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Review

Potential efficacy and mechanism of eight mild-natured and bitter-flavored TCMs based on gut microbiota: A review

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ABSTRACT

The mild-natured and bitter-flavored traditional Chinese medicines (MB-TCMs) are an important class of TCMs that have been widely used in clinical practice and recognized as safe long-term treatments for chronic diseases. However, as an important class of TCMs, the panorama of pharmacological effects and the mechanisms of MB-TCMs have not been systemically reviewed. Compelling studies have shown that gut microbiota can mediate the therapeutic activity of TCMs and help to elucidate the core principles of TCM medicinal theory. In this systematic review, we found that MB-TCMs commonly participated in the modulation of metabolic syndrome, intestinal inflammation, nervous system disease and cardiovascular system disease in association with promoting the growth of beneficial bacteria *Bacteroides*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, *Roseburia* as well as inhibiting the proliferation of harmful bacteria *Helicobacter*, *Enterococcus*, *Desulfovibrio* and *Escherichia-Shigella*. These alterations, correspondingly, enhance the generation of protective metabolites, mainly including short-chain fatty acids (SCFAs), bile acid (BAs), 5-hydroxytryptamine (5-HT), indole and gamma-aminobutyric acid (GABA), and inhibit the generation of harmful metabolites, such as proinflammatory factors trimethylamine oxide (TAMO) and lipopolysaccharide (LPS), to further exert multiplicative effects for the maintenance of human health through several different signaling pathways. Altogether, this present review has attempted to comprehensively summarize the relationship between MB-TCMs and gut microbiota by establishing the TCMs-gut microbiota-metabolite-signaling pathway-diseases axis, which may provide new insight into the study of TCM medicinal theories and their clinical applications.

Contents

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1. Introduction

Traditional Chinese medicine (TCM) has developed a series of theories to guide the appropriate use of traditional Chinese medicines (TCMs), including four natures, five flavors and meridian tropism, etc. (Li & Xu, 2011). According to TCM theory, the four natures and five flavors usually represent the major therapeutic effects of TCMs (Liu et al., 2013). Generally, TCMs with different natures and flavors show different effects in human body, which is an essential basis for accurately understanding and application of TCM theory (Gao et al., 2022). The mild-natured and bitter-flavored TCMs (MB-TCMs) are a class of herb medicines and have been widely used in clinical practice to treat various diseases. Some studies demonstrated that the mild nature of TCMs accounts for a large proportion (one-fifth to one-third) of the total amount of TCMs in the classical and authoritative TCM books, such as *Shennong's Classic of Materia Medica* (25–200 CE), *Chinese Pharmacopoeia*. In addition, TCM doctors believe that mild nature has the function of maintaining the balance of *yin* and *yang* in the human body, and has fewer adverse reactions than other natures (Deng, Guo, & Hao, 2013). Therefore, mild-natured TCMs have been recognized as safe and long-term strategy for chronic disease's treatment (Mu, Gu, Xu, Wang, & Tong, 2017). Traditionally, bitter-flavored TCMs are critical to human health and have the effects of drying dampness (regulation of body-fluid homeostasis), clearing heat (anti-inflammation and anti-infection), purging fire (detoxication) and consolidating *yin* (strengthening the activity of kidney and liver). According to a recent report, in the treatment of cardiovascular, respiratory and digestive diseases, bitter flavor accounted for a larger proportion (38 %) of all the tested TCMs (Xu et al., 2019). However, as a highly abstracted TCM theory, MB-TCMs are far from being completely understood and remain to be elucidated by scientific research.

Gut microbiota has emerged as a novel and significant frontier in the understanding of TCM and is a potential strategy to elucidate the core principles of TCM theory (Su et al., 2022; Yang et al., 2022; Zhang et al., 2021; Yang et al., 2023). It was found that tonic TCMs, which are warm nature and sweet flavor, can enhance physical health through special microbial alternations, including up-regulating *Flavonifractor* and *Acetatifactor* and down-regulating *Verrucomicrobia* (Li et al., 2019; Wang, Li, & Peng, 2017). The interventions of hot or cold nature TCMs could greatly shape the composition of gut microbiota (Liang et al., 2020). In the previous study, we have demonstrated that as the TCM natures change from cold, cool and warm to hot, the abundance of *Ruminococcaceae_UCG-010, Parasutterella* and *Bifidobacterium* continuously decreased (Zhang et al., 2021). Moreover, among all TCM natures, the mild nature has the optimal recovery ability to improve gut microbiota disorders (Guan et al., 2021). Therefore, gut microbiota may be an important biological indicator reflecting the nature of TCMs. In this review, we summarized the relationship between MB-TCMs and gut microbiota by establishing the TCMs-gut microbiota-metabolite-signaling pathway-diseases axis, which can help to elucidate their underlying mechanisms and provide guidance for drug research.

2. Literature survey

We conducted a comprehensive search of the literature on gut microbiota and TCM through PubMed, The Cochrane Library, SpringerLink, China National Knowledge Infrastructure, China Science and Technology Journal Database and Wanfang database from the inception to September 2022. The keywords for the search included "traditional Chinese medicine", "herbal medicine", "medicinal plant", "intestinal flora", "gut microbiota", "pharmacology" in both English and Chinese. Supplementary Appendix I provides a detailed search strategy. The inclusion criteria were as follows: (1) Single Chinese herb or herbal extracts; (2) The medicine is recorded in *Chinese Pharmacopoeia* (2020 edition); (3) The nature of TCM is "mild"; (4) The flavor of TCM contains "bitter"; (5) The article studies the effects of gut microbiota on TCM. The exclusion criteria were as follows: (1) Chinese herbal compound prescriptions; (2) Reviews, editorial, commentary, protocols, and clinical guidelines; (3) Repeated publication; (4) Full text not available.

After removing duplicates, we identified 1836 records through a comprehensive search. However, 648 records of TCM compounds were excluded and 1188 records of single Chinese herbs or herbal extracts were screened. Further, we analyzed and screened the study drugs in the records (Table 1). Among them, a total of 270 single Chinese herbs were included, of which 141 were recorded in *Chinese Pharmacopoeia*, and 129 herbs were not recorded. According to the guidance of *Chinese Pharmacopoeia*, we summarized the nature and flavor of each medicine. The medicine which

Table 1
Literature screening records for enclosed TCMs in this review.

Recorded in *Chinese Pharmacopoeia*	Nature is "mild"	Flavor contains "bitter"	Number
–	–	–	270
×	–	–	129
✓	–	–	141
✓	×	–	115
✓	✓	–	26
✓	✓	×	18
✓	✓	✓	8

Note: "-" means NOT consider; "×" means not fit; "✓" means fit.

nature property is not "mild" was excluded (n = 115, "cold" = 58, "hot" = 4, "warm" = 43 or "cool" = 10), and then 26 natural-mild medicines were screened. Next, these medicines which flavor property do not contain "bitter" were excluded (n = 18). Finally, eight drugs fit the inclusion criteria, requiring 34 full-text articles. Five articles were excluded because of the following reasons: reviews (n = 4) and full text not available (n = 1). As a result, 29 articles met eligibility criteria and were included in analysis.

3. Gut microbiota is a bridge linking pharmacological effect of MB-TCMs

To date, a mounting body of evidences have suggested that the composition and function of gut microbiota are closely associated with development of several diseases, along with mediate pharmacological activities (Dong et al., 2023; Wu et al., 2019a; Wu et al., 2022; Wu et al., 2019b). A total of eight mild and bitter herbs were included in this review, which includes *Ginkgo Folium* (Yinxing in Chinese), *Nelumbinis Folium* (Heye in Chinese), *Rhodiolae Crenulatae Radix* et *Rhizoma* (Hongjingtian in Chinese), *Chebulae Fructus* (Hezi in Chinese), *Mori Ramulus* (Sangzhi in Chinese), *Sinomenii Caulis* (Qingfengteng in Chinese), *Vaccariae Semen* (Wangbuliuxing in Chinese), *Viticis Negundo Folium* (Mujingye in Chinese). Furthermore, we summarized the correlation between the MB-TCMs and gut microbiota, and discussed the regulatory effects and efficacy in detail (Table 2).

3.1. Ginkgo Folium

Ginkgo Folium, the dried leaves of *Ginkgo biloba* L., has been widely used as a crude medicine for thousands of years. In TCM theory, *Ginkgo Folium* is mild in nature, bitter and sweet in flavor, with a meridian tropism in the heart and lung. It has the effects of activating blood and resolving stasis, unblocking the collaterals, relieving asthma, transforming turbidity and reducing lipids. Due to its function, *Ginkgo Folium* is mostly used to treat blood stasis obstructing collaterals, chest stuffiness and heartache, stroke, cough and panting, hyperlipidemia. In clinical applications, *Ginkgo Folium* is commonly used in the treatment of early-stage of Alzheimer's disease, vascular dementia, atherosclerosis, and vascular tinnitus. Currently, the identified bioactive constituents in *Ginkgo Folium* composed of flavonoid glycosides, terpene lactones, ginkgolic acids and polysaccharides (Liu et al., 2022; Mahadevan & Park, 2008). These components contribute to the extensive pharmacological activities of *Ginkgo Folium*, such as anti-oxidant, anti-cardiovascular diseases, anti-cerebrovascular diseases, anti-neurodegenerative diseases, anti-depression, anti-tumor and neuroprotective effect (Liu et al., 2022).

The extract of *Ginkgo Folium* is an extensively used medicine and dietary supplement in clinical to prevent and treat cardiovascular disease. In $Ldlr^{-/-}$ mice, one atherosclerosis animal model, Wang et al. found *Ginkgo Folium* leads to the decreasing of the *Firmicutes/Bacteroidetes* ratio and the elevating of *Akkermansia*, *Alistipes*, *Alloprevotella*, and *Parabacteroides*, further promotes the generation of gut microbial metabolites, such as short chain fatty acids (SCFAs), indole-3-acetate and secondary bile acids (BAs), which dramatically associate with the atherosclerotic plaque areas (Wang et al., 2022). Ginkgolide B, an active component of *Ginkgo Folium*, could also decrease the levels of trimethylamine (TMA) and trimetlylamine oxide (TMAO) in a gut microbiota-depended manner, which is mainly embodied by the enhancement of *Bacteroides* and the decline of *Helicobacter* and *Roseburia* (Lv et al., 2021).

In addition to cardiovascular protection effect, *Ginkgo Folium* also possesses neuroprotective effect via regulating gut microbiota, usually known as "gut-brain axis". It is demonstrated that administration with ginkgolide B could alleviate amyloid deposition and neuronal apoptosis, and suppress receptor for AGE (RAGE) activation. Concomitantly, ginkgolide B notably increased *Lactobacillus* and decreased *Bacteroidales*, *Muribaculaceae*, and *Alloprevotella* (Liu et al., 2021a). Moreover, Chen et al. found the depression-related gut dysbiosis was restored by the water-soluble polysaccharides from *Ginkgo Folium*, mainly reflected by the enrichment of *Lactobacillus* (Chen et al., 2019).

Some other studies also revealed that the anti-cancer and anti-inflammation activities of *Ginkgo Folium* are attributed to the alteration of gut microbial community. For example, one *in vivo* and *in vitro* research showed *Ginkgo Folium* extract induced down-regulation of breast cancer resistance protein was markedly related with the increasing of Bacteroidetes, TM7 phylum and the decreasing of Proteobacteria and Deferribacteres phylum (Kim et al., 2021). Besides that, as one extract from *Ginkgo Folium*, bilobalide protects DSS-induced model mice from ulcerative colitis injury by inhibiting inflammatory signaling pathway and reshaping of gut microbial community (Zhang, Wang, Su, Fang, & Guo, 2021).

3.2. Nelumbinis Folium

Nelumbinis Folium, the dried leaves of *Nelumbo nucifera* Gaertn., possesses excellent value as a dietary supplement and herbal medicine for thousands of years. In TCM theory, *Nelumbinis Folium* is mild in nature, bitter in flavor, with a meridian tropism in the liver, spleen, and stomach. It has the effects of clearing summer-heat, and removing dampness, invigorating and lifting *yang qi*, cooling blood and hemostasis. Its indications are used in wasting-thirst and diarrhea induced by summer heat-dampness, hematochezia, metrorrhagia. In addition, it is often used in conjunction with the roots of *Rehmannia glutinosa* for bleeding cessation. So far, the phytochemical analysis of *Nelumbinis Folium* is mainly concentrated on alkaloids, flavonoids, coumarins, lignans, polysaccharides, terpenes, and amino acids. Anti-inflammatory, anti-oxidant, anti-cancer, anti-virus, anti-bacteria, cardiovascular protection, hepatoprotection, hypoglycemia and hemostasis are the representative pharmacological effects corresponding to these bioactive constituents (Zheng et al., 2022).

Nelumbinis Folium has attracted wide attention of researchers due to its excellent nutrition and medicinal value. Most studies have demonstrated its potential in improving metabolism, and displayed the clinical practice value in obesity, diabetes and hyperlipidemia (Shen et al., 2023). In high-fat diet-induced obesity mice, nuciferine significantly reduced serum levels of triglyceride (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), as well as decreased body weight, liver weight, visceral and subcutaneous fat accumulation. Gut microbiota analysis from genus level showed an increased relative abundance of *Akkermansia*, *Alloprevotella*, *Turicibacter*, *Lactobacillus*, *Prevotella*_9 and *Bacteroides*, whereas a decreased percentage of *Butyricimonas*, *Helicobacter*, *Desulfovibrio*, Lachnospiraceae_NK4A136_group, Christensenellaceae_R-7_group, *Allobaculum*, *Anaerotruncus*, Ruminococcaceae_UCG-009 and *Enterorhabdus* (Shi et al., 2021; Wang et al., 2020; Xiong et al., 2021). Simultaneously, our previous study also found nuciferine notably enriched *Akkermansia muciniphila* and *Bacteroides uniformis*, but decreased *Lactobacillus* in hyperlipidemic mice (Yu et al., 2021). Additionally, another study also proved that the levels of *Akkermansia*, *Lactobacillus*, and *Bifidobacterium* were elevated by nuciferine in gestational diabetes mellitus mice (Tang et al., 2021). In Sprague-Dawley rats with non-alcoholic fatty liver disease (NAFLD), nuciferine up-regulated *Akkermansia*, norank_f_Erysipelotrichaceae and Lachnospiraceae_NK4A136_group while down-regulate *Lactobacillus*,

Table 2
Modulation of mild-natured and bitter-flavored TCMs on gut microbiota.

TCMs	Extracts	Diseases	Objects	Administration	Dosages	Efficacy	Increased gut microbiota	Decrease gut microbiota	References
Ginkgo Folium (Yinxing)	Ginkgolide B	Atherosclerosis	C57/BL6 ApoE^{-}/$^{-}$ mice	a	20 mg/(kg·d), 30 mg/(kg·d)	Reduce atherosclerotic lesions; hypoglycemic; lipid-lowering; anti-inflammation	*Bacteroides*	*Helicobacter* and *Roseburia*	Lv et al., 2021
	Ginkgo Folium extract	Atherosclerosis	Ldlr^{-}/$^{-}$ mice	a	–	Decrease proinflammatory cytokines; Enhance the expression of tight junction proteins	*Akkermansia*, *Alloprevotella*, *Alistipes*, and *Parabacteroides*	Firmicutes phylum	Wang et al., 2022
	Ginkgolide B	Alzheimer's disease	C57BL/6 mice	a	0.1-%	Alleviate cognitive dysfunction, neurodegeneration, and neuropathological changes; Alleviate amyloid deposition, neuronal apoptosis; Suppress RAGE activation	Lactobacillaceae family and *Lactobacillus* genus	Bacteroidota phylum, Muribacullaceae family, and *Alloprevotella* genus	Liu et al., 2021a
	Ginkgo Folium extract	Breast cancer	C57BL/6 mice and Caco-2 cell	a	34 mg/kg	Suppress Bcrp and P-gp expression; Elevate Mrp2 expression	Bacteroidetes and TM7 phylum	Proteobacteria and Deferribacteres phylum	Kim et al., 2021
	water-soluble polysaccharide from *Ginkgo Folium*	Depression	BALB/c mice	a	300 mg/kg	Reduce immobility times in the TST and FST; Ameliorate anxiety-like behavior in the OFT; Elevate serotonin and dopamine levels; Enhance the density of serotonin positive and dopamine-positive cells	Prevotellaceae, Erysipelotrichaceae, Family_XIII, Lactobacillaceae, and Deferribacteraceae family; *Lactobacillus* species		Chen et al., 2019
	Bilobalide	Ulcerative colitis	C57BL/6 mice	a	–	Reduce IL-1β, IL-6, and TNF-α; Increase colon length; Normalize colon histological characteristics; Enhance the expression of ZO-1, Occludin, and Claudin-3	*Lactobacillus*		Zhang et al., 2021
Nelumbinis Folium (Heye)	Nuciferine	Obesity	C57BL/6J mice, Caco-2 cell and HT-29 cell	b	0.3 % (g/kg of the HFD diet) nuciferine supplement diet	Reduce body and liver weight, as well as visceral and subcutaneous fat accumulation; Relieve lipid deposition; Rescue HFD-impaired autophagy in the colon; Alleviate LPS-increased intestinal permeability	*Akkermansia*	*Butyricimonas*	Shi et al., 2021
	Nuciferine	Obesity	C57BL/6 mice	a	20 mg/kg	Decrease body weight, Lee's index, weight percentage of inguinal subcutaneous fat; Reduce TC, TG, LDL-c; Decrease IL-6, IL-1β, TNF-α; Promote Occludin and ZO-1 expression	*Alloprevotella*, *Turicibacter*, *Lactobacillus*	*Helicobacter*	Xiong et al., 2021
	Nuciferine	Obesity	Sprague-Dawley rats	a	—	Reduce weight gain and fat Accumulation; Decrease serum TG, TC, and	*Prevotella_9* and *Bacteroides*	*Desulfovibrio*,	Lachnospiraceae_NK4A136_group, Christensenellaceae_R-7_group, *Allobaculum*, *Anaerotruncus*,

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Table 2 (*continued*)

TCMs	Extracts	Diseases	Objects	Administration	Dosages	Efficacy	Increased gut microbiota	Decrease gut microbiota	References
						LDL-c; Alleviate hepatic steatosis and liver injury			Ruminococcaceae_UCG-009, and *Enterorhabdus*
	Wang et al., 2020								
	Nuciferine	Hyperlipidemia	C57BL/6J mice	a	7.5 mg/kg; 15 mg/kg; 30 mg/kg	Decrease TC, TG, LDL-c; Reduce lipid accumulation in liver; Improve oral glucose tolerance	*Akkermansia muciniphila* and *Bacteroides uniformis*	*Lactobacillus*	Yu et al., 2021
	Nuciferine	Gestational diabetes mellitus	C57BL/6J mice	a	–	Improve glucose intolerance; Reduce lipid accumulation; Increase the glycogen content; Decrease placental lipid and glycogen deposition;	*Akkermansia*, *Lactobacillus*, and *Bifidobacterium*		Tang et al., 2021
	Nuciferine	Non-alcoholic steatohepatitis	Sprague-Dawley rats	a	10 and 25 mg/kg/day	Affect BA metabolism including synthesis, enterohepatic circulation, and excretion; Down-regulate *Fxr*, *Fgf15*, *Asbt*, *Ibabp*, *Ost-α*, and *Ost-β* mRNA	*Akkermansia*, *norank_f_Erysipelotrichaceae* and Lachnospiraceae_NK4A136_group	*Lactobacillus*, *Enterococcus*, *Clostridium* and *Eubacterium*	Sun et al., 2022
	Nuciferine	Ulcerative colitis	BALB/c mice	c	10 mg/kg/day 20 mg/(kg·d)	Rescue epithelial layer rupture, a reduction in goblet cell numbers, and inflammatory cell infiltration; Improve the Th1/Th2 and Treg/Th17 balance	Lachnospiraceae_Clostridium, *Bilophila* and *Halomonas*	*Bacteroides*, *Parabacteroides*, and *Paraprevotella*	Zhu et al., 2022
Lotus leaf extract	Immune response	Broiler chickens	b	1.0, 2.5, 5.0, 7.5, 10.0 g/kg	Enhance thymus index, spleen index, and bursa index; Increase serum total IgG and sIgA	concentrations; Increase IL-2 concentration	Clostridiaceae and Bacteroidales S24-7 family	Peptostreptococcaceae family	Cheng et al., 2021
Rhodiolae Crenulatae Radix et *Rhizoma* (Hongjingtian)	Salidroside	Furan-induced liver injury	BALB/c mice	a	10,20,40 mg/kg	Decrease AST, ALT and MDA; Enhance GSH, GST and SOD activity; Alleviate furan-induced local inflammation; Reduce serum IL-6 and TNF-α level; Enhance IL-10 level	*Akkermansia* and *Roseburia*	*Sporobacter*, *Blautia*, *Desulfovibrio*, *Anaerofustis*, *Olsenella*, *Bifidobacterium* and *Vasilyevaea*	Yuan, Wu, Zhang, Hong, & Yan, 2019
	Salidroside	Type 2 diabetes mellitus	db/db mice	a	1.5 g/kg	Reduce blood glucose; Ameliorate myocardial necrosis and mitochondrial injury; Reduce the expression of LC3II		*Enterobacter* and *Lactobacillus*	Shi et al., 2022
	Salidroside	Non-alcoholic steatohepatitis	C57BL/6 mice	a	20 (kg·d)	Reduce the body weight, liver wet weight, and liver index; Decrease liver NAS, TG content, and serum ALT		*Lactobacillus* and *Alloprevotella* spp.	Li, Xi, Xin, Tian&Hu, 2020

Table 2 (*continued*)

TCMs	Extracts	Diseases	Objects	Administration	Dosages	Efficacy	Increased gut microbiota	Decrease gut microbiota	References
						activity; Decrease IL-1a, IL-12, MCP-1, KC, MIP-1a, MIP-1β			
	Salidroside	Type 2 diabetes mellitus	db/db mice and C57BL/KSJ wild-type (WT) mice	a	200 mg/kg	Reduce diabetic kidney and liver damage; Weaken pathological changes;	*Prdiococcus*, *Alloprevotella*;	*Mycoplasma*, *Enterococcus*, *Candidatus*, *Arthromitus* and Lachnospiraceae UCG-006	Zhao et al., 2022
	Salidroside	Alzheimer's disease	SAMR1 mice and SAMP8 mice	a	50 (kg·d)	Reduce toxic Aβ peptide deposition	*Norank_f_Muribaculaceae*, *Alloprevotella* and *Parasutterella*	Prevotellaceae family,	Lachnospiraceae_NK4A136_group, *Unclassified_f_Lachnospiraceae*, *Alistipes*, *Norank_f_Lachnospiraceae*, *Odoribacter*, Rikenellaceae_RC9_gut_group, Ruminococcaceae_UCG-014 and Ruminiclostridium_9
									Xie et al., 2020
Cell wall-broken decoction pieces	—	C57BL/6 mice	a	1 g/22. 2 mL; 1 g/44.4 mL; 1 g/88.8 mL; 1 g/176.5 mL	—	*Lactobacillus* and *Bifidobacterium*	*Enterococcus* and *Escherichia coli bacillus*		Yang et al., 2015
Chebulae Fructus (Hezi)	Water extract	Arthritis	Sprague-Dawley rats	a	4 mg/kg 2 mg/kg 1 mg/kg	Alleviate the arthritis symptoms; Reduce the expressions of CD4 and CD25	*Lactobacillus*	*Escherichia coli*	Liu et al., 2020
Mori Ramulus (Sangzhi)	Alkaloids (SZ-A)	Type 2 diabetic	KKAy mice	a	100 mg/kg, 200 mg/kg	Ameliorate overall metabolic profile including glucose and lipid metabolism; Enhance insulin response and elevate GLP-1	Bacteroidaceae, Erysipelotrichaceae and Verrucomicrobia family	Rikenellaceae, Desulfovibrionaceae and Aerococcaceae family	Liu et al., 2021b
	Polysaccharide	DSS-induced colitis	C57BL/6 mice	a	30 (kg·d)	Attenuate the loss of body weight and pathological injury; Decrease DAI score; Restore colon length; Decrease IFN-γ and IL-6 but increase IL-10	Bacteroidetes phylum, *Barnesiella Mucispirillum* and *Clostridium XIVa*	Firmicutes phyla	Feng et al., 2021
Sinomenii Caulis (Qingfengteng)	Sinomenine	Septic acute lung injury	ICR male mice and Caco-2 cell	c	100 mg /kg	Decrease IL-6 and TNF-α mRNA levels; Repair the lung injury; Reduce the colon pathological damage; Improve the intestine barrier integrity	Prevotellaceae UCG-001	*Escherichia-Shigella*	Song et al., 2021
	Sinomenine hydrochloride	DSS-induced colitis	C57BL/6 mice	a	100 mg/kg	Decease DAI score and the expression of proinflammatory gene TNF α, IL 6 and iNOS; Increase IL 10 and arginine 1; Suppress the activation of NLRP3 inflammasome	*Bacteroidetes*	Proteobacteria	Zhou et al., 2021
	Sinomenine	morphine dependence	Zebrafish	c	80 mg/kg	Inhibit morphine-induced MGBA-relative gene alterations	Actinobacteria phylum	Fusobacteria phylum	Chen et al., 2020

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Table 2 (*continued*)

TCMs	Extracts	Diseases	Objects	Administration	Dosages	Efficacy	Increased gut microbiota	Decrease gut microbiota	References
Vaccariae Semen (Wangbuliuxing)	Vaccarin	Type 2 diabetes	C57BL/6J mice; Caco-2 cell	c	1 mg/kg	Reduce LPS, TNF-α and IL-1β levels and the weight of epididymal fat; Increase ZO-1, ICAM, mucin, Claudin-1, and Occludin expression	Rikenellaceae, Muribaculaceae family, *Bacteroides*	Lachnospiraceae family, *Lactobacillus*, and *Desulfovibrio*	Sun et al., 2021
Viticis Negundo Folium (Mujingye)	Vitexin	Neural oxidative stress and neuroinflammation	C57BL/6N mice; human neuroblastoma SH-SY5Y cells	a	10 mg/kg; 30 mg/kg	Reduce MDA, TNF-α and IL-1β level; Increase SOD, CAT activity	*Akkermansia*, *Lactobacillus* and *Romboutsia*;	Lachnospiraceae_NK4A136_group,	

norank_f__Eubacterium_coprostanoligenes_group, *unclassified_f__Lachnospiraceae*, *Blautia and Colidextribacter*Li et al., 2021VitexinUlcerative colitisBALB/c micea20 mg/kg; 80 mg/kgDecrease DAI score, IL1β, IL-6, and TNF-α production; Down-regulate phosphorylation levels of p65, IκB, and STAT1; Increase the expressions of muc-2, ZO-1, and Occludin proteins*Bacteroides* and *Helicobacter Alistipes*, Lachnospiraceae_NK4A136_group, and Lachnospiraceae_UCG-006Zhang et al., 2022*Note*: a, Gavage; b, Supplement diet; c, Intraperitoneal injection.

Enterococcus, *Clostridium* and *Eubacterium* (Sun, Fan, Li, Yan, & Jiang, 2022). All of these studies showed beyond doubt that *Akkermansia* is a key point for the improvement of metabolism. However, there is a contradictory result for *Lactobacillus*, which may result from the insufficient detection accuracy.

Except for improving metabolic activity, nuciferine can also regulate the immune response and alleviate inflammation. For example, intraperitoneal injection of nuciferine could promote the growth of Lachnospiraceae,_*Clostridium*, *Bilophila* and *Halomonas*, whereas inhibit the proliferation of *Bacteroides*, *Parabacteroides*, and *Paraprevotella*, further improve the Th1/Th2 and Treg/Th17 balance, and attenuate inflammatory cell infiltration in ulcerative colitis mice (Zhu et al., 2022). Similarly, supplementation with *Nelumbinis Folium* extract enhanced thymus index, spleen index, and bursa index, along with increased serum interleukin 2 (IL-2), total immunoglobulin G (IgG) and secretory immunoglobulin A (sIgA) concentrations, which correlated with the remodeling of gut microbiota (Cheng et al., 2021). Therefore, *Nelumbinis Folium* can be developed into a prebiotic, helping to modulate the gut microbiota and immune response to maintain human health.

3.3. Rhodiolae Crenulatae Radix et Rhizoma

Rhodiolae Crenulatae Radix et *Rhizome*, the dried roots and rhizomes of *Rhodiola rosea* L., has been considered as a valuable medicinal plant in China, Europe, and North America. In TCM theory, *Rhodiolae Crenulatae Radix* et *Rhizome* is mild in nature, bitter and sweet in flavor, with a meridian tropism in the lung and heart. It has the effects of promoting *qi* and blood circulation, invigorating pulse beat, relieving asthma. The indications of *Rhodiolae Crenulatae Radix* et *Rhizome* include *qi* deficiency and blood stasis, chest stuffiness and heartache, apoplexy hemiplegia, fatigue and asthma. In clinical use, *Rhodiolae Crenulatae Radix* et *Rhizome* is usually combined with *Carthamus* to treat angina pectoris. As a traditional Tibetan medicine, *Rhodiolae Crenulatae Radix* et *Rhizome* accumulates rich secondary metabolites, including monoterpene alcohols, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids, flavonoids, flavonlignans, essential oils, proanthocyanidins, organic acids, and gallic acid derivatives, during its growth (Panossian, Wikman, & Sarris, 2010). Results from many pharmacological studies proved that *Rhodiolae Crenulatae Radix* et *Rhizome* is widely used in the treatment of Parkinson's disease (Li et al., 2019b), diabetic nephropathy (Xue et al., 2019), colitis (Li et al., 2019a), cancer, cardiovascular disease (Pu et al., 2020) due to its anti-inflammation, antidepressive and anxiolytic effect, adaptogenic and stress-protective effect, cognitive-enhancing effect, cardioprotective effect and so on (Panossian, Wikman, & Sarris, 2010).

Salidroside is a phenolic glycoside isolated from *Rhodiolae Crenulatae Radix* et *Rhizome* that has several pharmacological activities like hepatoprotection and anti-diabetes. In both Furan-induced liver injury and high-fat diet (HFD)-induced non-alcoholic steatohepatitis mice, salidroside decreased serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and proinflammatory factor, accompanied by the enhancement of *Akkermansia* and *Roseburia*, and decline of *Sporobacter*, *Blautia*, *Desulfovibrio*, *Anaerofustis*, *Olsenella*, *Bifidobacterium*, *Vasilyevaea, Lactobacillus* and *Alloprevotella* (Li, Xi, Xin, Tian, & Hu, 2020; Yuan, Wu, Zhang, Hong, & Yan, 2019). Furthermore, salidroside could reduce the glucose level and protect heart, liver, kidney from diabetes-caused damage, which at least partly mediated by the alteration of gut microbiota, such as the increase of *Prdiococcus*, *Alloprevotella*, and decrease of *Enterobacter*, *Lactobacillus*, *Mycoplasm*a, *Enterococcus*, *Candidatus Arthromitus*, and Lachnospiraceae UCG-006 (Shi et al., 2022; Zhao et al., 2022). These results will shed a new light on the future of the targeted and precise modulation of microbiota to treat diabetes mellitus. Additionally, salidroside also

plays a role in preventing Alzheimer's disease. Xie et al. found salidroside may reconstruct the composition of gut microbiota to regulate "gut-brain-axis", then inhibit toxic $A\beta_{1-42}$ deposition and microglial activation, and suppress the secretion of proinflammatory factors interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor-necrosis factor-α (TNF-α) in the brain (Xie et al., 2020). In addition to salidroside, the cell wall-broken decoction pieces of *Rhodiolae Crenulatae Radix* et *Rhizome* also increased probiotics *Lactobacillus* and *Bifidobacterium*, and decreased harmful bacteria *Enterococcus* and *Escherichia coli* (Yang et al., 2015).

3.4. Chebulae Fructus

Chebulae Fructus, the desiccative ripe fruits of *Terminalia chebula* Retz. or *Terminalia chebula* Retz var. *tomentella* Kurt., is an important herbal remedy in various traditional medicine systems. In TCM theory, *Chebulae Fructus* is mild in nature, bitter and sour in flavor, with a meridian tropism in the lung and large intestine. It mainly plays the roles of relieving diarrhea with astringents, astringing the lung to stop cough and relieving sore-throat to restore voice. Therefore, the indications of *Chebulae Fructus* include prolonged diarrhea, lingering dysentery, hematochezia, prolapse of the rectum, serious cough and wheeze, sore-throat and aphonia. It is recorded that *Terminalia chebula Retz.* (Hezi in Chinese), *Coptis chinensis Franch.* (Huanglian in Chinese) and *Aucklandia lappa Decne.* (Muxiang in Chinese) have been used to treat prolonged dysentery and abdominal pain. The active constituents enriched in *Chebulae Fructus* mainly contained flavonoids, tannins, phenolic acids. Among which tannins consist of gallic acid, ellagic acid, chebulic acid, chebulinic acid, punicalagin, terflavin A, corilagin, galloylglucose, tannic acid, and flavonoids (quercetin, catechin and kaempferol) (Hassan Bulbul et al., 2022). It is found in practice that *Chebulae Fructus* has a potential in anti-oxidant, anti-aging, anti-diabetes, anti-hyperlipidemia, anti-inflammation, anti-arthritis, anti-tumor, anti-mutagenesis, hepatoprotection, neuroprotection, gastroprotection, cardioprotection, cytoprotection and radioprotection, and without adverse reactions and changes in biochemical, morphological and parameters via *in vitro* and *in vivo* along with acute and chronic toxicity tests (Hassan Bulbul et al., 2022).

Compared with other TCMs, a few studies focused on the modulation of gut microbiota by *Chebulae Fructus*. One *in vivo* study conducted in Sprague-Dawley rats showed that the water extract of *Chebulae Fructus* notably relieved the arthritis symptom and effectively reduced the expressions of CD4 and CD25 in serum. High throughput sequencing data displayed that the Chao and Shannon indices were increased by *Chebulae Fructus*, concomitantly, the relative abundance of *Lactobacillus* was elevated but *E. coli* was lowered (Liu et al., 2020). Such alteration of gut microbial community was closely related with the amelioration of arthritis symptom. Future study should elucidate the exact mechanism of *Chebulae Fructus* from the perspective of gut microbiota.

3.5. Mori Ramulus

Mori Ramulus, the tender twigs of *Morus alba* L., has been used as an herbal medicine for thousands of years in China. In TCM theory, *Mori Ramulus* is mild in nature, bitter in flavor, with a meridian tropism in the liver. It has the effects of expelling wind, eliminating dampness, relieving joint pain. The indications of *Mori Ramulus* include rheumatic arthralgia, shoulder/arm pain and numbness. In clinical practice, *Mori Ramulus* is commonly applied in treating limb and joint pain induced by related diseases, including rheumatoid arthritis, scapulohumeral periarthritis, cervical spondylosis. In 2020, *Mori Ramulus* alkaloids, was a group of effective alkaloids from natural *M. alba*, and was approved by The China National Medical Products Administration for the treatment of diabetes. *Mori Ramulus* is rich with terpenoids, flavonoids, stilbenoids, coumarins and so on. Modern pharmacological researches have proved that *Mori Ramulus* is a safe and effective agent for anti-bacteria, anti-inflammation, anti-oxidant, anti-diabetes, and anti-hyperlipidemia (Chan, Lye, & Wong, 2016).

Mori Ramulus alkaloid tablet is a new anti-diabetes TCM supervised and approved by The China National Medical Products Administration. However, its potential mechanism has not been investigated. Recently, an *in vivo* study showed that *Mori Ramulus* could promote the colonization of Bacteroidaceae and Verrucomicrobia, whereas inhibit the growth of Rikenellaceae and Desulfovibrionaceae. This alteration will enhance the concentrations of fecal SCFAs, thereby elevating glucagon-like peptide-1 (GLP-1) and insulin secretion, and ameliorating systemic inflammation (Liu et al., 2021b). Additionally, indextran sulfate sodium (DSS)-induced colitis mice, polysaccharides of *Mori Ramulus* notably attenuated the loss of body weight and pathological injury, reduced disease activity index (DAI) score, interferon-γ (IFN-γ) and IL-6, along with increased the colon length and interleukin-10 (IL-10) level. Meanwhile, the disorder of gut microbiota caused by DSS goes on well step by step, which was characterized by the enhancement of Bacteroidetes phyla and *Paraprevotella*, *Mucispirillum* and *Clostridium XIVa* genus, as well as the decline of Firmicutes phyla (Feng et al., 2021).

3.6. Sinomenii Caulis

Sinomenine Caulis, the dry rattan of *Sinomenium acutum* (Thunb.) Rehd. et Wils. and *Sinomenium acutum* (Thnnh.) Rehd. et Wils. var. *cinereum* Rehd. et Wils. It is believed to relieve rheumatism in the folk by making it into medicinal wine. In TCM theory, *Sinomenine Caulis* is mild in nature, bitter and pungent in flavor, with a meridian tropism in the liver and spleen. It has the effects of expelling wind-damp, dredging the channel, diuresis. The indications of *Sinomenine Caulis* include rheumatic pain, joint swelling, paralysis and pruritus. Sinomenine is a morphine-type alkaloid isolated from *Sinomenine Caulis* that contains four rings and presents an extensive spectrum of bioactivities, such as anti-inflammatory and immuno-suppressive activities (Tang et al., 2018).

Sinomenine is an active component of *Sinomenine Caulis*, which presents potent anti-inflammatory activity in several related diseases. Song et al. assessed the role of sinomenine in septic acute lung injury mice and investigated related mechanisms. As results shown, sinomenine significantly restored the lung injury and reduced IL-6 and TNF-α mRNA levels caused by cecum ligation and puncture; meanwhile, it also attenuated the pathological damage of colon and enhanced the intestine barrier integrity. Mechanically, sinomenine activated aryl hydrocarbon receptor/nuclear factor erythroid-2 related factor 2 (Nrf2) pathway and reshaped gut microbiota with increased Prevotellaceae UCG-001 and decreased *Escherichia-Shigella* (Song et al., 2021). Similarly, sinomenine also ameliorated the inflammation status in DSS-induced colitis by increasing *Bacteroidetes* but decreasing Proteobacteria, as well as inactivating NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome (Zhou et al., 2021). In addition to anti-inflammation, sinomenine is also an effective agent to resist morphine-induced addiction, which relies on the modulation of gut microbiota to some extent (Chen et al., 2020).

3.7. Vaccariae Semen

Vaccariae Semen, the dry mature seeds of *Vaccaria segetalis* (Neck.) Garcke, was attached to the selected auricular points on each ear. In TCM theory, *Vaccariae Semen* is mild in nature, bitter in flavor, with a meridian tropism in the liver and stomach. It

has multiple effects, including activating blood to promote menstruation, promoting milk secretion, reducing breast pain and inducing diuresis for treating stranguria. The indications of *Vaccariae Semen* include amenorrhea, dysmenorrhea, breast milk stoppage, acute mastitis and stranguria. However, pregnant women were advised to use the drug with caution. It is reported that saponins, cyclic peptides, flavonoids, polysaccharides, volatile oils, coumarins, lipids and fatty acids are the dominant constituents of *Vaccariae Semen* (Tian et al., 2021). Traditionally, *Vaccariae Semen* is widely used in practice due to its anti-inflammatory, anticancer and antioxidant activity, along with inhibition of apoptosis, dilation of blood vessels and promotion of lactation (Tian et al., 2021).

Hitherto, the modulation of *Vaccariae Semen* on gut microbial community is relatively scarce. As an active constituent of *Vaccariae Semen*, vaccarin markedly reduced LPS, TNF-α and IL-1β levels and the weight of epididymal fat in diabetic mice, while ameliorated intestinal barrier via increasing zonulaoccluden-1 (ZO-1), intercellular adhesion molecule-1(ICAM), mucin, Claudin-1, and Occludin expression. 16S rRNA gene sequencing data revealed that vaccarin enriched Rikenellaceae, Muribaculaceae and *Bacteroides*, but lowered *Lactobacillus* and *Desulfovibrio*, which partly contributed to the anti-diabetes effect of vaccarin (Sun et al., 2021). Further study should pay more attention to the modulation effect of other components of *Vaccariae Semen* on gut microbiota.

3.8. Viticis Negundo Folium

Viticis Negundo Folium, the fresh leaves of *Vitex negundo* L. var. *cannahifolia* (Sieb.et Zucc.) Hand.-Mazz., is widely used as Chinese folk medicine, especially in Fujian. In TCM theory, *Viticis Negundo Folium* is mild in nature, bitter and pungent in flavor, with a meridian tropism in the lung. It has the effects of expectorant, antitussive, relieving asthma. The indications of *Viticis Negundo Folium* are mainly used in coughs with excessive phlegm. Sometimes, fresh *Viticis Negundo Folium* are also decocted to treat acute gastroenteritis and prolonged dysentery. Enrichment of flavonoids, lignans, diterpenoids, iridoids and aromatic acids is its phytochemical characteristics. Its anti-oxidant, anticancer, anti-inflammatory, anti-diabetic and neuroprotective effects, as well as no toxic effects determine its extensive appliances in multiple diseases (Khan et al., 2018; Vinuchakkaravarthy, Kumaravel, Ravichandran, & Velmurugan, 2011).

Vitexin, also known as apigenin-8-C-glucoside, is a flavonoid found in *Viticis Negundo Folium*. It is reported that vitexin has potent anti-inflammatory activities, thus can be used in the treatment of colitis and high-fat diet induced brain inflammation. Li et al. reported that the levels of malondialdehyde (MDA), proinflammatory factor TNF-α and IL-1β were reduced by vitexin, whereas antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) were elevated (Li et al., 2021). Importantly, they found this beneficial effect of vitexin was partly achieved via up-regulating *Akkermansia*, *Lactobacillus*, *Romboutsia*, and down-regulating Lachnospiraceae_NK4A136_group, *norank_f_Eubacterium_coprostanoligenes_group*, *unclassified_f__Lachnospiraceae*, *Blautia*, *Colidextribacter* (Li et al., 2021). Moreover, vitexin could regulate the abundance of *Bacteroides*, *Helicobacter*, *Alistipes*, Lachnospiraceae_NK4A136_group, and Lachnospiraceae_UCG-006 to attenuate DSS-induced inflammation, intestinal barrier dysfunction, thereby can be regarded as an effective agent for colitis treatment (Zhang et al., 2022).

4. Gut microbiota-depended mechanism of MB-TCMs

According to the included 29 literatures, we found that MB-TCMs were mainly used to treat metabolic syndrome (10/29), intestinal inflammation (5/29), nervous system disease (4/29) and cardiovascular system disease (3/29) by modulating gut microbiota, and their common characteristics include significantly up-regulating the abundance of *Bacteroides*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, *Roseburia*, as well as down-regulating the abundance of *Helicobacter*, *Enterococcus*, *Desulfovibrio* and *Escherichia-Shigellav*. Interestingly, these studies also found eight MB-TCMs could modulate these microbiomes to generate several metabolites, such as SCFAs, BAs, TMAO, gamma-aminobutyric acid (GABA), 5-hydroxytryptamine (5-HT), indole and its derivatives, and LPS, to regulate corresponding signaling pathways to maintain human health. Although it cannot be proven that these pathways are unique mechanisms of MB-TCMs, it can be proposed that MB-TCMs can exert its efficacy through these pathways. Therefore, we described the potential mechanism of action of MB-TCMs on gut microbiota (Fig. 1).

4.1. SCHAs-depended mechanism

In human intestine, gut microbiota could metabolize insoluble fiber to generate SCFAs, including acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid, valeric acid. It is proved that propionate and butyrate could strongly promote the production of glucagon-like peptide-1 (GLP-1) and peptide-YY via activating G-protein receptor 41/G-protein receptor 43 (GPR41/GPR43) (Christiansen et al., 2018; Larraufie et al., 2018). GLP-1 and PYY are of great value in anti-diabetes and anti-obesity, indicating the enrichment of SCFA-producing bacteria, such as *Lactobacillus* and *Bifidobacterium*, *Akkermansia*, *Roseburia*, *Bacteroides*, is highly contributed to the metabolic regulation effect of mild-natured and bitter-flavored TCMs. In addition to improving metabolism, the elevating of SCFAs is also conducive to the immunomodulation and anti-inflammation. Yang et al. revealed that SCFA also obviously stimulated $CD4^+$ T cells and innate lymphoid cells to secrete interleukin-22 (IL-22) via activating GPR41 and inactivating histone deacetylase (Yang et al., 2020), thus could prevent human from colitis-caused intestinal injury.

4.2. Bas-depended mechanism

Primary BAs are synthesized in liver and then secreted into the intestine to transform into secondary BAs via gut microbiota. Concomitantly, gut microbiota-owned bile salt hydrolase (BSH), an enzyme hydrolyzed glycine and/or taurine conjugated bile acid into free bile acid and amino acid residues, determined the activation or inactivation of farnesoid X receptor (FXR) signaling (Yang & Wu, 2022). *Lactobacillus* and *Bifidobacterium* are two genera with the abundant BSH, implying the increasing of those two genera by MB-TCMs might mediate their pharmacological effects via FXR signaling pathway. It is reported that *Lactobacillus* strains, such as *L. reuteri* and *L. plantarum*, could activate FXR to promote fibroblast growth factor 15/19 (FGF15/19) production, which then combine with hepatic fibroblast growth factor receptor 4 (FGFR4) and small heterodimer partner (SHP) to suppress hepatic cholesterol 7a-hydroxylase (CYP7A1) and oxysterol 7a-hydroxylase (CYP7B1) expression, thereby attenuating hepatic steatosis and hyperlipidemia (Ye et al., 2022). Simultaneously, overexpression of liver sterol 12a-hydroxylase (CYP8B1) will potentiate intestinal injury, suggesting activation of liver FXR and inhibition of CYP8B1 expression could alleviate colitis (Chen et al., 2022).

4.3. Indole and its derivatives-depended mechanism

Metabolites in the tryptophan metabolic process will regulate several inflammatory conditions, such as neuroinflammation, obesity, diabetes, colitis and atherosclerosis. Indole and its derivatives

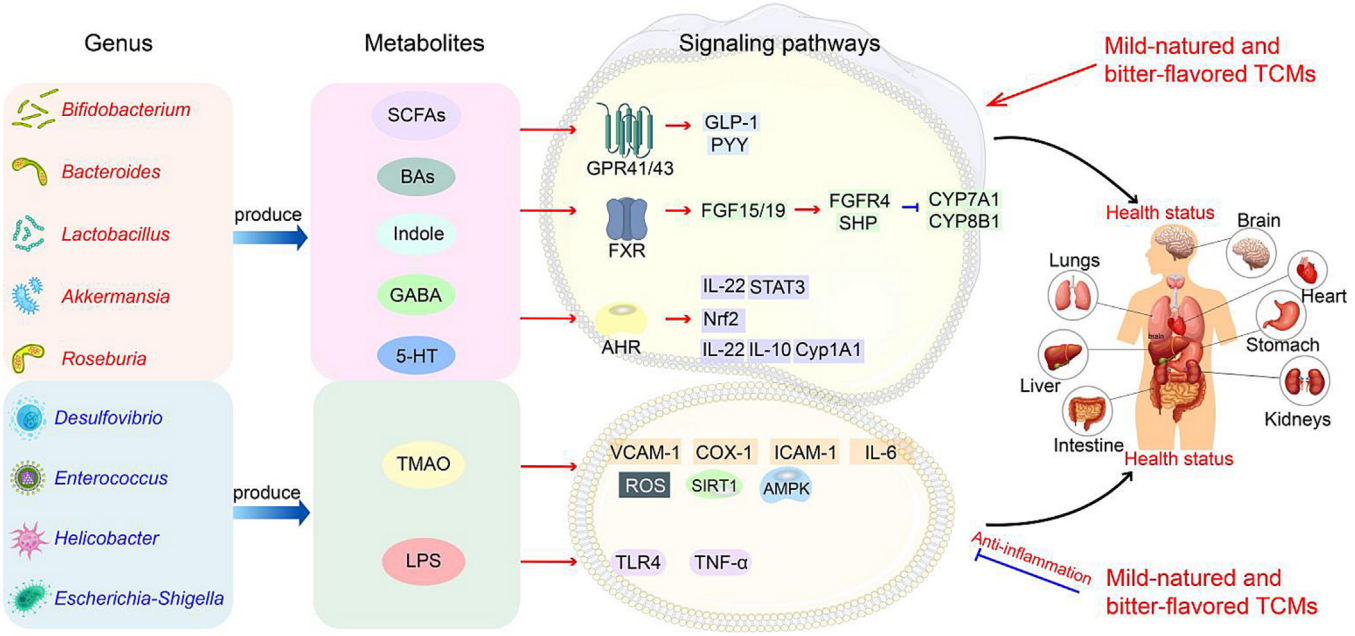

Fig. 1. Gut microbiota-depended potential mechanism of MB-TCMs.

are important metabolites in tryptophan metabolism pathway with potent activation effect for aryl hydrocarbon receptor (AhR). Singh et al. found activation of AhR-nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent pathway could resist inflammation in colitis mice, along with regulate innate and adaptive immune balance (Singh et al., 2022). Similarly, the therapeutic effect of baicalein on colitis also depends on the activation of AhR/IL-22 pathway (Li et al., 2022b). Gut microbiota is a key factor mediated the tryptophan metabolism. One study demonstrated that combined consumption of *Lactobacillus plantarum* KLDS 1.0386 and tryptophan could enhance the level of indole-3-acetic acid (IAA), further stimulate the expression of AhR mRNA to activate interleukin-22/signal transducer and activator of transcription 3 (IL-22/STAT3) signaling pathway, which is beneficial to the treatment of ulcerative colitis (Shi et al., 2020). Two strains from *Bifidobacterium bifidum* also maintained the integrity of intestinal barrier and promoted anti-inflammatory activity to alleviate DSS-induced colitis based on the AhR pathway (Cui et al., 2022). Moreover, *Akkermansia* could notably stimulate AhR targeted genes expression, such as Cytochrome P450, family 1, subfamily A, and polypeptide 1 (CYP1A1), IL-10 and IL-22, implying that *Akkermansia* could activate AhR signaling to attenuate colonic inflammation (Gu et al., 2021). In recent studies, *Akkermansia* is enriched in almost all mild-natured and bitter-flavored TCMs, most of which can also increase the abundance of *Lactobacillus* and *Bifidobacterium*. (Gu et al., 2021).

4.4. Neurotransmitter-depended mechanism

Neurotransmitters, such as GABA and 5-HT, play a crucial role in early neurodevelopment, regulating processes like cell proliferation, neural outgrowth and apoptosis, and maintaining neurochemical balance. It is reported that a great mounting of gut microbiota has an ability to produce GABA, thus participating in regulating nervous system diseases via the gut-brain axis. For example, genus of *Lactobacillus* (*L. brevis*, *L. paracasei*, *L. delbrueckii* subsp. *Bulgaricus*, *L. lactis*, *L. plantarum*), *Bifdobacterium* (*B. dentium*, *B. adolescentis*), and *Bacteroides* (*B. thetaiotaomicron*) could produce GABA, further regulate GABA receptors GABAAα2 and GABAB1b in the brain, and thereby participating in the amelioration of depression and anxiety-like behaviour (Barrett, Ross, O'Toole, Fitzgerald, & Stanton, 2012; Duranti et al., 2020; Otaru et al., 2021; Siragusa et al., 2007). Except for GABA, 5-HT is another neurotransmitter, about 90 % of them are synthesized in intestinal chromaffin cells via the enzyme tryptophan hydroxylase-1 (TTHP-1). It is reported that gut microbiota-derived metabolite SCFAs could modulate the secretion of 5-HT in a GPR-41/43-depended manner, suggesting that the SCFAs-producing bacteria enriched by MB-TCMs, such as *Lactobacillus* and *Bifidobacterium*, *Akkermansia*, *Bacteroides*, could also influence the 5-HT level, which is associated with the progress of depression. Additionally, 5-HT also possessed the ability to inhibit the generation of pro-inflammatory cytokines, such as IL-6 and TNF-α (Kubera, Maes, Kenis, Kim, & Lason, 2005), thereby involving in the alleviation of inflammatory status of brain.

4.5. TMAO depended pathway

TMAO is a metabolite stemmed from dietary choline or carnitines via gut microbial TMA lyases cntA/B, yeaW/X, and cutC/D (Cai et al., 2022), which gradually becomes a convincing bridge to mediate the development of cardiovascular diseases. Mechanically, TMAO could stimulate the expression of vascular cell adhesion molecule-1 (VCAM-1) and some inflammatory markers like cyclooxygenase 2 (COX2), IL-6, E-selectin, and intercellular adhesion molecule-1 (ICAM-1), along with activate mitogen-activated protein kinase (MAPK), extracellular signal-related kinase (Erk), and nuclear factor-κB (NF-κB) signaling cascade, further increase arterial burden and lead to the occurrence of atherogenesis (Ma et al., 2017; Seldin et al., 2016). Additionally, TMAO also markedly promotes inflammation by regulating cellular reactive oxygen species (ROS) levels and modulating complex signaling pathways related to adenosine monophosphate-activated protein kinase (AMPK) and Sirtuin1 (SIRT1) (Zhou et al., 2022). Both *Enterococcus* and *Desulfovibrio* contain *cutC/D* genes, and both *Shigella* and *Escherichia* contain *cntA/B* and *yeaW/X* gene, suggesting these genera could encode corresponding TMA-lyase to generate TMAO (Cai et al., 2022). Intriguingly, these genera are reduced by mild-

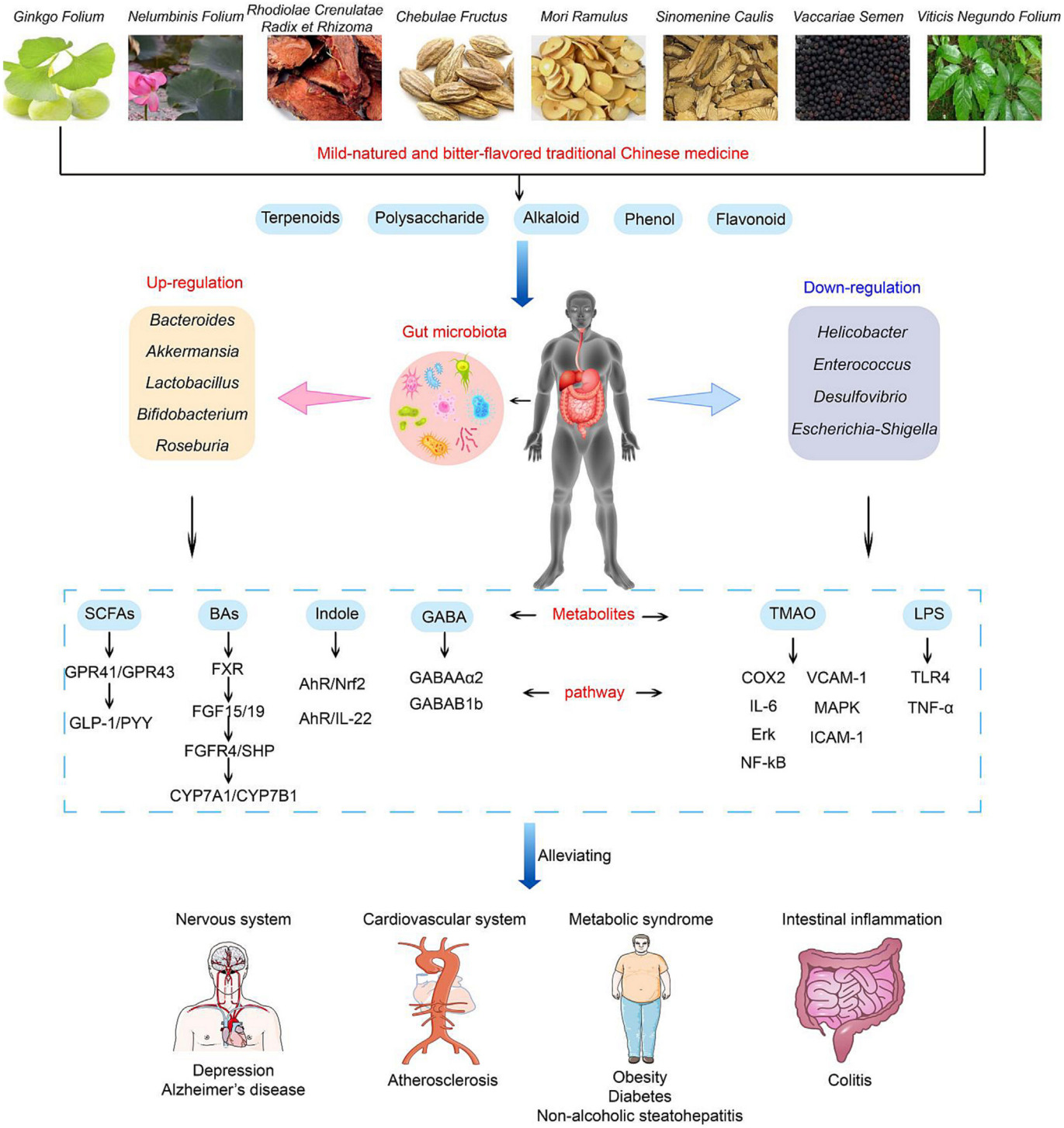

Fig. 2. TCMs-gut microbiota-metabolite-signaling pathway-diseases axis. MB-TCMs could modulate the structure and composition of gut microbiota, futher affect their metabolites, which regulate related signaling pathways to ameliorate symptoms of human disease.

natured and bitter-flavored TCMs, which result in their anti-atherogenesis effect (Kubera, Maes, Kenis, Kim, & Lason, 2005).

4.6. LPS-related pathway

LPS, produced by some harmful gut bacteria, is notoriously known to induce systemic inflammation and damage intestine, cardiovascular system and nervous system. Several studies have demonstrated that acute LPS treatment significantly promoted the protein expression of toll-like receptor 4 (TLR4) and TNF-α in paraventricular nucleus, and leaded to the activation of microglia (Masson et al., 2015; Sandiego et al., 2015), displaying the pro-inflammatory, sympathetic activating, and neuroinflammatory effects of LPS. Hence, the down-regulation of LPS-producing bacteria is a promising approach to attenuate the systemic inflammation. In this review, we found MB-TCMs notably decreased the relative abundance of LPS-producing bacteria, such as *Escherichia-Shigella, Helicobacter* and *Desulfovibrio* (Masson et al.,

2015; Sandiego et al., 2015). Simultaneously, MB-TCMs enriched bacteria *Akkermansia* could decrease the fecal and circulate LPS concentration. Both of these beneficial effects contributed to the pharmacological activities of MB-TCMs (Masson et al., 2015; Sandiego et al., 2015).

5. Limitations of present study

Owing to its wide clinical practice, the property theory of TCM has garnered immense interest, however, the modern interpretation of TCM property theory is generally weak. Therefore, taking MB-TCMs as an example, the present review identified the characteristics of gut microbiota community after these TCMs treatment. However, based on our investigation, we found less studies reported the modulative effect of MB-TCMs on gut microbiota. Hence, only eight TCMs are included in present review, which resulted in the unrepresentative conclusion. Additionally, the TCM formulas are usually used to treat disease in clinical practice. So there is limited researches and reports on single TCMs, leading to the scarce clinical effects and mechanisms of the corresponding TCM. Although these limitations are appeared in this review, we proposed a novel perspective that the TCM property theory may be interpreted by the modern findings in gut microbiome.

6. Conclusion

With the development of high-throughput sequencing technology, culturomics approach, coupled with bio-informatics analysis, great progress has been achieved in elucidating the mechanism of how gut microbiota regulate human health and how to mediate drug's efficacy (Li, Zhou, Zhao, & Jia, 2009). Increasing studies have revealed that gut microbiota is an essential target of TCMs, which exert their medicinal effects by modulating the composition and function of gut microbiota (Gong et al., 2020). According to a systematic review, we found that MB-TCMs could improve cardiovascular disease, nervous system disease, metabolic syndrome and intestinal inflammation by increasing the abundance of beneficial microbes (*Bacteroides, Akkermansia, Lactobacillus, Bifidobacterium* and *Roseburia*) and decreasing the abundance of harmful microbes (*Helicobacter, Enterococcus, Desulfovibrio* and *Escherichia-Shigellav*). On the one hand, these beneficial microbes are associated with protective metabolites, such as SCFAs, BAs, 5-HT, indole and GABA, which may have the potential to modulate concentrations of neurotransmitters, regulate endocrine signals, alleviate the systemic inflammation status and improve lipid and glucose metabolism through GRP41/43, FXR and AHR signaling pathways. On the other hand, MB-TCMs lower harmful microbes to inhibit the generation of proinflammatory factors including TAMO and LPS, which may affect human health through the ROS, VCAM-1 and TLR4 signaling pathways (Fig. 2).

Altogether, we proposed a gut microbiota-dependent biological indicator for MB-TCMs and established the TCMs-gut microbiota-signaling pathway-metabolite-diseases axis for their clinical application and drug research. Recently, some advanced studies have also supported the gut microbiota as an effective indicator of the response index to the natures and flavors of TCMs. The bitter taste receptors (TAS2Rs) are expressed throughout the gastrointestinal tract, respond to microbial-quorum sensing molecules, and regulate gut microbiota composition and its metabolites (Vascellari et al., 2020). The bitter components extracted from bitter flavored TCM, such as salicin, amarogentin, cascarillin, flavone and quinine, could treat many diseases of the cardiovascular, respiratory, gastrointestinal, bladder and uterine systems by activating TAS2Rs (Luo et al., 2019). Therefore, TAS2Rs are important targets to elucidate the potential interaction mechanism between TCMs and gut microbiome. In the future, cross-sectional studies could find the special characteristics of MB-TCMs through comparing the different impact with different mild and flavored TCMs. In addition, longitudinal studies could continuously observe gut microbial changes in MB-TCMs and create more rigorous evidence. TCM experts always highlight that elucidating the scientific connotation of TCM theory is the critical basement for developing modern TCM. Our review might just suit this purpose to provide new insight into the study of TCM medicinal theory.

CRediT authorship contribution statement

Wenquan Su: Writing – original draft, Formal analysis, Visualization, Data curation. **Yanan Yang:** Writing – original draft, Formal analysis, Visualization, Data curation. **Xiaohui Zhao:** Investigation. **Jiale Cheng:** Investigation. **Yuan Li:** Formal analysis, Investigation. **Shengxian Wu:** Conceptualization, Resources, Supervision, Funding acquisition, Writing – review & editing. **Chongming Wu:** Conceptualization, Resources, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2023.08.001.

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