuvants. However, it is a challenge to study the effects and underlying mechanisms of tonics due to their multiple components and multiple targets; OMICS were introduced to facilitate the investigation of the complex mixture of tonics. In this review, the online databases PubMed, ProQuest, Web of Knowledge, China National Knowledge Infrastructure (CNKI), Chongqing VIP, and Wanfang were retrieved from 1 January 2011 to 31 May 2022, in an aim to summarize and discuss the research progress of the effects and, especially, the underlying mechanisms of tonics for antigastrointestinal cancers via OMICS. The results showed that through the combination of OMICS and other technologies, tonics have been used for gastrointestinal cancer by targeting cancer hallmarks, enhancing body resistance to carcinogenesis, enhancing therapeutic effects, and/or decreasing side effects. In conclusion, tonics may play a promising role in gastric, liver, and colorectal cancers as adjuvants and can be well investigated via the combination of OMICS and other technologies, which deserves further study.
1 Introduction

Gastrointestinal (GI) cancers are one of the most threatening diseases in the world. There were approximately 5,142,192 new cases and 3,628,920 deaths from GI cancers in the world in 2020 (Sung et al., 2021). Based on disease sites, GI cancers are divided into two families: upper digestive tract cancers (including esophageal, stomach, pancreatic, liver, gallbladder, and lymphoma involving the mucosa-associated lymphoid tissue, gastrointestinal stromal, and biliary tree) and lower cancers (including colorectal, anal, and gastrointestinal carcinoid). The order of the mortality rate from high to low for cancer sites was liver (8.3%), stomach (7.7%), colon (5.8%), esophagus (5.5%), pancreas (4.7%), rectum (3.4%), gallbladder (0.9%), and anus (0.2%) (Sung et al., 2021). The total new deaths of GI cancers (36.7%) exceeded those of lung cancer (18.0%) and GI cancers ranked as the leading cause of death (Sung et al., 2021). The conventional treatments of GI cancers include surgical resection, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, some patients cannot tolerate surgical resection. Chemotherapy and radiotherapy induce toxicity and side effects. Targeted therapy and immunotherapy are often expensive, especially for patients in developing countries. Thus, natural medicines have drawn attention due to their lower toxicity and effectiveness as adjuvant strategies and have been widely used in clinical practice to adjust patients’ constitution and reduce toxicity and side effects after surgery, chemotherapy, and radiotherapy.

Tonics of Chinese medicines (CMs) refer to medicines that can supplement Qi, blood, Yin, and Yang of the human body, relieve deficiency and weakness syndromes, enhance visceral function, and improve the body’s ability to resist disease. Their pharmacological actions include enhancing immunofunction, regulating metabolism of substances, improving the endocrine system, anti-aging, and anticancer (Chen, 2017). Tonics are divided into four categories, Qi tonics (e.g., Panax ginseng C.A.Mey and Astragalus membranaceous (Fisch.) Bge. var. mongholicus (Bge.) Hsiao), blood tonics (e.g., Angelica sinensis (Oliv.) Diels and Polygonum multiflorum Thunb.), Yin tonics (e.g., Lycium barbarum L. and Ophiopogon japonicus (L. f) Ker-Gawl.), and Yang tonics (e.g., Epimedium brevicomum Maxim.) (Chen, 2017). Some Chinese formulas are also believed to be tonics such as Liu Wei Di Huang pills (Xiong et al., 2022). There are 72 tonics out of 371 CMs for anti-GI cancers, which ranked the second class of the most frequently used CMs following the clearing heat and detoxifying class (Xu et al., 2018) (Figure 1).

However, it was difficult for the research community to explore the effects, and particularly the underlying mechanisms of tonics due to their multiple components (Yang et al., 2018; Yang et al., 2019), complex pharmacokinetic (PK) processes (Wang et al., 2021a; Wang et al., 2021b), and multiple targets until OMICs were introduced (Li et al., 2019; Wang et al., 2019; Wang and Lu, 2019; Li et al., 2020; Liu et al., 2021a; Li et al., 2022b). OMICs are novel technologies that have been dramatically developed in the last 2 decades. Small size samples and large-scale and high-throughput screening make OMICs possible to apply to various disciplines in biology including complex pharmacological mechanisms (Li et al., 2022a). OMICs include genomics, proteomics, metabolomics (or metabonomics), metagenomics, transcriptomics, epigenomics, glycomics, and lipomics. In this review, we retrieved online databases, aiming to summarize and discuss the OMICs-based research progress of adjuvant effects, especially underlying mechanisms, and provide insights into the complex multiple components and targets of tonics on GI cancers.

2 Materials and methods

2.1 Data retrieval and collection

The keywords “OMICs or genomics/proteomics/metabolomics/metabonomics/metagenomics/transcriptomics/epigenomics/glycomics/lipomics” and “tonics” and “gastrointestinal cancer” were used to retrieve studies of tonics for GI cancers from the online databases of PubMed, ProQuest, Web of Knowledge, China National Knowledge Infrastructure (CNKI), Chongqing VIP, and Wanfang from 1 January 2011 to 31 May 2022. Duplicates were discarded. The effects, overall
efficacy, and underlying mechanisms via OMICs technologies in these studies were summarized and analyzed. All plant names were checked with the World Flora Online (www.worldfloraonline.org) or MPNS (http://mpns.kew.org).

2.2 Inclusion criteria

The inclusion criteria were as follows (Ding et al., 2019):

- The contents of the literature involve the in vitro, in vivo, and clinical effects of tonics on GI cancers
- The references included pure compounds, single herbal fractions, and formulas of tonics
- The methodologies were designed using OMICs

2.3 Exclusion criteria

The exclusion criteria were as follows (Ding et al., 2019):

- The literature was associated with neither tonics nor OMICs
- The pure compounds were not naturally from tonics but were chemical derivatives
- The species of tonics were not clearly presented, or the plant names were not checked in the “World Flora Online” (www.worldfloraonline.org) or MPNS (http://mpns.kew.org)
- The fractions and/or formulas of tonics were described with neither the extraction methodology nor quality control
- The components of the formulas were not given
- The concentration/dose of tonics was not given
- The clinical studies were not randomized and controlled
- The in vivo and clinical studies did not claim any ethical approvals, and the clinical studies were conducted without the declaiming of patients’ agreement or signing informed consent

3 OMICS for adjuvant effects and mechanisms of tonics on gastric, liver, and colorectal cancers

3.1 Gastric cancer

The effects and mechanisms of tonics on gastric cancer via OMICs are listed in Table 1.

3.1.1 Proteomics

Ginsenosides are the major bioactive constituents in ginseng (roots and rhizomes Panax ginseng C. A. Mey.), a famous Qi-tonifying CM. Among these, ginsenoside F2 possesses anticancer effects in the human gastric carcinoma cell line SGC7901 (Mao et al., 2016). An iTRAQ-based proteomic analysis in combination with western blotting (WB) revealed that ginsenoside F2 induced autophagic cell death in the human gastric carcinoma cell line SGC7901 via an increase in Atg5, Atg7, Atg10, and PUMA, the ribosomal protein-p53 signaling pathway, and Beclin-1, UVRAG, and AMBRA-1, important molecules in the Becl-xl/Beclin-1 pathway (Mao et al., 2016).

3.1.2 Transcriptomics

Angelicae Sinensis Radix (roots of Angelica sinensis (Oliv.) Diels, Danggui) is a blood-tonifying CM (Xu et al., 2018). It was reported that Angelicae Sinensis Radix can treat patients with gastric cancer. The transcriptomic results showed that n-butylidenephthalide, the active compound in Angelicae Sinensis Radix, induced REDD1 (regulated in development and DNA damage responses 1) and consequently inhibited its downstream factor mammalian target of rapamycin (mTOR) in gastric cancer (Liao et al., 2018).

3.1.3 Genomics

The effects and the substantial basis of Guiqi Baizhu prescription, a complex formula, including Angelicae Sinensis Radix, Astragali radix (roots of Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao and Astragalus membranaceus (Fisch.) Bge., Huangqi), Atractylodis macrocephalae Rhizoma (rhizomes of Atractylodes macrocephala Koidz., Baizhu), Paeoniae Radix Alba (roots of Paeonia lactiflora Pall., Baishao), Pericarpium Citri Reticulatae (peels of Citrus reticulata Blanco, Chenpi), Rhei Radix et Rhizoma (roots and rhizomes of Rheum palmatum L., Rheum tanguticum Maxim. ex Balf. and Rheum officinale Baill, Dahuang), and Glycyrrhizae Radix et Rhizoma Praeparata cum Melle (processed roots and rhizomes of Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat., or Glycyrrhiza glabra L., Zhigancao), are remained to be explored. The genomic assay combined with network pharmacology showed that quercetin, daidzein, and isorhamnetin had potential antiproliferative effects on HER-2 and PD-L1 in human gastric cancer (GC) MKN-45 cells. Quercetin, daidzein, and isorhamnetin are the components in Astragoli Radix, indicating that Astragali Radix instead of Angelicae Sinensis Radix played the main role in the proliferation of GC (Li et al., 2021a), although Astragali Radix may have a synergistic effect in the formula (Liao et al., 2018).

Another role of genomics is in the shortage of chemotherapy—drug resistance. How to reverse drug resistance via OMICs has drawn attention from the medical community. Paeoniae Radix Alba is one of the blood tonics used for nourishing the blood and regulating menstruation, astringing Yin and checking sweeting, emolliating the liver, relieving pain, and depressing the liver Yang. Although Paeoniae Radix Alba reversed the drug resistance of GC
| Compound, herb, and formula | Tonics (in formula) | Study form | OMICs and role | Dose or concentration | Mechanism | Targeted hallmark | Reference |
|----------------------------|---------------------|------------|---------------|----------------------|-----------|------------------|-----------|
| Guiqi Baizhu               | Angelicae Sinensis Radix*, Astragal Radix*, Atractylodis macrocephalae*, Paeoniae Radix Alba*, and Glycyrrhizae Radix et Rhizoma Praeparata cum Melle* | In vitro | Genomics and network analysis for identifying the active compounds | 570.07 nmol/L | ↓HER-2 and PD-L1 | Sustaining proliferative signaling pathways | Li et al. (2021a) |
| N-butylidenephthalide (BP) | Angelicae Sinensis Radix* | In vitro and in vivo | Transcriptomics combined with qPCR, WB, and siRNA transfection for studying effects and mechanisms | In vitro: 50 μg/ml AGS or BP 75 μg/ml, and in vivo: 300, 500, and 700 mg/kg | ↑REDD1; ↓mTOR signaling | Sustaining proliferative signaling pathways | Liao et al. (2018) |
| Ginsenoside F2              | Ginseng Radix et Rhizoma* | In vitro | Proteomics for screening the signaling pathways | 20 μM | ↑p53 and Bcl-xl/Beclin-1 | Resisting cell death | Mao et al. (2016) |
| Dendrobium extract (DOE)   | Dendrobium officinale Kimura et Migo (Tiepishihai)* | In vitro | Metabolomics with qPCR for screening the metabolic and signaling pathways | DOE (polysaccharides 45%) | ↓VEGF, ↓SPHK1, and ↓S1PR1 mRNA by metabolite sphingosine-1-phosphate (S1P) | Inducing angiogenesis | Zhao et al. (2017) |
| 18β-Glycyrrhetinic acid (GRA) | Glycyrrhizae Radix et Rhizoma* | In vitro, in vivo, and human GC tissue collection | Genomics with qRT-PCR for screening the methylation genes and targeted genes | 50–200 μM for in vitro and 0.05% GRA for in vivo | ↑ATP4a activation and ↓DNMT1 | Genome instability mutation | Cao et al. (2020) |
| Paeonol                    | Paeonia lactiflora Pall.* | In vitro and in vivo | Genomics with qPCR, CCK-8, and TUNEL for studying the synergistic mechanisms | In vitro 60 μg/L and in vivo: 30 and 50 mg/kg/d i.p | ↑LINC00665 and MAPK1 and ↑miR-665 | Enhancing therapeutic effects and/or decreasing side effects via drug interactions | Li et al. (2022b) |
| Jianpi Yangzheng Xiao sheng recipe | Astragal Radix*, Codonopsis Radix*, Atractylodis Macrocephalae Rhizoma*, Dioscoreae Rhizoma (whole herbs of Hedysperis diffusa Willd., Baishuashencao), Angelicae Sinensis Radix*, Paeoniae Radix Alba*, and Glycyrrhizae Radix et Rhizoma* | In vitro | Metabolomics for screening the metabolic pathways | 37.15 and 74.30 g/kg | ↓arachidonic acid and ↓α-linolenic acid and linoleic acid metabolic pathway | Deregulating cellular energetics | Xu et al. (2021) |
| Yiqi Fusheng recipe        | Atractylodis Macrocephalae Rhizoma*, Astragal Radix*, Myristicae Semen, Codonopsis Radix*, Portia, and Akebiae Fructus | In vitro | Metabolomics for screening the metabolic pathways | 1 g/ml | ↓(3-hydroxybutyric acid, methionine, valine, and glutamine), ↑(low density lipoprotein/LDL, very low density lipoprotein VLDL, glutamic acid, triglycerides, unsaturated fatty acids, and choline) | Deregulating cellular energetics | He et al. (2016) |
| Yiwei decoction            | Astrapagulus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) | In vivo | Metabolomics and bioinformatics for studying the | 1.09 g/ml | Intervened gastric precancerous lesions via regulating 13 metabolites that | Deregulating cellular energetics | Dong et al. (2020) |

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cells, the mechanism was unknown until paenol (the active compound in Paeoniae Radix Alba) was reported using genomics—data showed that paenol inhibited the malignancy of apatinib-resistant GC cells through the LINC00665/miR-665/MAPK1 axis (Li et al., 2022b).

### 3.1.4 Metabolomics

*Dendrobium officinale* Kimura et Migo (Tiepishihu) is one of the sources of Dendrobii Caulis (Shihu). To investigate the substantial basis of Dendrobii Caulis on gastric cancer, blood metabolites were analyzed to screen the active compounds using UPLC-Q-TOF-MS. The metabolomics results showed that among five candidate metabolites, phingosine-1-phosphate (S1P) inhibited GC angiogenesis by inhibiting VEGF, SPHK1, and S1PR1 mRNA in rats (Zhao et al., 2017). Another urine metabolomics study showed that Dendrobii Caulis aqueous extracts inhibited the progression of gastric precancerous lesions. The mechanism is related to porphyrin metabolism, tryptophan metabolism, folic acid and pterin biosyntheses, and galactose and arachidonic acid metabolisms (Wang et al., 2018).

Yiwei decoction is a tonic formula that includes *Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao (Huangqi), *Ophiopogon japonicus* (L. f) Ker-Gawl. (Maidong), *Tetrastigma hemsleyanum* Diels et Gilg (Sanqing), *Pinellia ternata* (Thunb.) Breit. (Banxia), *Taraxacum mongolicum* Hand.-Mazz. (Pugongying), *Paeonia lactiflora* Pall. (Shaoyao), *Actinidia chinensis* Planch. (Tengligen), *Cix lacryma-jobi* L. var. ma-yuen (Roman.) Stapf (Yiyiren), and *Rabdosia amethystoides* (Benth.) Hara. (Xiangchacai). The serum metabolomics results showed that Yiwei decoction intervened in gastric precancerous lesions by regulating 13 metabolites involved in the biosynthesis of unsaturated fatty acids, biosynthesis of valine, leucine and isoleucine, sphingolipid metabolism, arachidonic acid metabolism, and steroid hormone synthesis (Dong et al., 2020).

| Compound, herb, and formula | Tonics (in formula) | Study form | OMICs and role | Dose or concentration | Mechanism | Targeted hallmark | Reference |
|----------------------------|--------------------|------------|----------------|-----------------------|-----------|------------------|-----------|
| Hsiao (Huangqi)
*Ophiopogon japonicus* (L. f) Ker-Gawl. (Maidong)
*Tetrastigma hemsleyanum* Diels et Gilg (Sanqing)
*Pinellia ternata* (Thunb.) Breit.
(Banxia), *Taraxacum mongolicum* Hand.-Mazz. (Pugongying), *Paeonia lactiflora* Pall. (Shaoyao), *Actinidia chinensis* Planch.
(Tengligen), *Cix lacryma-jobi* L. var.
ma-yuen (Roman.) Stapf (Yiyiren), and *Rabdosia amethystoides* (Benth.) Hara. (Xiangchacai) | energetic signaling pathways | involved in the biosynthesis of unsaturated fatty acids, biosynthesis of valine, leucine and isoleucine, sphingolipid metabolism, arachidonic acid metabolism, and steroid hormone synthesis | 0.06–0.24 g/kg DOE can block the progression of gastric precancerous lesions, its mechanism may be related to porphyrin metabolism, tryptophan metabolism, folic acid and pterin biosynthesis, galactose metabolism, and arachidonic acid metabolism | Deregulating cellular energetics | Wang et al. (2018) |

*Tonics.
↑: induction, upregulation, or activation; ↓: reduction, downregulation, or inactivation.

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Radix (roots of Codonopsis pilosula (Franch.) Nannf., Codonopsis pilosula Nannf. var. modesta (Nannf.) L. T. Shen, and Codonopsis tangshen Oliv., Danshen), Poria (sclerotium of Poria cocos (Schw.) Wolf (Fuling), Danshen), Akebia Fructus (immature fruits of Akebia quinate (Thunb.) Decne., Akebia trifoliate (Thunb.) Koidz., Akebia trifoliate (Thunb.) Koidz. var. australis (Diels) Rehd., Yuzhizi). The metabolomics results showed that the Yiqi Fusheng recipe can be used to treat spleen-Qi deficient mice with gastric cancer by targeting energy metabolism reprogramming. The mechanisms may lie in lowering the content of 3-hydroxybutyric acid, methionine, valine, and glutamine, and increasing low density lipoprotein (LDL)/very low density lipoprotein (VLDL), glutamic acid, triglycerides, unsaturated fatty acids, and choline (He et al., 2016).

The Jianpi Yangzheng Xiaozheng recipe comprises Astragali Radix, Atractylodis Macrocephalae Rhizoma, Codonopsis Radix, Poria, Dioscoreae Rhizoma (rhizomes of Dioscorea opposita Thunb., Shanyao), Coicis Semen (seeds of Coix lacryma-jobi L. var. ma-yuen (Roman.) Stapf, Yi-yiren), Citri Reticulatae Pericarpium, Aucklandiae Radix (roots of Aucklandia lappa Decne., Muxiang), Angelicae Sinensis Radix, Paeoniae Radix Alba, Smilacis Chines Rhizoma (rhizomes of Smilax china L., Baqia), Salviae Chinensis Herba (whole herbs of Salvia chinensis Benth., Shijianchuan), and Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle. The Jianpi Yangzheng Xiaozheng recipe is reported to enhance body resistance to GC. The serum metabolomics results showed that this effect was associated with an increase in the serum levels of α-linolenic acid, linoleic acid (LA), and arachidonic acid (AA) (Xu et al., 2021). LA can be metabolized to AA. LA/AA plays an important role in enhancing body resistance, i.e., the inflammatory response and immune function (e.g., natural killer cell activity). Although certain arguments show the relationship between LA/AA and breast cancer (Gago-Dominguez et al., 2003; Murff et al., 2011), dietary intake of LA/AA was reported to decrease the risk of colorectal cancer (Kuriki et al., 2006) and liver cancer (Bao et al., 2017). This indicates that the Jianpi Yangzheng Xiaozheng recipe may enhance immunofunction through LA/AA metabolism.

3.2 Colorectal cancer

OMICs for the adjuvant effects and mechanisms of tonics on colorectal cancer (CRC) are listed in Table 2.

3.2.1 Proteomics

Proteomic data showed that 20S-ginsenoside Rg3, an active compound in ginseng, induced colon cancer apoptosis by downregulating the Rho GDP dissociation inhibitor (RhoGDI), together with upregulating tropomyosin 1, annexin 5, and glutathione s-transferase p1 (GSTP1) (Lee et al., 2009).

3.2.2 Transcriptomics

There is an interesting concept, namely, the Chinese herb pair (Yao Dui). In this case, two herbs are commonly included at an appropriate ratio in some formulas for enhancing effects and/or decreasing toxicity. Gegen Qinlian decoction (GQD) is an ancient formula from the Han dynasty. Since it consists of four herbs, Puerariae Lobatae Radix (roots of Pueraria lobata (Willd.) Ohwi, Gegen), Scutellariae Radix (roots of Scutellaria baicalensis Georgi, Huang Qin), Coptidis Rhizoma (rhizomes of Coptis chinensis Franch., Coptis deltoidea C. Y. Cheng et Hsiao and Coptis teetta Wall., Huanglian), and Glycyrrhizae Radix et Rhizoma (roots and rhizomes of Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat., or Glycyrrhiza glabra L., Gancao), the dominant herbs have not yet been clarified. The transcriptomics data by Li et al. (2021b) showed that two active compounds, puerarin (PUE) and glycyrrhetinic acid (GLY) without other active compound pairs, influenced the Wnt signaling pathway by upregulating GSFK3B and downregulating CTNNB1 synergistically in colon SW480 cells. As PUE and GLY are the main components of Puerariae Lobatae Radix and Glycyrrhizae Radix et Rhizoma, respectively, the results confirmed the pharmacological role of the herb pair, Puerariae Lobatae Radix and Glycyrrhizae Radix et Rhizoma, in GQD.

3.2.3 Genomics

Accumulating evidence suggests that aberrant DNA methylation and gene silencing of tumor suppressors are pervasive in GI cancers (Cao et al., 2020). ATP4a is an important tumor suppressor gene, encoding H+, K+-ATPase, and there is an inverse correlation between methylation and gene expression in ATP4a. Genomics evidence showed that isoquertiginin (ILTG), an active compound in Glycyrrhiza inflata L., exhibited a demethylating activity on HT-29 colon cancer by increasing ATP4a (Zorko et al., 2010).

3.2.4 Metabolomics

Astragalus membranaceus and Carcina wenyujin (AC) are classic Chinese herb pairs for colon cancer metastasis. Metabolomics data indicate that AC inhibits liver and spleen metastases of colon cancer by disturbing energetic dysfunction including valine, leucine, and isoleucine biosyntheses, aminoacyl-tRNA biosynthesis, caffeine metabolism pathway, and retinol metabolism pathways (Sun et al., 2021b).

The metabolomic studies showed that Panacis Quinquefolii Radix (roots of Panax quinquefolium L., American ginseng or Xianyshen) attenuated colitis-associated colon carcinogenesis in mice via a decrease in the inflammatory cytokines IL-1α, IL-1β, IL-6, G-CSF, and GM-CSF. Panacis Quinquefolii Radix also decreased the impaired metabolism of arachidonic acid, linoleaidic acid, glutamate, docosahexaenoate, tryptophan, and fructose, all of which are associated with inflammation and oxidation (Xie et al., 2015).
| Compound, herb, and formula | Tonics (in formula) | Cancer | Study form | OMIcs and role | Dose or concentration | Mechanism | Targeted hallmark | Reference |
|---------------------------|---------------------|--------|------------|----------------|----------------------|-----------|------------------|-----------|
| Ginsenoside-Rp1 Ginseng Radix et Rhizoma' | Colorectal | *In vitro* | Proteomics with proliferation assay and propidium iodine staining for screening the signaling pathway | 60 mM | ↑ Apo-A1 | Sustaining proliferative signaling pathways | Kim et al. (2014) |
| Gegen Qinlian decoction (GQD) Puerariae Lobatae Radix, Scutellariae Radix, Coptidis Rhizoma, and Glycyrrhizae Radix et Rhizoma' | Colon | *In vitro* | Transcriptional and network pharmacology for screening the drug compatibility and the signaling pathway | GLY-PUE combination (GLY, 60 and 70 μM) | ↑ GSK3B and ↓ CTNNB1 | Sustaining proliferative signaling pathways | Li et al. (2021b) |
| Jujube polysaccharides Zizyphus jujuba cv. Mucao' | Colorectal | *In vivo* | Metabolomics and transcriptomics for screening the effects on metabolisms and the gut microbiota | 200 and 1,000 mg/kg | ↑ short-chain fatty acids (SCFAs) and Bifidobacterium, Bacteroides, and Lactobacillus | Inflammation-mediated carcinogenesis | Ji et al. (2019) |
| American ginseng Panacis Quinquefolii Radix' | Colon | *In vivo* | Metabolomics for screening the dysregulated metabolism pathways | 10 and 20 mg/kg/d | ↓ (IL-1α, IL-1β, IL-6, G-CSF, and GM-CSF), ↓ (arachidonic acid, linoleic acid, glutamate, docosahexaenoic acid, trefoil factor, and fructose) | Inflammation-mediated carcinogenesis | Xie et al. (2015) |
| Jujube polysaccharides Jujubae Fructus' | Colorectal | *In vivo* | Transcriptional and transcriptomics for screening the effects on the gut microbiota | 1,000 mg/kg/d | ↑ short-chain fatty acids (SCFAs) and ↓ Firmicutes/Bacteroidetes | Inflammation-mediated carcinogenesis | Ji et al. (2020) |
| American ginseng Panacis Quinquefolii Radix' | Colon | *In vitro and in vivo* | Metabolomics and transcriptomics for studies on restoring the metabolic and microbiota profiles | 15 and 30 mg/kg/d | ↓ (IL-1α, IL-1β, IL-6, G-CSF, GM-CSF), ↓ malic acid and 2-hydroxybutyrate acid, and ↓ Bacteroides and Verrucomicrobia | Inflammation-mediated carcinogenesis | Wang et al. (2016a) |
| Glycyrrhiza polysaccharide (GCP) Glycyrrhiza Uralensis Fisch.' | Colon | *In vivo* | Transcriptional and network pharmacology for screening the effects on the gut microbiota | 500 mg/kg | ↑ (Enterorhabdus, Odoribacter, Ruminococcaceae_UCG_014, Ruminococcaceae_UCG_010, Enterococcus, Ruminoclostridium_5), and ↓ (Parasutterella, Clostridium_sensu_stricto_1, Blautia) | Inflammation-mediated carcinogenesis | Zhang et al. (2018) |
| Isoliquritigenin (ILTG) Glycyrrhiza glabra L.' | Colon | *In vitro* | Epigenomics with cytotoxicity assay and an ethidium bromide displacement assay for screening the methylation genes | 11.1 μg/ml | ↓ DNA methylation | Genomic instability and mutation | Zorko et al. (2010) |

(Continued on following page)
| Compound, herb, and formula | Tonics targeting hallmarks as adjuvants in gastric, liver, and colorectal cancers via OMICs. |
|-----------------------------|------------------------------------------------------------------------------------------|
| **Compound, herb, and formula** | **Tonics (in formula)** | **Cancer** | **Study form** | **OMICs and role** | **Dose or concentration** | **Mechanism** | **Targeted hallmark** | **Reference** |
| **Astragalus membranaceus extract** | *Astragalus membranaceus* (Fischer) Bge. var. mongolicus (Bge.) Hsiao (AM)*a | Colorectal | *In vivo* | Transcriptomics for screening the mechanisms | 500 mg/kg/d | Regulating epigenetic-related genes including KMT2D, BRD2, CREBBP, and ARID1A | Genome instability mutation | Tseng et al. (2016) |
| **Compound K** | Ginseng Radix et Rhizoma* | Colon | *In vitro* | Genomics for screening the signaling pathways | 20 ± 1.0 μg/ml | ↓ histone deacetylase (HDAC) activity, mRNA, and protein expression. ↑ RUNX3 and p21 | Genome instability mutation | Kang et al. (2013) |
| **Daikenchuto (DKT)** | Ginseng Radix et Rhizoma* | Colon | Clinical study (after laparoscopic colectomy) | Metabolomics and transcriptomics for screening the effects on metabolomic pathways and gut microbiota | 5g. t.i.d | ↓ arachidonic acid cascade and ↓ Serratia and Bilophila | Enhancing body resistance by reduction gastrointestinal symptoms | Hanada et al. (2021) |
| **Quxie capsules** | Ginseng Radix et Rhizoma*, Zingiberis Rhizoma, Aquilariae Lignum Resinatum, Crotonis Fructus, Gleditsiae Spina | Colorectal | Clinical study (after chemotherapy, radiotherapy, targeted therapy, and immunotherapy) | Metabolomics and transcriptomics for screening the effects on metabolomic pathways and gut microbiota | 0.05 g/kg, b.i.d | Improving beneficial bacteria in the intestinal tract and reducing the distribution ratio of harmful bacteria via modulating nicotinic acid and nicotinamide, anthocyanin and tryptophan metabolism pathway | Enhancing body resistance to carcinogenesis | Sun et al. (2021a) |
| **Astragalus membranaceus-Curcuma wenyujin (AC)** | *Astragalus membranaceus* | Colorectal | *In vivo* | Metabolomics for screening the drug compatibility and the signaling pathway and the energetic signaling pathways | AC at the ratio of 2:1 | ↓ valine, leucine, and isoleucine biosynthesis, aminoaetyl-tRNA biosynthesis, caffeine metabolism pathway, and retinol metabolism pathways) | Activating invasion and metastasis and deregulating cellular energetics | Sun et al. (2021b) |
| **Polysaccharides and ginsenosides** | American Ginseng (*Panax quinquefolius* L.)* | Gastrointestinal | *In vitro and in vivo* | Metabolomics and transcriptomics for studying synergistic mechanisms | 1,500 mg/kg/d + ginsenoside (150 mg/kg/d, AGP_AGG | ↓ CTX-induced intestinal immune disorders and gut barrier dysfunctions | Enhancing body resistance to carcinogenesis | Zhou et al. (2021a) |

*aTonics. ↓: induction, upregulation, or activation; ↑: reduction, downregulation, or inactivation.
Quxie capsules (QXC) are the adjuvant drugs for CRC to reduce intestinal complication, which comprise Ginseng Radix et Rhizoma, Zingiberis Rhizoma (rhizomes of Zingiber officinale Rose., Galangang), Aquilariae Lignum Resinatum (resinatum of Aquilaria sinensis (Lour.) Gilg, Chenxiang), Crotonis Fructus (fruits of Croton tiglium L., Badou), and Gleditsiae Spina (fruits of Gleditsia sinensis Lam., Dazaojiao). The serum metabolomics data showed that QXC improved beneficial bacteria in the intestinal tract and reduced the distribution ratio of harmful bacteria by modulating the nicotinic acid and nicotinamide, anthocyanin, and tryptophan metabolism pathways in patients with CRC (Sun et al., 2021a).

3.2.5 Multi-OMICs

Jujubae Fructus (Dazao) is the fruit of Zizyphus jujuba Mill. for tonifying Qi in CMs. The transcriptomic and metabolomic profiles showed that its polysaccharide consumption prevented mouse CRC and decreased colon mortality, reduced proinflammatory cytokines, increased the concentration of total short-chain fatty acids (SCFAs) and gut microbiota Bifidobacterium, Bacteroides, and Lactobacillus, and decreased gut microbiota Firmicutes/Bacteroidetes in mouse feces, indicating that Jujubae Fructus polysaccharides prevented inflammation-mediated carcinogenesis by restoring the balance of the gut microbiota in CRC (Ji et al., 2019; Ji et al., 2020).

Cyclophosphamide (CTX) is a widely used chemotherapy drug. However, it may result in complicated adverse effects including vomiting, diarrhea, and abdominal pain, related to the disruption of the mucosal barrier, bacterial translocation, and changes in microbial composition. Polysaccharides and ginsenosides are the two classes of active compounds in American ginseng. Through metabolomic and transcriptomic analyses, these polysaccharides and ginsenosides were found to exert synergistic effects to ameliorate CTX-induced intestinal immune disorders and gut barrier dysfunctions (Zhou et al., 2020).

3.3 Liver cancer

OMICs for the adjuvant effects and mechanisms of tonics on liver cancer are listed in Table 3.

3.3.1 Proteomics

Concerning complications, patients with liver cancer may suffer from depression, which is also an inducing factor in hepatocellular carcinogenesis. The Jiawei Xiaoyao pulvis is a formula and was reported as an adjuvant to relieve liver carcinogenesis-induced depression. The proteomic results showed that Jiawei Xiaoyao pulvis reversed depression-like behaviors by regulating GSTM1, PDK1, and HSP90AB1 (Wen et al., 2022) (Table 3).

3.3.2 Transcriptomics

*Astragalus* protein is the active compound from the tonics Astragalus membranaceus (Fisch.). Transcriptomic data in combination with qRT-PCR and WB showed that Astragalus protein induced programmed necrosis of liver cancer HepG2 cells via the p53 signaling pathway (Wang et al., 2020b). Transcriptomics and network pharmacology studies have shown that daidzein (an active compound in Astragali Radix) induces ferroptosis by downregulating MT1G in liver cancer (Liu et al., 2021).

3.3.3 Metabolomics

According to Chinese medicine philosophy, one of the typical syndromes of liver cancer is spleen deficiency, with which patients may suffer from cancer pain, ascites, fatigue, etc. (Xu et al., 2018). Sijunzi decoction (Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Poria, and Glycyrrhizae Radix et Rhizoma) is a tonifying formula for spleen deficiency. However, because of the complex mixture of multiple components and multiple targets, how to profile spleen deficiency and how to interpret Chinese herbs treating such a syndrome pharmacologically are challenges. Based on blood plasma metabolomics using UPLC-HDMS, Wang et al. found that Sijunzi decoction treated spleen deficiency with metabolic dysfunctions in liver cancer via regulating the metabolisms of amino acids, arachidonic acid, fatty acids, and glutathione (Wang et al., 2020).

3.3.4 Multi-OMICs

Using metabolomics for fecal metabolites and transcriptomics for gut microbiota, Panax Ginseng was found to regulate bile acid biosynthesis, unsaturated fatty acid biosynthesis, tryptophan metabolism, arachidonic acid metabolism, pyrimidine metabolism, and vitamin B6 metabolism. Furthermore, 25 species of bacteria with significant differences in effective parts in liver cancer and 23 species of bacteria with significant differences in synergistic action of ginsenosides and polysaccharides indicated that Qi deficiency liver cancer was associated with bile acid biosynthesis, unsaturated fatty acid biosynthesis, tryptophan metabolism, arachidonic acid metabolism, pyrimidine metabolism, vitamin B6 metabolism, and certain gut microbiota (Hou et al., 2022).

4 Discussion

Due to the heterogeneity of cancer, different molecular targets achieve different effects, and even cancers of one organ require different treatment strategies. This leads to the challenges for anti-GI cancers, especially in terms of understanding their underlying mechanisms. Thus, Hanahan introduced a new concept, hallmark, to distinguish the different mechanisms and potential targets for anticancer (Hanahan and Weinberg, 2022).
Tonics are effectively complementary and alternative medicines to conventional treatments with less toxicity. OMICs are novel technologies with a small sample size, and large-scale and high-throughput screening. These properties make it possible to apply OMICs for exploring the pharmacological mechanisms of tonics, especially targeting cancer hallmarks. In this study, the data showed that the targets of tonics included sustaining proliferative signaling, resisting cell death, activating invasion and metastasis, inducing angiogenesis, deregulating cellular energetics, inflammation-mediated carcinogenesis, and genomic instability and mutation (Table 1, Table 2, and Table 3; Figure 2).

However, there are still some challenges to limit the applications of OMICs. To further explore the role of OMICs in tonics on GI cancer, we focused on the active compounds, mechanisms, and compatibility of tonics, combined with basic experiments and novel technologies, and emphasized minimal injury methodologies.

First, tonics in clinical use are herbs, especially in formulas. This means that tonics for anti-GI cancer have multiple components and targets (signaling pathways) and complex mixtures. Thus, OMICs for tonics in anti-GI cancer research should focus on the active compounds, mechanisms, and compatibility of tonics to determine the relationship between the active compounds of tonics and their effects and underlying mechanisms, e.g., using comprehensive two-dimensional liquid chromatography (2DLC), Qiao et al. found 311 compounds from the extract of *Glycyrrhiza uralensis* Fisch. within 40 min, of which the method was superior to high-performance liquid chromatography (HPLC). Then, cheminformatics and metabolomics are matched, where metabolomics facilitates the exploration of the active compounds and analysis of the responding signaling pathways via metabolites, while transcriptomics easily uncovers the differentially expressed genes via RNA sequencing (Gong et al., 2012). Another strategy for exploring the compound-herb-disease relationship is polypharmacokinetics (Poly-PK), a novel technology for OMICs comparison. For example, Xie et al. identified 84, 292 and 532 compounds in extracts of Huang Qin decoction (including *Scutellaria baicalensis* Georgi and *Glycyrrhiza uralensis* Fisch.) and serum metabolites before and after oral administration, respectively. Among these compounds, 485 were changed after oral administration, of which 56 were from the extract of Huang Qin decoction, 292 were metabolites in the PK process, and 166 were metabolites from endogenous components. This methodology may profile a complex network between tonics, drug metabolites, and body metabolism function and provide insights into the holistic effect of a complex of tonics formulas (Xie et al., 2018).

Second, there are often inconsistencies between different results of OMICs, at least partially caused by the small size of the sample and systematic deviation. It is necessary to integrate basic experimental methods such as real-time PCR and WB, to confirm OMICs data and obtain more accurate results. Additionally, only genomics, transcriptomics, epigenomics, metabolomics, and proteomics among OMICs were used in this study, while glycomics and lipomics were not applied. Moreover, with the development of modern technologies, novel methods can be introduced in the research of tonics on GI cancer. For example, hepatocellular carcinoma (HCC) is characterized by high heterogeneity and metastatic potential and leads to poor prognosis. Thus, single-cell transcriptomic and proteomic data may identify mutations in small populations of cells and distinguish metastatic potential cells from HCC. A number of studies show that Chinese medicines can be used for HCC metastasis (Guo et al., 2022), and most of the mechanisms have been unknown, single-cell multi-OMICs may be a useful tool to unveil the metastatic mechanisms (Peng et al., 2018; Sun et al., 2021c; Wang et al., 2022) of tonics including *Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao, *Panax quinquefolium* L., *Atractylodes macrocephala* Koidz., *Glycyrrhiza uralensis* Fisch., and *Polygonum multiflorum* Thunb (Xu et al., 2018, Yang et al., 2022). These potential findings may offer more individual and precise strategies for patients with GI cancer (Lu et al., 2021).

Third, decreased quality of life may worsen for patients suffering from GI cancers, so it is essential to choose simple, non-invasive, or minimally invasive ways for subjects to reduce injuries. The methods include metabolomic or genomic analysis of a small sample of blood, metabolomic analysis of urine, feces, and saliva, or transcriptomics combined with X-ray, computed tomography (CT), magnetic resonance imaging (MRI) scanning, or small animal in vivo imaging technology. OMICs in combination with network pharmacology and bioinformatics are another effective way to obtain ideal results (Liu et al., 2021b).

Of note, GI cancers include two families based on disease sites, upper digestive tract cancers (including esophageal, stomach, pancreatic, liver, gallbladder, and lymphoma involving the mucosa-associated lymphoid tissue, gastrointestinal stromal, and biliary tree) and lower cancers (including colorectal, anal, and gastrointestinal carcinoid); however, to the best of our knowledge, only gastric cancer, liver cancer, and colorectal cancer have been reported using tonics via OMICs. The literature of tonics on the other kinds of GI cancers may have not been reported using OMICs, or, unfortunately, it may be filtered via inclusive and/or exclusive criteria because of low quality of the studies.

Another limitation of this review is that the primary therapies in most studies were not introduced and discussed although most CMs, including tonics, are add-on therapies. In this review, Ginseng Radix et Rhizoma treated colon cancer patients to reduce gastrointestinal symptoms after laparoscopic colectomy (Hanada et al., 2021). The Quixie capsules enhanced body resistance to colorectal cancer after chemotherapy, radiotherapy, targeted therapy, and immunotherapy (Sun et al., 2021a). Polysaccharides and ginsenosides in American Ginseng had effects on CTX-induced intestinal immune disorders and gut barrier dysfunctions (Zhou et al., 2021a) (Table 2). However, for most in vitro and in vivo studies in this review, in which tonics were used for exploring mechanisms, few primary therapies are
### Table 3: Applications of OMICs on tonics as adjuvants in liver cancer.

| Compound, herb, and formula | Tonics (in formula) | Study form | OMICs and role | Dose or concentration | Mechanism | Targeted hallmark | Reference |
|----------------------------|---------------------|------------|----------------|-----------------------|-----------|--------------------|-----------|
| Xiao Jie recipe            | Hedyotis diffusa, Scutellaria barbata, Panax ginseng, *Atractylodes macrocephala* | In vivo    | Proteomics for screening the signaling pathway | 1.83 and 3.86 g/ml | Regulating glutathione metabolism, PPAR, toll-like receptors, HIF-1, NF-kB, mTOR, and p38 signaling pathway | Surviving proliferative signaling pathways | Liu et al. (2016b) |
|                           | Hedyotis diffusa, Scutellaria barbata, Panax ginseng, *Atractylodes macrocephala* | In vitro   | Transcriptomics with CCK-8, ELISA for screening the signaling pathways | 10, 50, and 100 μg/ml | Regulating oxidative stress and detoxification including cytokines, HMOX1, HIF-1, NF-κB, and PPAR signaling pathways | Genome instability | Wang et al. (2016a) |
|                           | Bismuth (whole herbs of *Semen Lycii*, *Semen Gardeniae*), *Astragalus radix* | In vivo    | Proteomics with network pharmacology and HEM and histopathological analysis for screening the mechanisms | 3055 μg/ml | Regulating body temperature via inhibiting proliferation of PPAR, toll-like receptors, HIF-1, NF-κB, and PPAR signaling pathways | Enhancing body resistance to carcinogenesis | Wei et al. (2022) |
|                           | Ophiopogon japonicus (L. f) Ker-Gawl., *Gardenia jasminoides* Fructus | In vivo    | Proteomics and transcriptomics for screening the signaling pathways | 0.47 μg/ml | Regulating the expression of HMOX1, HIF-1, NF-κB, and PPAR signaling pathways | Gene expression | Wang et al. (2016a) |
|                           | Ophiopogon japonicus (L. f) Ker-Gawl., *Gardenia jasminoides* Fructus | In vivo    | Proteomics and transcriptomics for screening the signaling pathways | 0.94 μg/ml | Regulating the expression of HMOX1, HIF-1, NF-κB, and PPAR signaling pathways | Gene expression | Wang et al. (2016a) |
|                           | Ophiopogon japonicus (L. f) Ker-Gawl., *Gardenia jasminoides* Fructus | In vivo    | Proteomics and transcriptomics for screening the signaling pathways | 1.93 μg/ml | Regulating the expression of HMOX1, HIF-1, NF-κB, and PPAR signaling pathways | Gene expression | Wang et al. (2016a) |
|                           | Ophiopogon japonicus (L. f) Ker-Gawl., *Gardenia jasminoides* Fructus | In vivo    | Proteomics and transcriptomics for screening the signaling pathways | 3.86 μg/ml | Regulating the expression of HMOX1, HIF-1, NF-κB, and PPAR signaling pathways | Gene expression | Wang et al. (2016a) |

*Tonic.
↓ induction, upregulation, or activation.
↓ reduction, downregulation, or inactivation.
discussed. This indicates that high quality studies and more evidence are necessary for tonics as adjuvants. Furthermore, for a high quality of pharmacological study, detailed information (positive and negative controls, minimal active concentration, the model used, concentration or dose, duration, extract process, in vitro/in vivo/clinical study, etc.) are essential. In this study, 12 out of 34 studies (Tables 1, Table 2, and Table 3) were in vitro, although they were screened via inclusion and exclusion criteria. This may be the result from that the mechanism studies did not involve in in vivo and clinical data. However, high-quality studies should be guaranteed.

5 Conclusion

With the data from OMICS, tonics were found to be adjuvants for gastric, liver, and colorectal cancers with mechanisms including for targeting cancer hallmarks (sustaining proliferative signaling pathways, resistance to cell death, activation of invasion and metastasis, inducing angiogenesis, deregulating cellular energetics, inflammation-mediated carcinogenesis, genomic instability, and mutation), enhancing body resistance to carcinogenesis, and enhancing therapeutic effects and/or decreasing side effects via drug interactions. However, more investigations and evidence are necessary for tonics being used as adjuvants.

Author contributions

XW, YF, and ML designed the study; ZZ, JJ, and HL collected and double-checked the data and wrote the draft; and RS, DW, K-WZ, HN, X-GW, ML, WL, YF, and XW revised the manuscript. All authors reviewed and approved the submission of this manuscript.


Funding

This study was financially supported by the National Natural Science Foundation of China (81874356 and 82274155), the Open Project of Hubei Key Laboratory of Wudang Local Chinese Medicine Research from Hubei University of Medicine (WDCM2018002; WDCM201917; and WDCM201918), the Chinese Medicine Project of Health Commission of Hubei Province (ZY2021Z010 and WJ2021M055), and the Advantages Discipline Group (Medicine) Project in Higher Education of Hubei Province (2022KQY3). The funders did not play any role in the design of this study or in the collection, analysis, and interpretation of data and writing of the manuscript, which are completely the responsibilities of the authors.

Acknowledgments

The authors thank Prof. Haifeng Cao (Shanghai University of Traditional Chinese Medicine) and Ming Liu, Kaiqi Liu, and Yingying Guo (Renmin Hospital, Hubei University of Medicine) for their technical support. They also thank Bigui Wang, Dan Wang, Guobing Zhang, Chuhao Zhang, Xuanfeng Wang, Xianguo Wang, and Xuanhua Wang for their moral encouragement and support under the hard condition of COVID-19.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Astragalus membranaceus extract. in vivo (2016). An association with gut microbiome distribution—an RCT study. Oncotarget 7, 60270–60280. doi:10.18632/oncotarget.11201

Wang, C. Z., Yu, C., Wen, X. D., Chen, L., Zhang, C. F., Calway, T., et al. (2016a). American ginseng attenuates colitis-associated colon carcinogenesis in mice. Impact on gut microbiota and metabolomics. Cancer Prev. Res. 9, 803–811. doi:10.1158/1940-6207.CAPR-15-0372

Wang, D., Hu, B., and Xuan, L. (2012b). Effect of fuzheng kawei decoction on gastrointestinal function, proteomics and hedgehog signaling pathway in patients with gastric precancerous lesions after ESD. Liao Ning Zhong Yi Yao Da Xue Bao 23, 133–139. doi:10.13194/jissn.1673-842x.2012.10.030

Wang, D., Li, J., and Lv, S. (2020a). Study on plasma metabolomics of liver cancer patients with syndrome of dampness excessiveness due to spleen deficiency based on UPLC-HDMR. Zhong Guo Shi Yan Fang. Ji Xue Za Zhi 24, 77–85. doi:10.32534/j бумаг 20181901

Wang, X., Li, H., Li, G., and Yang, F. (2019). Exploration on pharmacological mechanism of Chinese medicines targeting cancer hallmarks. Shi Ji Ye Xue Ji Shang Zhong Yi Yan Xian Dai Hua 21, 25–32. doi:10.11842/wst.2019.03.005

Wang, X., and Lu, J. (2019). Overview on good pharmacological practice on Chinese medicine research. Shi Ji Ye Xue Ji Shang Zhong Yi Yan Xian Dai Hua 21, 1846–1854. doi:10.11842/wst.2019.02.004

Wen, X., Sun, Y., Li, Z., Xu, L., and Xia, M. (2022). Network pharmacology and proteomics analysis of Jiawei Xiaoyao San in the treatment of liver cancer complicated with depression in rats. Zhong Guo Shi Yan Fang. Ji Xue Za Zhi 26, 512–514. doi:10.13567/j бумаг 2022.0905

Xie, G., Wang, C. Z., Yu, C., Qiu, Y., Wen, X. D., Zhang, C. F., et al. (2015). Metabolic profiling reveals cancer chemopreventive effects of American ginseng on colon carcinogenesis in a p53 quadruple-knockout mouse model. J. Proteome Res. 14, 3336–3347. doi:10.1021/acs.jproteome.5b00388

Xie, G., Wang, S., Zhang, H., Zhao, A., Liu, J., Ma, Y., et al. (2018). Polypharmacokinetic study of a multicomponent herbal medicine in healthy Chinese volunteers. Clin. Pharmacol. Ther. 103, 692–702. doi:10.1002/cpt.784

Xiong, Y., Li, Q., Chen, X., Zhu, T., Lu, Q., and Jiang, G. (2022). Identification of the active compound of Liu Wei Di Huang wan for treatment of gestational diabetes mellitus via network pharmacology and molecular docking. J. Diabetes Res. 2022, 4808303. doi:10.1155/2022/4808303

Xu, H., Feng, Y., and Zhang, G. (2018). Anti-cancer Chinese medicines: Modern research and clinical application. 1 edn. Shanghai: Shanghai Science and Technology Press.

Xu, H., Xiao, S., Wen, W., Tan, J., Xu, C., Sun, D., et al. (2020). Proteomic analysis for the effect of lipid metabolism in hepatocellular carcinoma rats intervened by Xiaoai Jiedu Decoction. Zhong Hua Zhong Yi Yao Za Zhi 35, 3155–3159.

Xu, T., Xiong, Y., Zhang, T., Yan, S., Wu, J., Liu, S., et al. (2021). Analysis of serum metabolome in mice with gastric cancer treated with PYZZX prescription based on liquid chromatography-mass spectrometry. Nan Jing Zhong Yi Yao Da Xue Xue Bao 37, 237–243. doi:10.11484/j бумаг 1672-0482.2021.0237

Yang, N., Cao, F., Huo, J., Li, H., Li, C., Wang, Q., et al. (2018). SREBP1-based active compound screening of anthraquinones in radix polygoni multiflori preparata for lowering lipid metabolism in hepatocellular carcinoma cells. Hu Bei Yi Xue Xue Yuan Xue Bao 37, 156–160. doi:10.13819/j бумаг 1006-9674.2018.02.014

Yang, N., Li, C., Li, H., Liu, M., Cai, X., Cao, F., et al. (2019). Emodin induced SREBP1-dependent and SREBP1-independent apoptosis in hepatocellular carcinoma cells. Front. Pharmacol. 10, 709. doi:10.3389/fphar.2019.00709
Yang, P. H., Jin, L. J., Liao, J., Shao, X., Cheng, J. Y., Li, L., et al. (2022). Modern research on Chinese medicine based on single-cell omics: Technologies and strategies. Zhongguo Zhong Yao Za Zhi 47, 3977–3985. doi:10.19540/j.cnki.cjcmm.20220601.702

Zhang, X., Zhao, S., Song, X., Jia, J., Zhang, Z., Zhou, H., et al. (2018). Inhibition effect of glycyrrhiza polysaccharide (GCP) on tumor growth through regulation of the gut microbiota composition. J. Pharmacol. Sci. 137, 324–332. doi:10.1016/j.jphs.2018.03.006

Zhao, Y., Zhang, Q., Liu, Y., Wang, G., Ge, S., and Liu, H. (2017). Study on regulation effect of dendrobium extracts on endogenous metabolites S1P and related gene expression in the prevention of gastric cancer. Zhong Hua Zhong Yi Yao Za Zhi 32, 1910–1914.

Zhou, R., He, D., Xie, J., Zhou, Q., Zeng, H., Li, H., et al. (2021a). The synergistic effects of polysaccharides and ginsenosides from American ginseng (Panax quinquefolius L.) ameliorating cyclophosphamide-induced intestinal immune disorders and gut barrier dysfunctions based on microbiome-metabolomics analysis. Front. Immunol. 12, 665901. doi:10.3389/fimmu.2021.665901

Zhou, R., Luo, Z., Zhang, B., Wang, W., Sun, R., Yu, G., et al. (2021b). Mechanism of albulin against hepatocellular carcinoma based on transcriptomics. Zhong Nan Yao Xue Yi Chuan 19, 1074–1079.

Zorko, B. A., Pérez, L. B., and De Blanco, E. J. (2010). Effects of ILTG on DAPK1 promoter methylation in colon and leukemia cancer cell lines. Anticancer Res. 30, 3945–3950.