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The exciting and magical journey of components from compound formulae to where they fight

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Abstract

With its long-term empirical clinical practice and increasing number of health benefits reported, Chinese Materia Medica (CMM) is gaining increasing global acceptance. Importantly, the identification of chemical constituents *in vitro* and exposed forms *in vivo* is a prerequisite for understanding how CMM formulae prevent and treat diseases. This review systematically summarizes the exciting and magical journey of CMM components from compound formulae to where they fight, the possible structural transformation of CMM components *in vitro* and *in vivo*, and their pharmacological contribution. When a decoction is prepared, significant chemical reactions are observed, including degradation and production of polymers and self-assembling supramolecules, leading to the construction of a component library with diverse decoction structures. After ingestion, compounds pass through the intestinal and blood-brain barriers and undergo a more wonderful journey involving the gut microbiota, microbial enzymes, and endogenous drug-metabolizing enzymes (mainly liver enzymes). At this stage, they are modified and assembled into novel and complex compounds, such as newly generated metabolites, conjugates, and self-assembling superamolecules. This review might provide a strategic orientation to explore the active compounds of CMM formulae *in vivo*.

Keywords: Chinese Material Medica, Formulae, Gut microbiota, Metabolites, Prototype components, Self-assembling supramolecule

Introduction

Traditional Chinese medicine (TCM), a medical system that differs from modern Western Medicine in theory, methodology, and substances[1], has been proven to be effective in clinical practice for more than 2000 years. TCM practitioners differentiate a patient's TCM syndrome through TCM pathogenesis after a comprehensive analysis of information obtained from diagnostic methods, including visual inspection, listening and smelling examination, inquiry, and palpation. Subsequently, a suitable Chinese Materia Medica (CMM) formulae or other traditional treatment procedures, such as acupuncture, cupping, tuina (massage therapy), qigong (movement and breathing exercises), and moxibustion, are chosen to help the patient recover from an abnormal body state. This clinical diagnosis and treatment process is known as TCM syndrome differentiation and treatment[1–4]. As one of the important therapeutic methods of TCM, CMM formulae, usually composed of the monarch, minister, assistant, and servant ingredients, is prescribed by practitioners following the compatibility law of "seven emotions", namely single action, mutual reinforcement, mutual assistance, mutual restraint, mutual suppression, mutual inhibition, and antagonism[5–6]. Through reasonable compatibility, CMM formulae show more potent therapeutic effects and weaker adverse reactions than single herb. Long-term empirical information from clinical practice shows that CMM formulae have better therapeutic effects on cardiovascular, metabolic, gynecological, and pediatric diseases. For example, compound Danshen formula (CDF) is effective against angina pectoris in patients with coronary heart disease. CDF has been formulated as dripping pills, tablets, etc, and has been comprehensively studied in various clinical trials. Notably, CMM formulae also show curative effects in infectious diseases[7]. This therapeutic connection between CMM formulae and infectious diseases has become particularly consequential during the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with three traditional Chinese patent medicines (Jinhua Qinggan granule, Lianhua Qingwen capsule, and Xuebijing injection) and three CMM formulae (Xuanfei Baidu decoction, Qingfei Paidu decoction, and Huashi Baidu formula) improving symptoms, shortening the course, and preventing progression of the disease in China[8]. In particular, Lianhua Qingwen capsules demonstrated anti-viral activity by significantly repressing SARS-CoV-2 in African green monkey kidney epithelial (Vero E6) cells[9]. In addition to the individual

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therapeutic effects of CMM formulae, there is growing interest in the combination of CMM formulae and Western Medicine[10] because a combination exhibits profound efficacy against diseases and reduces the side effects mediated by individual treatment. Currently, this integrative treatment approach is advocated as a strategy to diminish the serious adverse effects associated with Western chemotherapeutic drugs during cancer management in clinics[11]. In contrast, an increasing number of bioactive compounds with excellent pharmacological activity and definite action mechanisms have been isolated from CMM, such as artemisinin[12] and berberine[13].

The journey of CMM components from compound formulae to where the components fight is a long, exciting, and mysterious process, accompanied by interesting chemical and enzyme-catalyzed reactions. First, following the processing and compatibility of Chinese herbs, the components in the compound formulae undergo decoction *in vitro*. After oral administration, the components of the compound formula decoction enter the gastrointestinal tract, where they are partly or wholly transformed by the gut microbiota. The migrating compounds in the intestine exhibit curative effects through three main processes: retention in the intestine, absorption into the blood, and absorption into the lymph. The compounds that are not absorbed are retained in the intestine and might play therapeutic roles by regulating the immune response of intestinal mucosa, remodeling the gut microbiota, and inducing the biological effects of active products on gut microbiota[14]. Commonly, compounds absorbed into the blood vessel are metabolized by liver enzymes and migrate within the systemic blood circulation, exerting pharmacological effects. Meanwhile, a small portion of the migrating compounds in the intestine would be absorbed into the lymph vessels, performing a conducive effect. Furthermore, compounds that can pass through the blood-brain barrier (BBB) are transported into the cerebrospinal fluid and serve as neuroprotective agents.

CMM formulae with multi-herbs and multi-compounds have multiple targets and pathways to prevent and cure diseases. From the China National Knowledge Infrastructure and PubMed, we collected relevant literature on the structural transformation of CMM components and provided an overview of exposed molecular forms originating from CMM formulae *in vitro* and *in vivo* (Figure 1), with the aim to identify active components and elucidate the underlying mechanisms for preventing and treating diseases. The cited references were published between the years 2000 and 2020.

Transformation of compounds from CMM formulae during decocting

Under the guidance of TCM theory, CMM formulae mostly reach an ideal therapeutic effect when the quality of CMM and CMM materials compatibility is strictly controlled, and performed extensively. Miraculously, compounds from CMM formulae undergo metamorphosis during decocting, which usually gives rise to four classes of compounds: prototype compounds, degraded products, polymers with covalent interactions, and self-assembling superamolecules.

Common types in CMM formulae: prototype compound and degraded product

Prototype and degraded compounds from CMM formulae are an important source of active compounds. Prototype molecules are primary and secondary metabolites isolated from Chinese herbs, which are categorized as low molecular weight compounds (such

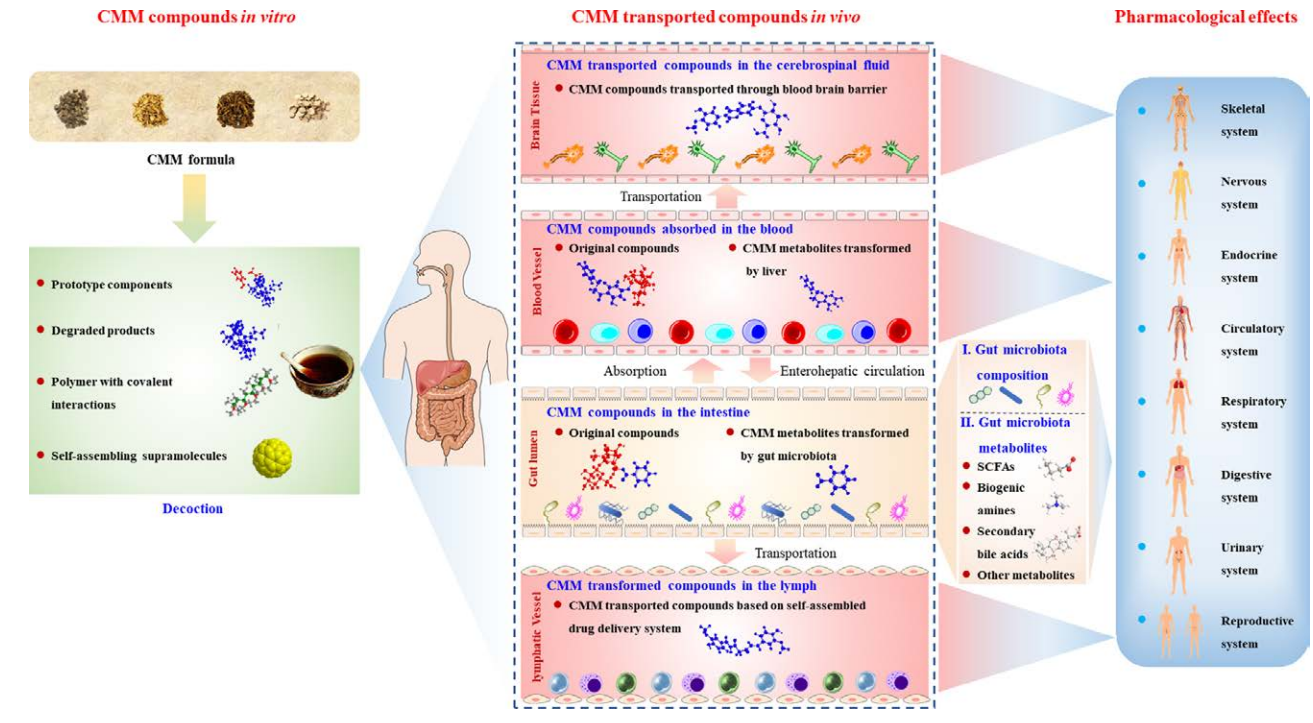

Figure 1. The possibly exposed molecular forms of CMM components from compound formulae to where they act. CMM: Chinese Materia Medica; SCFAs: short-chain fatty acids.

as flavonoids, saponins, and alkaloids) and high molecular weight compounds (such as polysaccharides and proanthocyanidins). These prototype molecules have shown beneficial effects in the amelioration of cardiovascular diseases, diabetes, and other acute[15] or chronic[16] diseases. For example, sodium tanshinone IIA sulfonate, a water-soluble derivative of tanshinone IIA, has been approved for the treatment of cardiovascular diseases in China[17].

The degraded products originate from susceptive compounds exposed to light, heating, and pH fluctuations during the decoction of the CMM formulae. This triggers diverse chemical reactions, such as hydrolysis, redox reactions, neutralization, and complex reactions, leading to toxicity reducing or efficiency enhancement. For example, after the co-decoction of aconite roots and licorice roots, the toxicity of aconite roots was drastically decreased, wherein highly toxic diester alkaloids were hydrolyzed into low-toxicity monoester alkaloids[18]. The coexistence of acidic and basic compounds can produce a soluble salt, which plays a critical role in increasing their dissolution[19]. In addition, the action of trace elements cannot be neglected despite their low content in the CMM formulae. Metal complexes, formed by metal ions and organic molecules with coordination groups (such as carboxyl, phenol hydroxyl, amino, and hydrosulfonyl groups), have received increasing attention with the advent of coordination chemistry in TCM theory[20–21]. Evidence indicates that baicalin, a flavonoid from Scutellariae Radix, has better anti-microbial, anti-tumor, and immunoregulation[22] effects through coordinated formation with copper or aluminum ions. Intriguingly, the profound coordination complex-induced pharmacological activity is partly attributed to the synergistic effect between the metal ions and prototype compound[23]. Their characteristics are generally described using a combination of multiple analytical methods. For example, with the assistance of infrared radiation spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, elemental analysis, and mass spectrometry (MS) techniques, Chen et al.[24] identified the crystal structures of metal complexes synthesized by oxoglaucine and transition metal salts using X-ray diffraction.

Polymer with covalent interaction

Polymers are macromolecules cross-linked by multiple simple chemical units (monomers). Derived from various intense conditions during the decoction of CMM formulae, polymers, such as the products of the Millard reaction and cross-linking color reaction, are one of the most important molecular forms in the CMM formulae.

The Maillard reaction, a complicated cascade of non-enzymatic browning between reducing sugars and amino compounds[25], is a common pathway for polymer production during the preparation of CMM formulae. For instance, the steaming and drying processes of the Chinese herbs Rehmanniae Radix[26] and Polygoni Multiflori Radix[27] led to polymer formation. The final product of the Maillard reaction, collectively known as melanoidin, is a mixture of multiple brown polymers generated by the condensation of cyclic subunits[28]. Emerging evidence has shown that melanoidins possess anti-tumor[29], anti-bacterial, and other enzyme-inhibitory bioactivities[30]. Nevertheless, the deleterious effects of Maillard reaction products on human health have also been studied; for instance, the negative effects of advanced glycation end products on Alzheimer disease have been reported[31].

The Zhizichi decoction, composed of Gardeniae Fructus and Sojae Semen Praeparatum, a classical CMM formula used to treat depression[32], is usually decocted in sequence, that is, Gardeniae Fructus followed by Sojae Semen Praeparatum. Furthermore, owing to the high content of iridoid glycosides, that is geniposide, in Gardeniae Fructus, and β-glucosidase and tyrosine in Sojae Semen Praeparatum, Cui et al.[33] proposed and validated the hypothesis that geniposide originated from Gardeniae Fructus was primarily converted into genipin by β-glucosidase, followed by a reaction with tyrosine to form a genipin-tyrosine complex (GTC), which might be responsible for the anti-depressant effects[34]. GTC, also known as gardenia blue pigment, is the product of a cross-linking reaction that occurs spontaneously between iridoid aglycones and compounds containing primary amine groups[35]. It is well established that genipin forms a cross-linked structure with a primary amine group through active intermediates by nucleophilic ring-opening reactions in the dihydropyran ring[36–38].

With the existence of proteins and amino acids in the CMM formulae, critical attention should be given to polymers analogous to melanoidins and gardenia blue pigment. Moreover, reports on the exact structure of such polymers in the CMM formulae remain missing because of many reaction products formed and challenges in their purification and identification. In the case of melanoidins, on the one hand, Maillard products contain not only complex melanoidins but also several low molecular weight intermediates[39]. On the other hand, Maillard products lack stability and are easily transformed[39–40]. Finally, there may be various interfering factors[41] (such as temperature, pH, and coexisting compounds) that disturb the detection. Characterization and formation mechanisms of melanoidin have been explored, which were experimentally introduced by the reaction between mono-reducing sugars and mono-amino compounds[42], and several known intermediates[43], and isolation of products from enzymatic hydrolysis of melanoidin[44]. For example, Rodríguez et al.[44] isolated melanoidins from dulce de leche (DL) through dialysis, enzymatic hydrolysis, and fractionation, followed by characterization using ultraviolet-visible spectra, elemental analysis, NMR, and high-performance liquid chromatography (HPLC), suggesting that DL melanoidins are mainly protein complexes formed by cross-linking reactions between proteins, which probably contain aromatic groups and sulfur. Its formation involves the condensation of lactose and lysine residues from the protein. Such efforts have not been entirely successful, and more efforts for polymer identification in CMM formulae should be made.

Self-assembling supramolecules

Self-assembling supramolecules are complexes formed spontaneously by individual molecules *via* non-covalent bonds. In the past decade, there has been an increasing interest in self-assembling supramolecules, which have also facilitated the elucidation of the pharmacological effects of CMM formulae.

Zhuang et al.[45] detected aggregates in 84 solution mixtures of 60 medicinal herbs and 24 CMM formulae using dynamic light scattering. They observed that the activities of two CMM formulae, Xuefu Zhuyu decoction and Jingguan decoction, were aggregates-related, against plasminogen activator inhibitor one, angiotensin-converting enzyme, and inducible nitric oxide synthase. The mechanism behind this phenomenon is that large colloid-like aggregates formed through the self-association of candidate organic molecules reversibly sequester the enzymes, thereby inhibiting the action[45–48]. The colloid-like aggregates showed promiscuous inhibition and may present activity opposite to the inherent activity of the compound. For example, Zhou et al.[49] evaluated the differences in bioactivities among Maxing Shigan decoction (MXSGT), ephedrine-loaded colloid nanoparticles (NPs) fractionated from MXSGT, and ephedrine. They found that MXSGT and ephedrine-loaded NPs showed higher cell proliferation in human hepatoblastoma (HepG2) cells, whereas ephedrine showed higher cytotoxicity in HepG2 cells. The differences between the activities of colloid-like aggregates and pure compounds might depend on the structure of the compound from the CMM formulae, which remains to be further investigated. In addition, owing to the occurrence of colloid-like forms, aggregates can be protected from the gastrointestinal environment, and nano-aggregates are readily absorbed through the intestine, increasing the bioavailability of compounds with poor aqueous solubility and chemical instability. From this perspective, multiple reports have documented that many proteins from Chinese herbs can be organized as nano-carriers based on their self-assembly aggregation, such as licorice protein[50], and Radix Pseudostellariae protein[51].

With the requirements of high-loading content, low toxicity, and biodegradability for drug delivery systems, supramolecular self-assembled compounds formed by non-covalent bonds (such as hydrogen bands and electrostatic and hydrophobic interactions) have gained popularity[52–53], owing to excellent stability, better pharmacological activity, and no need for extra delivery carriers. For example, Li et al.[52] achieved a self-assembled nanomedicine formed with berberine and baicalin (isoquinoline alkaloid and flavonoid glycoside from Coptidis Rhizoma-Scutellariae Radix). The primary anti-bacterial mechanism of the NPs, mainly assembled by their electrostatic and hydrophobic interactions, was that the peripheral hydrophilic glucuronic acid of berberine–baicalin NPs showed stronger affinity for bacteria, inducing aggregation and adhesion behavior of NPs on Staphylococcus aureus.

Taken together, self-assembling supramolecules might be an approach for understanding the mechanisms underlying pharmacological effects and will also pave the way for seeking pharmaceutical molecules from CMM formulae.

Transformation of CMM formulae decoction-derived parent compounds and production of endogenous metabolites by gut microbiota in the intestine

After the oral administration of the CMM formulae, the decoction-derived components were exposed to the gut microbiota. Gut microbiota not only produces endogenous metabolites, such as short-chain fatty acids (SCFAs), trimethylamine (TMA), and secondary bile acids, but also participates in various processes of host metabolism and immune regulation, consequently influencing the effectiveness and safety of CMM formula decoctions[14]. As shown in Figure 2, CMM formula decoction-derived parent compounds, their secondary gut microbiota-dependent compounds, and CMM metabolites transformed by enterohepatic circulation are regarded as transitional compounds in the intestines.

CMM formulae decoction-derived parent compounds and their secondary compounds in the intestine

CMM formulae decoction-derived parent compounds

After the oral administration of the CMM formula decoction, which emerged as prototype compounds, degraded products, polymers, and self-assembling superamolecules, parent components traveled within the gastrointestinal tract. The oral bioavailability of CMM formulae is a conundrum[54] because most CMM decoction-derived parent compounds are unabsorbed into circulation. However, parent CMM components in the intestine, coordinating with their gut microbiota-dependent metabolites, could modulate therapeutic effects by improving intestinal barrier function or remodeling the gut microbiota. Gegen Qinlian decoction (GQLD), a CMM formula composed of Puerariae lobatae Radix, Scutellariae Radix, Coptidis Rhizoma, and Glycyrrhizae Radix et Rhizoma, was orally administered to rats, and 95 decoction-derived parent compounds and 24 metabolites were detected in the fecal samples using ultra-performance liquid chromatography (UPLC) coupled with Fourier transform ion cyclotron resonance MS[55]. Moreover, with the improvement of symptoms of type 2 diabetes (T2D) after 12-week treatment with GQLD, including the reduction of fasting blood glucose and glycated hemoglobin, the amounts of beneficial bacteria from T2D patients were enriched in a randomized, double-blinded, and placebo-controlled clinical trial[56].

Gut microbiota-derived transformation of parent compounds originated from CMM formulae decoction

Due to pH fluctuations within the stomach (acidity), small intestine (alkalinity), and large intestine (acidity), and exposure to drug-metabolizing enzymes mainly from gut microbiota, CMM formula decoction-derived parent compounds are bio-transformed into diverse structural orientations[57]. Gut microbiota enzymes are the most important catalyzers involved in biochemical

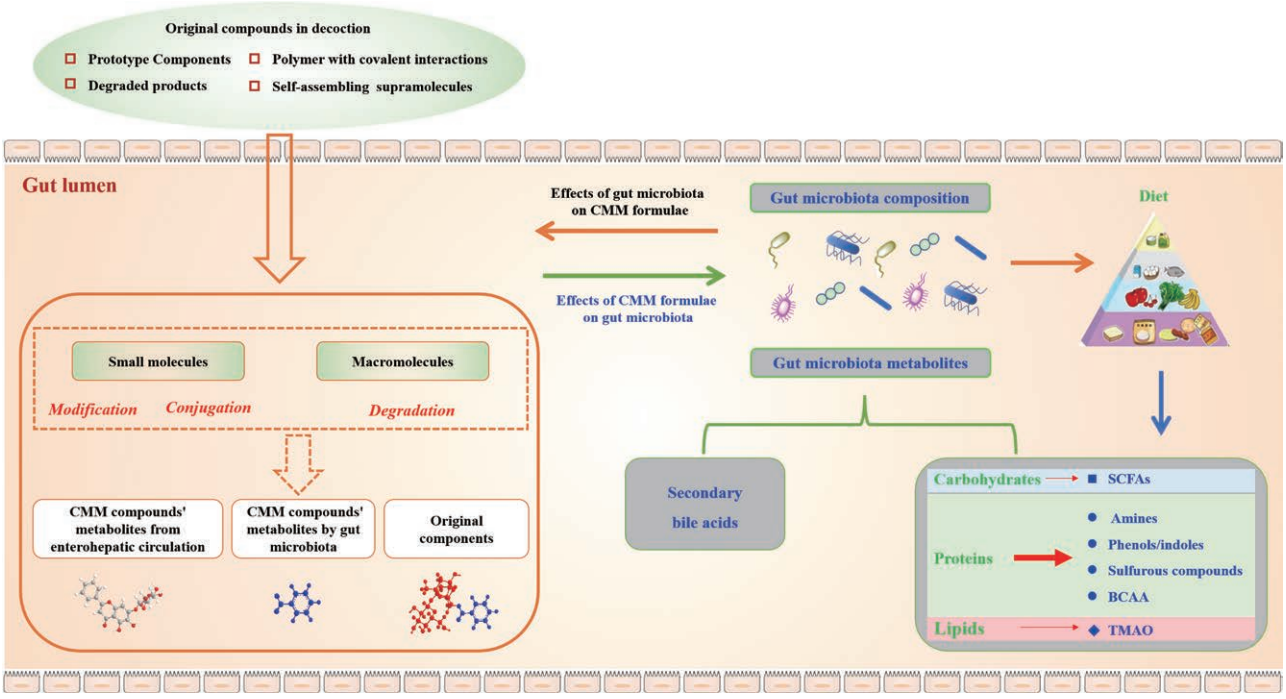

Figure 2. The interaction between CMM formulae and gut microbiota in intestines. BCAA: branched-chain amino acids; CMM: Chinese Materia Medica; TMAO: trimethylamine N-oxide.

and metabolic processes outside the intrinsic metabolic machinery of the host[58]. They usually trigger hydrolytic, deglycosylated, and reductive reactions primarily[59]. As listed in Table 1, we summarized the metabolic pathways mediated by gut microbiota on different CMM compounds and highlighted their pharmaceutical contributions after modification.

Alkaloids, triterpene glycosides, flavonoids, anthraquinones, steroidal, lignan, and tannins are highly abundant phytochemical classes in most CMM extracts. However, the bioavailability of these phytochemical classes is extremely low because of structural limitations, such as high hydrogen-bonding capacity, high molecular flexibility, and poor lipophilicity[54]. Gut microbiota structurally modifies medicinal-based natural products (i.e., parent compounds undergoing hydrolysis, deglycosylation, deacetylation, etc), consequently improving their bioavailability[74], reducing toxicity, and enhancing efficacy[61]. For example, albiflorin, an anti-depressant compound isolated from

Table 1

The metabolic pathways mediated by gut microbiota on representative CMM compounds

Classification	Representative compounds	Reactions of metabolism	Pharmaceutical contribution	References
Alkaloids	Berberine	Reduction	Improvement of absorption	[60]
	Diester diterpenoid alkaloids	Hydroxylation, deoxylation, demethylation, demethylation, deoxylation, and ester hydrolysis	Reduction of toxicity	[61]
Glycosides	6‴-*p*-coumaroylspinosin (flavonoid glycosides)	Hydrolysis	Enhancement of lipid solubility	[62]
	Anemoside B4 (triterpenoids)	Oxygenation and deglycosylation	Enhancement of anti-tumor activity against SMMC-7721, Hela, and MCF-7 cell	[63]
	Albiflorin (terpenoids)	Hydrolysis	Improvement of absorption across the blood-brain barrier	[64]
	Sennosides (anthraquinones)	Hydrolysis	Promotion of intestinal peristalsis	[65]
Tannis	Ellagitannins	Hydrolysis, fissuration, and dehydroxylation	Improvement of absorption	[66–67]
Steroids	Cinobufagin and cinobufotalin	Deacetylation	Inactivation	[68]
Polysaccharides	Lycium barbarum polysaccharides	Hydrolysis	Promotion of SCFAs production	[69]
	Chondroitin sulfate	Hydrolysis	Improvement of intestinal absorption	[70]
Conjugates	Shikonin	Inter-polymerization	–	[71]
	(-)-Epigallocatechin-3-gallate	Conjugation	Elimination of toxic reactive metabolic wastes	[72]
	Prenylated flavonol glycosides (Xian-Ling-Gu-Bao capsule)	Conjugation	Improvement of the gastrointestinal environment	[73]

CMM: Chinese Materia Medica.

Paeoniae Radix Alba, is hydrolyzed into benzoic acid by intestinal carboxylesterase, which crosses the BBB and exerts anti-depressant activity[64]. To determine the metabolites and metabolic pathways of compounds from CMM formulae in the intestine, *in vitro* co-incubation for target compounds and intestinal flora is an alternative approach to the routine methods[75]. Through the anaerobic incubation of Mogroside V and human intestinal bacteria, Xu et al.[76] identified 14 metabolites using HPLC-ion trap (IT)/time-of-flight (TOF)-MS in the coculture, whose transformation involved isomerization and deglycosylation.

As macromolecular compounds, carbohydrates and proteins are prevalent in CMM formulae. Polysaccharides and oligosaccharides, for example, are abundant in most CMM, but humans are unable to utilize them because of the lack of digestible enzymes in the human genome. Intriguingly, they can be fermented[77] into SCFAs by enzymes of the gut microbiota. SCFAs function as crucial physiological signaling molecules, and during pathophysiological conditions such as obesity, inflammation, and hyperlipidemia, they act to inhibit inflammation and improve dysregulated glucose and lipid metabolism[78]. Growing evidence from studies has revealed profound pharmacological effects (including immunomodulatory, anti-tumor, and hypoglycemic effects) mediated by plant-based carbohydrates. The emerging therapeutic effects of plant-based carbohydrates can be partly attributed to SCFAs[78].

Stable polymers are synthesized within the intestine through conjugation reactions owing to the high reactivity of metabolic intermediates from CMM compounds. For example, gut microbiota facilitates the emergence of reactive carbonyl species (RCS) conjugates of (-)-epigallocatechin-3-gallate (EGCG) and aminated EGCG by trapping RCS, which prevents the development of many chronic diseases[72].

CMM metabolites transformed by enterohepatic circulation

As the important part of enterohepatic circulation, the gut microbiota coordinates with the liver to participate in the relay-reaction of CMM metabolism, which prolongs the residence time of CMM compounds *in vivo* and is of particular significance in clinical application. For example, after absorption, baicalin is transformed into glucuronidated metabolites, which are subsequently excreted into the gut through bile, where it is readily hydrolyzed by β-glucuronidase from the gut microbiota into the free aglycone form[79], which begins the new journey from the gut to the blood.

Endogenous metabolites derived from gut microbiota regulated by CMM formulae

The gut microbiota and CMM formulae are involved in mutually beneficial interactions. Gut microbiota ferment compounds from CMM formulae into structurally modified metabolites. In turn, the gut microbiota is regulated by CMM formulae, resulting in its rebalance and consequently improving gut microbiota metabolic activity and endogenous metabolite production[80]. Endogenous metabolites are synthesized or structurally modified from dietary components and primary bile acids[81]. The most widely known and characterized gut microbiota-dependent metabolites include SCFAs, TMA, and secondary bile acids (Table 2).

With a key role in governing the homeostasis of the human body, the gut microbiota positively synthesizes beneficial metabolites when exposed to CMM formula decoction.

SCFAs, important functional microbiota-emanated metabolites, are primarily fermented from plant-based carbohydrates and dietary fibers[110]. SCFAs not only have various bioactivities but also facilitate host-gut microbiota axis communication by acting as carbon sources for the generation of endogenous host metabolites[83]. Derived from ruminant meat and dairy products, branched-chain fatty acids (BCFAs) with structures different from those of SCFAs have also gained attention recently because of their perceived health benefits, such as anti-inflammatory and anti-carcinogenic activities[111]. After oral administration for 8 weeks, feruloylated oligosaccharides and ferulic acid slightly restored BCFAs concentrations (including isobutyric acid and isovaleric acid) to a level that significantly inhibited diabetes in rats[112]. In addition, as an important endocrine organ, intestinal microbiota can generate neurotransmitters and neuromodulators (mainly by tryptophan metabolism), such as serotonin (5-HT), dopamine, kynurenic acid, and indole derivatives[113–114]. Through metabolomic studies, Tiansi liquid was found to ameliorate depressive symptoms by increasing plasma kynurenic acid and 5-HT levels through the gut microbiota-dependent tryptophan-kynurenine metabolic pathway[96].

Additionally, gut microbiota can negatively regulate detrimental metabolites after the oral administration of CMM. A prime example of deleterious metabolites of the gut microbiota is TMA. TMA is metabolized by the gut microbiota from western diets enriched in lecithin, L-carnitine, and choline, which are absorbed and oxidized into trimethylamine N-oxide (TMAO) by flavin-containing monooxygenase 3 in the liver. Recently, reports have defined TMA and TMAO as possible biomarkers of cardiovascular disorders[87]. After resveratrol treatment, serum TMA and TMAO levels were reduced in choline-challenged female C57BL/6J mice, and TMA production in cecal content collected from 1% choline-fed ApoE$^{-/-}$ mice was significantly decreased, suggesting resveratrol may suppress TMA generation[88]. Furthermore, undigested proteins and unabsorbed amino acids within the gastrointestinal tract can be primarily fermented into detrimental nitrogen-and sulfide-containing compounds by the gut microbiota[115]. As shown in Table 2, these gut microbiota-dependent nitrogen-and sulfide-containing metabolites (including branched-chain amino acids [BCAAs], indoles, sulfurous compounds, and *N,N,N*-trimethyl-5-aminovaleric acid) are associated with T2D, cardiovascular diseases, cancer, and nonalcoholic fatty liver diseases. The combination of Moutan Cortex and Paeoniae Radix Rubra (PRR) reduced the serum levels of BCAAs by modulating gut microbiota,

Table 2

Endogenous metabolites from gut microbiota regulated by CMM

Origin of endogenous metabolites	Food origin	Endogenous metabolites	Analytical techniques	Potentially biological functions or hazards	Regulation by CMM
Metabolites transformed by gut microbiota from diets	Carbohydrates	SCFAs	Gas chromatography-mass spectrometry (GC-MS)[82]	Enhancement of host health by suppressing inflammatory responses, maintaining intestinal barrier function, and modulating colonization resistance to enteric pathogens[83]	A Chinese herbal formula composed of 8 herbs, namely, Anemarrhenae Rhizoma, Momordica charantia, Coptidis Rhizoma, Salviae miltiorrhizae Radix et Rhizoma, Fermentum Rubrum, Aloe, Schisandrae Chinensis Fructus, and Zingiberis Rhizoma, enriched the SCFAs-producing bacteria, such as *Blautia* spp., in type 2 diabetic patients with hyperlipidemia[84]
	Phospholipids	TMAO	Liquid chromatography-tandem mass spectrometry (LC-MS/MS)[85] and facile fluorescence detection[86]	Biomarker for cardiovascular disorders[87]	Resveratrol attenuated serum TMA and TMAO levels in mice administered choline intragastrically[88]
	Proteins	BCAAs	LC-MS[89]	A possible biomarker for cancer, obesity, insulin resistance and type 2 diabetes[90–91]	Berberine decreased BCAAs-producing bacteria and serum BCAAs in high-fat diet-fed mice[92]
		Serotonin	GC-MS[93], LC-MS and imagingMS[94]	Neurotransmitters[95]	Tiansi Liquid increased plasma kynurenic acid and 5-HT levels in rats with hydrocortisone-induced depression[96]
		Phenols/ indoles	GC-MS[97], LC-MS[98] and nuclear magnetic resonance spectroscopy (NMR)[99]	A risk factors for damaging epithelial barrier function and inducing oxidative stress in endothelial cells, the incidence of tumors and chronic renal failure[100–101]	Compatibility of Euphorbiae Semen and Glycyrrhizae Radix et Rhizoma enhanced the metabolic ability of gut microbiota on aromatic amino acids, which might increase the levels of its metabolites, such as indole and *p*-cresol[102]
		Sulfurous compounds	Gas-profiling technology[103] and colorimetric method[104]	A beneficial substance of reducing dysbiosis and helping mucus layer reconstitution in colitis, and a health hazard at high concentration in inflammatory bowel disease[105]	Glycyrrhizae Radix et Rhizoma-Genkwa Flos combination induces fecal H_2S production in mice[104]
		TMAVA	LC-MS and NMR[106]	Exacerbation for fatty liver[106]	–
Metabolites excreted from bile and modified by gut microbiota	–	Secondary Bile acids	GC-MS[107]	Contribution to the pathogenesis of obesity colon cancer, gallstones, and inflammatory diseases of the digestive system[108–109]	Berberine inhibited the conversion of cholic acid to deoxycholic acid (secondary bile acids)[107]

BCAA: branched-chain amino acid; CMM: Chinese Materia Medica; SCFAs: short-chain fatty acids; TMAVA: N,N,N-trimethyl-5-aminovaleric acid.

providing new pharmacological understanding and strategies against obesity and T2D[116].

Finally, bile acids (primary bile acids), which favor the hypolipidemic effect by promoting the conjugation and excretion of lipids, are produced in the liver from cholesterol and metabolized into secondary bile acids (e.g., deoxycholic acid) by gut microbiota-mediated bile salt hydrolysis and bile acid 7α-dehydroxylation. In a multicenter, randomized, double-blind, placebo-controlled clinical trial, berberine exerted a hypoglycemic effect by inhibiting deoxycholic acid transformation in newly diagnosed T2D patients, thereby increasing primary bile acid (glycochenodeoxycholic acid) and decreasing secondary bile acid (deoxycholic acid) content[117].

CMM compounds absorbed in the blood

Despite the caveats highlighted above, massive data from studies show that some CMM formula decoction-derived parental compounds are absorbed into the circulation. Research on bioactive compounds detected within the blood can be traced back to the discovery of the antibiotic sulfonamide in the 1930s, the serum metabolite metabolized from Prontosil (first sulfonamide

antibiotic)[118]. Until the late 1980s, Japanese scholar Hiroko Iwama conducted relevant research and first proposed the concept of serum pharmacology and serum pharmacochemistry[119]. In the early 1990s, Chinese scholar Professor Xijun Wang introduced serum pharmacochemistry regarding CMM formulae[119]. Here, we divided CMM compounds that circulate within the blood into original compounds from the intestine, their metabolites, and other molecular forms for the convenience of understanding.

Original compounds absorbed from the intestine

The original compounds detected in the blood primarily contained the CMM formula decoction-derived compounds, as well as their gut microbiota metabolites. Liang et al.[120] detected these compounds in rat plasma using the HPLC-IT/TOF-MS^n technique after the oral administration of Chishao decoction. In this study, 15 PRR parent chemical compounds and 90 metabolites were identified. Moreover, 7R-paeonimetabolin I, 7S-paeonimetabolin I, and paeonimetabolin II are metabolites of paeoniflorin transformed by intestinal microflora[121–122].

CMM metabolites transformed by enzymes in the liver

In the process of screening active compounds from traditional Chinese herbs, some compounds only exhibited excellent activity *in vivo* but not *in vitro*, or the active compounds screened possessed low bioavailability due to the hepatic first-pass effect. The therapeutic effects of most CMM formulations are mediated by their hepatic metabolites. For example, demethyleneberberine, the plasma metabolite of berberine, exhibits better hepatoprotection than berberine[123]. Considering the abundance of inherent enzymes in the liver, the hepatic metabolites of CMM compounds account for a substantial proportion of the blood, including phase I and phase II metabolites. Consistent with Western medicine, phase I metabolites from CMM formulae involve compounds produced *via* functionalization reactions, such as oxidation, reduction, hydrolysis, and demethylation. Phase II metabolites refer to conjugation reaction products such as glucuronidation, sulfation, methylation, and acetylation[124]. Among the metabolites produced in rat plasma after oral administration of Gegen Qinlian pills, *p*-Hydroxyphenylpropionic acid, a hydrolytic product, was the phase I metabolite, and puerarin-*O*-glucuronide, daidzein-*O*-glucuronide, and chrysin-7-*O*-glucuronide, glucuronides conjugates, were phase II metabolites[125]. Interestingly, some phase I and II metabolites usually undergo enterohepatic circulation, leading to their reabsorption into the blood as active compounds. Evidence from Yang et al.[126] projected that berberrubine, a demethylation metabolite of berberine, might exert a glucose-lowering effect when it undergoes glucuronidation in the liver, hydrolysis in the intestine, and is subsequently absorbed into the blood[127–128]. Based on serum metabolite activities, a serum pharmacology approach has been used to study CMM formulae. For example, Song et al.[129] observed that serum containing Qili Jiegu capsules promoted osteogenesis by activating the Wnt/β-catenin pathway.

On the one hand, the hepatic enzymes could transform compounds from CMM formulae, while on the other hand, electrophilic reactive species of compounds (such as nitidine chloride[130] and geniposide[131]) could covalently integrate with hepatic enzymes[132] or other macromolecules (protein[133] and DNA), leading to inactivation of hepatic enzymes and unexpected adverse reactions. The covalent binding of reactive species to proteins or DNA circulating within the blood results in the formation of covalent adducts, which are involved in nucleophilic substitution and Schiff base mechanism[134]. Using UPLC-MS^n, Yun et al.[135] quantified 7-(deoxyadenosine-N^6-yl) aristolactam I (dA-AL-I) and 7-(deoxyguanosine-N^2-yl) aristolactam I (dG-AL-I)-DNA adducts in the mouse liver and kidney, and in patients with upper urinary tractcarcinomas, which are associated with the carcinogenesis and nephrotoxicity of aristolochic acid.

Other molecular forms formed by compounds from CMM and endogenous substances

Clinically, Epimedii Folium is traditionally processed by frying with suet oil. Jiang et al.[136] found that suet oil could interact with sodium deoxycholate, an inherent bile acid salt *in vivo*, to prepare self-assembled micelles, which serve as carriers for active compounds (icariin and circinal-icaritin) from *Epimedium brevicornu* Maxim. This accounts for the increase in solubility and intestinal absorption, and enhancement of the anti-osteoporosis effect[136–137]. Collectively, owing to the complex environment of blood, other special forms of CMM formulae-derived compounds in the blood, such as self-assembled supramolecules and their metal complexes, might be responsible for the pharmacological activity. Hopefully, studies on detecting and evaluating special molecules in plasma will emerge in the future.

CMM compounds detected in other interstitial fluids

Besides transportation into the blood, compounds from CMM formulae might be transported through other body fluids to the brain, lymph, and other target tissues or organs. Of importance, particularly in the BBB and lymph, we introduce CMM compounds transported through the cerebrospinal fluid and lymph.

CMM compounds migrating in cerebrospinal fluid

In the central nervous system, the BBB is composed of endothelial cells, pericytes, and astrocytes, which regulate the influx of compounds from the blood to the brain[138]. Therefore, a great disparity is often observed between compounds circulating within the blood and cerebrospinal fluid. In 2000, based on the question of how CMM formulae treat cerebrovascular diseases, Professor Boli Zhang proposed a new concept in cerebrospinal fluid pharmacology. The study confirmed different pharmacological effects of serum-containing CMM and cerebrospinal fluid-containing CMM *in vitro*[139]. This cerebrospinal fluid pharmacology approach effectively employs the idea of collecting cerebrospinal fluid containing CMM compounds from animals and subsequently utilizing CMM-enriched cerebrospinal fluid on

in vitro central nervous disorder assays. This approach helps investigate the efficacy and exact mechanisms of action mediated by CMM formulae for central nervous disorders[140].

The CMM compounds present in the cerebrospinal fluid are usually decoction-derived parent compounds and their secondary compounds metabolites derived from the action of gut microbiota and liver drug enzymes. These compounds may be responsible for the neuroprotection mediated by CMM formulae, such as benzoic acid (gut microbiota metabolites of paeoniflorin)[141] and quercetin-3-*O*-glucuronide (hepatic metabolites of quercetin)[142]. Using UPLC-quadrupole (Q)/TOF-MS combined with orthogonal partial least-squares discriminant analysis, Mi et al.[143] identified 17 parent constituents and 14 metabolites from CMM formulae (Danzhi tablet) in rat cerebrospinal fluid.

For screening, permeation, and metabolism studies for neuroprotective agents *in vitro*, conventional static BBB models, such as transwell co-cultured models[144] and multidrug-resistant Madin-Darby Canine kidney (MDCK-MDR1) cell line[145], have been employed in studying CMM formulae. Yu et al.[146] established a BBB model by co-culturing rat primary astrocytes seeded on the opposite side of the microporous membrane and rat primary cerebral microvascular endothelial cells incubated on the positive side of the microporous membrane. Using the above BBB model and glucocorticoid-induced BBB damage, they demonstrated that Xiaoyao powder has neuroprotective effects. In addition, several emerging *in vitro* BBB models, including microfluidic models[147], BBB-on-chip models, and *in silico* models[148], have been developed to assist with the investigation of BBB permeability and metabolism. Maoz et al.[149] constructed a coupled organ-on-chip of the human neurovascular unit using microfluidic organ chips to model influx/efflux across the BBB and the brain parenchymal compartment. This model mimics the metabolic and physiological functions of the neurovascular unit, thereby facilitating the assessment of drug delivery systems aiming at the human BBB. With emerging *in vitro* BBB models, it is possible to uncover the metabolic situation of CMM formulae in brain tissue *in vitro*.

CMM compounds migrating in lymph

Lymphatic transport plays a crucial role in the absorption and pharmacological action of poorly water-soluble and highly lipophilic compounds from CMM formulae and their intestinal microbiota metabolites *in vivo*. After being absorbed into enterocytes from orally administered CMM formulations, the vast majority of compounds are directly transported into the systemic circulation *via* the portal vein. Highly lipophilic compounds with log octanol/water partition coefficients >5 and high affinities for enterocyte lipoproteins access systematic circulation through intestinal lymphatics. This route of transport effectively bypasses hepatic first-pass metabolism (Figure 3), namely intestinal lymphatic transport[150–151].

Given the permeation of small molecules from the systemic circulation to the peripheral lymph, decoction-derived parent compounds, intestinal microbiota-dependent CMM formula metabolites, and low molecular weight hepatic metabolites will occur in the lymph. Lymph duct cannula surgery is used to collect lymph samples[152]. For example, after intraduodenal administration of quercetin and quercetin-3-glucoside, and thoracic lymph-cannulated surgery in rats, Nakamura et al.[153] revealed quercetin lymphatic metabolites and

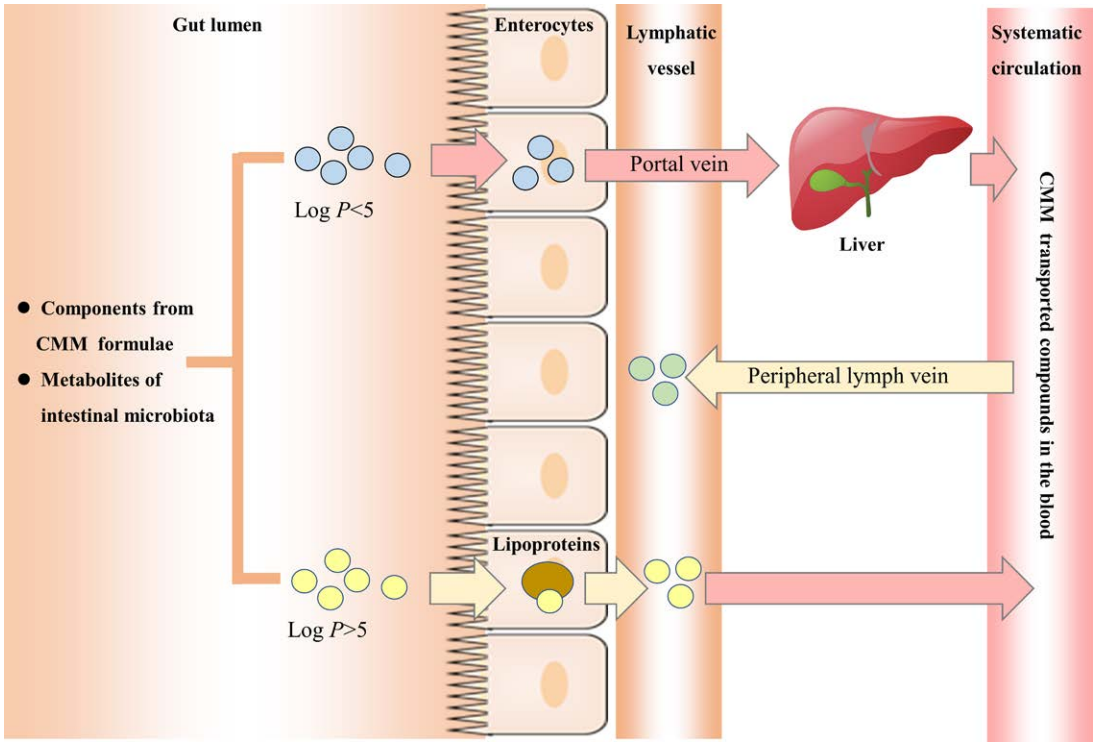

Figure 3. Lymphatic transport of compounds from CMM formula. CMM: Chinese Materia Medica.

putative metabolic pathways for quercetin and its glucoside using HPLC-MS/MS. However, because of the cumbersome nature of lymph-cannulated surgery, recent studies related to lymphatic transport have used an intraperitoneal injection of cycloheximide, an inhibitor of lymphatic transport, to investigate the lymphatic transport of CMM compounds, such as curcumin[154] and huperzine A[155]. Considering their contribution to immunomodulation, anti-cancer treatment, and avoidance of first-pass metabolism[156], intestinal lymphatic transport has been accepted as an alternative avenue for increasing the bioavailability of active compounds originating from CMM formulae by designing lipid-based drug delivery systems[154–155,157] (self-assembled polymeric micelles, self-assembled micro/nanoemulsions) and lipid-mimic prodrugs[158] in recent years.

Conclusions and future perspectives

Chemical substances in the decoction determine the efficacy and safety of the CMM formulae. Complex biotransformations occur after oral administration of the CMM formulae. The more active compounds produced requires more investigations. Notably, CMM formula-derived compounds undergo degradation, polymerization, supramolecular self-assembly, and modification by endogenous host enzymes from decoction to circulation in the body, giving rise to the magical production of bioactive compounds and sophisticated chemical composition. More focus is required on project CMM formulae as a great treasure for discovering therapeutically active compounds against several diseases. In our opinion, the introduction of interdisciplinary methods and technologies will bolster the unveiling of bioactive compounds *in vivo*, which is important for scientific connotation of CMM formulae.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Kefeng Li and Yuefei Wang proposed the idea. Ning Meng and Yun Lyu designed, wrote, and revised the manuscript. Xiaoyu Zhang reviewed the literature. Xin Chai revised the manuscript. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

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