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REVIEW

Rhubarb: Traditional Uses, Phytochemistry, Multiomics-Based Novel Pharmacological and Toxicological Mechanisms

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Abstract: Traditional Chinese medicines (TCMs) are practiced in clinical and healthcare settings and are widely employed as essential therapies for intervening diverse refractory illnesses. Rhubarb, which is prescribed as the root and rhizome of *Rheum officinale* Baill. *Rheum tanguticum* Maxim. ex Balf. and *Rheum palmatum* L. has been widely recognized as an important natural medicine for the management of cardiovascular diseases, cancer, and kidney disorders. The available information on traditional uses, phytochemistry, multiomics-based pharmacological and toxicological studies of rhubarb species and their components including anthraquinones, such as emodin, rhein, chrysophanol, aloe-emodin and physcion as well as their glycoside derivatives published from 2010 to 2025 was searched by several electronic database such as Web of Science, PubMed, Springer, ScienceDirect, Scopus, Google Scholar, CNKI, etc. Increasing evidence has indicated that rhubarb contain various bioactive compounds, such as anthraquinones, anthrones, stilbenes, and saccharides. Numerous studies have demonstrated that rhubarb exerts a broad spectrum of pharmacological effects, including anticardiovascular, anticancer, hepatoprotective, renoprotective, pulmoprotective, antidiabetic, anti-colitis, and antibacterial activities. In this review, traditional applications and major components of rhubarb are presented, and their diverse pharmacological and toxicological effects are discussed. Novel multiomics-based molecular mechanisms of the treatment of various diseases of rhubarb have been highlighted. Key challenges, such as rhubarb effect on cardiorenal syndrome and cardiovascular-kidney-metabolic syndrome, are also addressed. Current evidence suggests that rhubarb is a promising candidate drug for the prevention and treatment of various diseases. Mounting publications show that targeting multiomics-related targets are a promising therapeutic strategy in a myriad of refractory diseases. Rhubarb improves various diseases by reshaping microbial dysbiosis, restoring aberrant expression of ncRNAs and regulating maladaptive metabolite disorder that may provide new therapeutic targets for treatment of various diseases of rhubarb. This review is expected to development of rhubarb-derived anthraquinones as novel therapeutic agents for clinical applications in the future.

Keywords: rhubarb, gut microbiota, long non-coding RNAs, metabolome, anticardiovascular disease, anticancer, renoprotective activity, cardio-renoprotective effect, hepatotoxicity and nephrotoxicity

Introduction

Traditional Chinese medicines (TCMs) have accumulated extensive clinical experience and are recognized as essential therapeutic strategies for the prevention and treatment of various diseases and physiological conditions.[1–3] Rhubarb (*Rhei Radix* et Rhizome) is a TCM primarily used as a strong purgative to remove pathogenic heat or toxins from the body.[4,5] In the *Chinese Pharmacopoeia*, rhubarb is prescribed as the root and rhizome of *Rheum officinale* Baill. *Rheum tanguticum* Maxim. ex Balf., and *Rheum palmatum* L.[6] Rhubarb has also been officially listed in the *European Pharmacopoeia* and *Japanese Pharmacopoeia*.

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Several unofficial rhubarb species have been identified, although they display much weaker purgative effects than the official species, largely due to the absence of sennosides and their relatively low anthraquinone content. According to previous studies, 22 medicinal plants related to rhubarb have been used as folk medicines in Chinese Qinghai and Sichuan provinces as well as in the Xinjiang Uygur and Tibet Autonomous Regions.[7] The major components of rhubarb include anthraquinones, anthrones, stilbenes, tannins, butyrophenones, and saccharides[8,9] (Figure 1). More than 100 phenolic compounds have been identified, including sennosides, stilbenes, anthraquinones, glucose gallates, naphthalenes, and catechins.[10] Rhubarb exhibits diverse biological effects, including anticancer, anti-inflammatory, antifibrotic, and antibacterial activities (Figure 2).

In this review, the traditional uses and major components of rhubarb are presented, and their diverse pharmacological and toxicological effects are discussed. Novel multiomics-based molecular mechanisms underlying the therapeutic effects of rhubarb are also highlighted. Furthermore, key challenges, such as the role of rhubarb in cardiorenal syndrome, are addressed.

Traditional Uses

Rhubarb (*Polygonaceae*) was first documented in the classic herbal text *Sheng Nong's Herbal Classic*.[11] Traditionally, rhubarb has been described as effective for "eliminating extensive accumulation with catharsis", "dampening heat and purging fire", "cooling blood and detoxifying", "removing blood stasis and obstructions", and "disinhibiting dampness to ameliorate jaundice".[12] Rhubarb is considered as the first-line treatment for stagnation and constipation in clinical practice. Its primary cathartic components are sennosides and anthraquinone derivatives.[13] Additionally, tannins are believed to cool the blood, flavonoids activate blood circulation, and free anthraquinones clear heat, remove dampness, and reduce jaundice.

Pharmacological differences between raw and steamed rhubarb have been reported. A previous study demonstrated that chrysophanol and emodin exhibited higher bioavailability in steamed rhubarb than in raw rhubarb.[14] Traditionally, prepared rhubarb is obtained by steaming raw rhubarb with wine. This preparation process reduces the purgative effect while enhancing its efficacy in alleviating pathogenic heat and toxins, particularly in the treatment of noxious heat–blood stasis syndrome. Rhubarb can also be stir-fried to diminish its purgative effect, when such an action is considered a side effect.

Chemical Components

Anthraquinone

Among anthraquinones, the chemical structure of 9,10-anthraquinone was identified as the most abundant. The anthraquinone content in different rhubarb species ranges from 3% to 5%.[15] These compounds can be classified into free and bound types (Figure 1).

Anthranone

Anthranones, including palmatal dianthranones A–C, rhubarb dianthranones A–C, and sennosides A–F, are considered the principal purgative components of rhubarb. As the reduced derivatives of anthraquinones, anthranones are the main active constituents of rhubarb-derived medicinal preparations. To date, 29 anthranones have been identified (Table 1 and Figure 1). These natural compounds are derived primarily from plants and microorganisms. Owing to their diverse and unique structural characteristics, anthranones have been shown to exert various biological activities, including immunoregulatory, antitumor, antibacterial, antioxidant, and anti-inflammatory effects.[16] Sennosides have demonstrated therapeutic potential in the prevention and treatment of constipation, diabetes, obesity, fatty liver disease, and cancer.[17] After administration, sennosides are metabolized to anthraquinones in vivo and exhibit strong laxative effects. In addition, earlier research identified anthranone esters (revandchinone-1 and revandchinone-2) and anthranone ethers (revandchinone-3 and revandchinone-4), which possess both antibacterial and antifungal activities.[18]

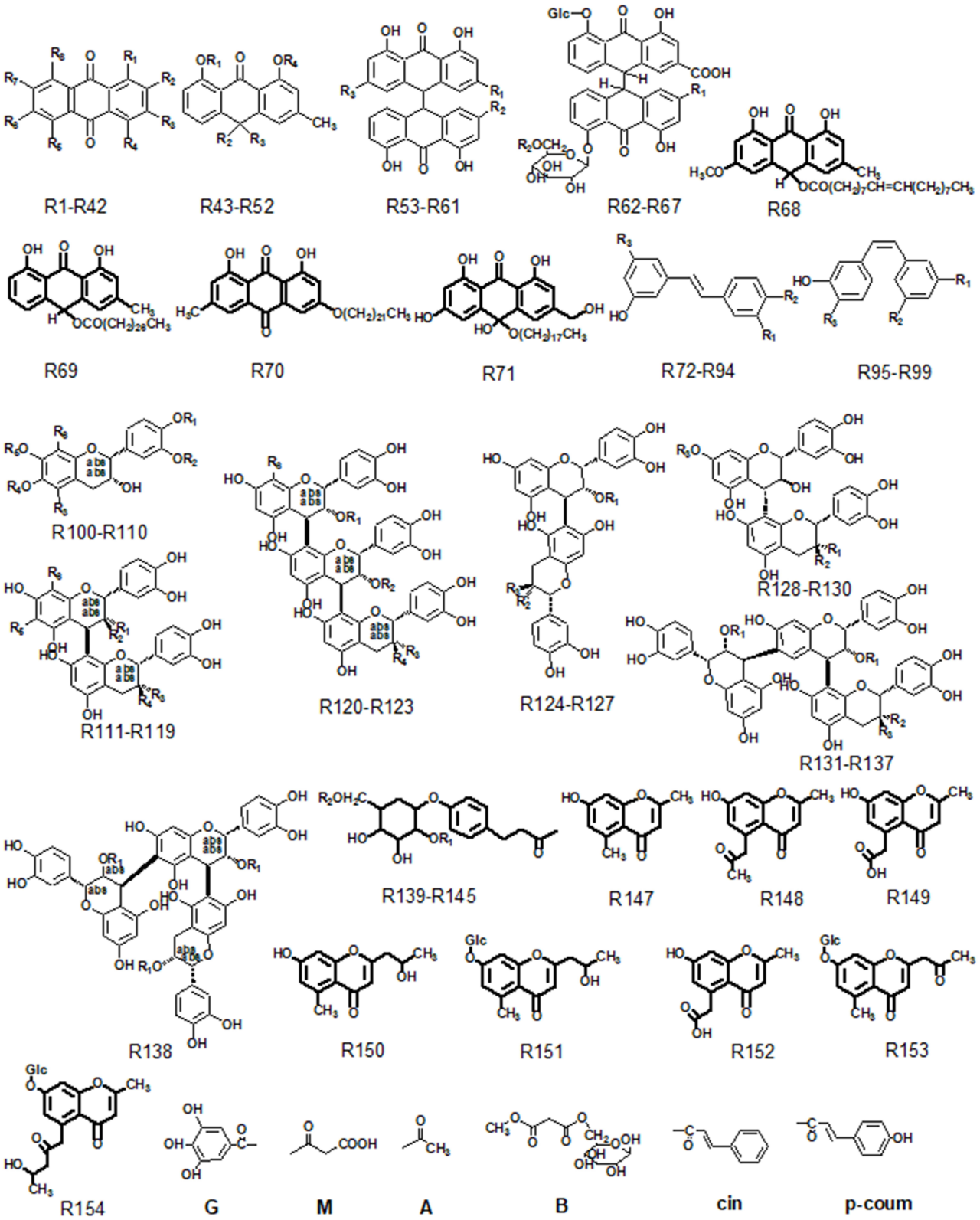

Figure 1 Structure of the main rhubarb compounds.

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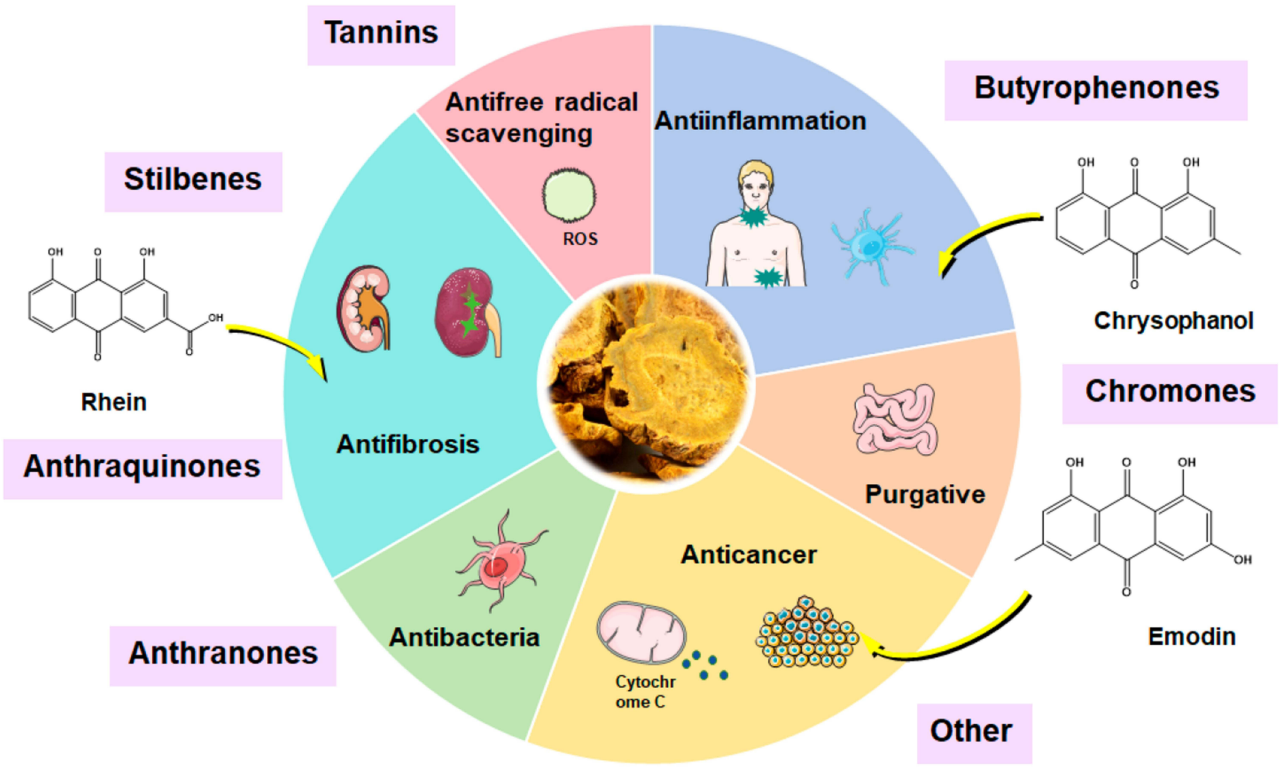

Figure 2 Main components and pharmacological effects of rhubarb. Rhubarb contains various active components and has a wide range of pharmacological effects.

Stilbene

Stilbenes, another key component of rhubarb, have been reported to possess strong free radical-scavenging and anti-aging properties.[21] The primary active stilbenes were rhapontigenin and piceatannol (Table 2 and Figure 1). Among

Table 1 Main Anthrones of Rhubarb

No.	Compounds	Substituents	Ref(s)
R43	10-hydroxycascaroside C	R_1=R_2=Glc R3=OH R_4=H	[19]
R44	10-hydroxycascaroside D	R_1=R_3=Glc R_2=OH R_4=OH	[19]
R45	10r-chrysaloin1-O-β-D-glucopyranoside	R_1=R_2=H R_3=R_4=Glc	[19]
R46	Cascaroside C	R_1=R_2=Glc R_3=R_4=H	[19]
R47	Cascaroside D	R_1=R_3=Glc R_2=R_4=H	[19]
R48	Cassialoin	R_1=R_4=H R_2=OH R_3=Glc	[19]
R49	Rheinoside A	R_1=R_2=Glc R_3=OH R_4=H	[20]
R50	Rheinoside B	R_1=R_3=Glc R_2=OH R_4=H	[20]
R51	Rheinoside C	R_1=R_2=Glc R_3=R_4=H	[20]
R52	Rheinoside D	R_1=R_3=Glc R_2=R_4=H	[20]
R53	Palmidin A	R_1=CH_3 R_2=CH_2OH R_3=OH	[20]
R54	Palmidin B	R_1=CH3 R_2=CH_2OH R_3=H	[20]
R55	Palmidin C	R_1=R_2=CH_3 R_3=OH	[20]
R56	Rheidin A	R_1=CH_3 R_2=COOH R_3=OH	[20]
R57	Rheidin B	R_1=CH_3 R_2=COOH R_3=H	[20]
R58	Rheidin C	R_1=CH_3 R_2=COOH R_3=OCH_3	[20]
R59	Sennidin A	R_1=COOH R_2=COOH R_3=H	[20]

(*Continued*)

Table 1 (Continued).

No.	Compounds	Substituents	Ref(s)
R60	Sennidin B	R_1=COOH R_2=COOH R_3=H	[20]
R61	Sennidin C	R_1=COOH R_2=CH_2OH R_3=H	[20]
R62	Sennoside A	R_1=COOH R_2=H	[20]
R63	Sennoside B	R_1=COOH R_2=H	[20]
R64	Sennoside C	R_1=CH_2OH R_2=H	[20]
R65	Sennoside D	R_1=CH2OH R_2=H	
R66	Sennoside E	R_1=COOH R_2=oxalyl	
R67	Sennoside F	R_1=COOH R_2=oxalyl	
R68	Revandchinone-1		[18]
R69	Revandchinone-2		[18]
R70	Revandchinone-3		[18]
R71	Revandchinone-4		[18]

Abbreviation: Glc, glucose.

Table 2 Main Stilbenes of Rhubarb

No.	Compounds	Substituent	Ref(s)
R72	Rhapontigenin	R_1=R_3=OH R_2=OCH_3	[20]
R73	Rhapontigenin-3'-O-β-D-glucopyranosid	R_1=OGlc R_2=OCH_3 R_3=OH	[24]
R74	Isorhapontigenin	R_1=OCH_3 R_2=R_3=OH	[25]
R75	Rhapontin	R_1=OH R_2=OCH_3 R_3=OGlc	[26]
R76	Rhapontin-2''-O-gallate	R_1= OH R_2=OCH_3 R_3=OGlc-(2→2)-OG	[22]
R77	Rhapontin-6''-O-gallate	R_1= OH R_2=OCH_3 R_3=OGlc-(6→6)-OG	[22]
R78	Rhapontin-2''-O-p-coumarate	R_1= OH R_2=OCH_3 R_3=OGlc-Op-coum	[22]
R79	Isorhapontin	R_1=OCH_3 R_2=OH R_3=OGlc	[27]
R80	4'-Methoxyresveratrol	R_1=H R_2=OCH_3 R_3=OH	[28]
R81	Deoxyrhaponticin	R_1=H R_2=OCH_3 R_3=OGlc	[29]
R82	Deoxyrhaponticin-6''-O-gallate	R_1=H R_2=OCH_3 R_3=OGlc-(6→6)-OG	[29]
R83	Piceatannol	R_1=R_2=R_3=OH	[28]
R84	Piceatannol-3-O-β-D-glucopyranoside	R_1=R_2=OH R_3=OGlc	[30]
R85	Piceatannol-3'-O-β-D-glucopyranoside	R_2=R_3=OH R_1=OGlc	[30]
R86	Piceatannol-4'-O-β-D-glucopyranoside	R_1=R_3=OH R_2=OGlc	[31]
R87	Piceatannol-3'-O-β-D-xylopyranoside	R_1=O-xyl R_2=R_3=OH	[30]
R88	Piceatannol-3'-O-β-D-(6''-O-galloyl)-glucopyranoside	R_1=OGlc-(6→6)-G R_2=R_3=OH	[30]
R89	Piceatannol-4'-O-β-D-(6''-O-galloyl)-glucopyranoside	R_1=R_3=OH R_2=OGlc-(6→6)-OG	[10]
R90	Resveratrol	R_1=H R_2=R_3=OH	[24]
R91	Resveratrol-3-O-β-D-glucopyranosie	R_1=H R_2=OH R_3=OGlc	[24]
R92	Resveratrol-4'-O-β-D-glucopyranoside	R_1=H R_2=OGlc R_3=OH	[10]
R93	Resveratrol-4'-O-β-D-(6''-O-galloyl)-glucopyranoside	R_1=H R_2= OGlc-(6→6)-OG R_3=OH	[24]
R94	Resveratrol-4'-O-β-D-(2''-O-galloyl)-glucopyranoside	R_1=H R_2= OGlc-(2→2)-OG R_3=OH	[24]
R95	Cis-3,5,3'-trihydroxyl-4''-methoxystibene	R_1=R_3=OH R_2=OCH_3	[32]
R96	Cis-3,5,3'-trihydroxyl-4'-methoxystibene-3-O-β-D-glucopyranoside	R_1=OH R_2=OCH_3 R_3=OGlc	[32]
R97	Cis-3,5-dihydroxyl-4'-methoxystibene-3-O-β-D-glucopyranoside	R_1=H R_2=OCH_3 R_3=OGlc	[33]
R98	Cis-3,5,3'-trihydroxyl-4'-methoxystibene-3-O-β-D-(2''-O-galloyl)-glucopyranoside	R_1=OH R_2=OCH_3 R_3=OGlc-(2→2)-OG	[32]
R99	Cis-3,5,3'-trihydroxyl-4'-methoxystibene-3-O-β-D-(6''-O-galloyl)-glucopyranoside	R_1=OH R_2=OCH_3 R_3=OGlc-(6→6)-OG	[32]

Abbreviations: Glc, glucose; OG, O-gallate; O-glc, O-glucose; Op-coum, O-p-coumarate.

them, two stilbene glucoside gallates, rhaponticin 2″-O-gallate and rhaponticin 6″-O-gallate, have shown inhibitory effects on nitric oxide production by lipopolysaccharide-activated macrophages.[22] Furthermore, rhapontigenin has been shown to scavenge reactive oxygen species (ROS), 1,1-diphenyl-2-picrylhydrazyl radicals, and hydrogen peroxide.[23]

Tannin

Tannins are among the most important constituents of rhubarb. Two major types of tannins, hydrolyzable tannins and condensed tannins, have been identified. The principal monomers included gallic acid and D-catechins. Tannins are considered the bioactive components responsible for the styptic and constipating properties.[34] Notably, the purgative activity of rhubarb increased significantly when tannin content was reduced. Forty tannins have been identified in rhubarb (Table 3 and Figure 1).[35] Earlier studies identified several tannin compounds in rhubarb, including gallic acid, galloyl glucose, di-O-galloyl-glucose, glucopyranosyl-galloyl-glucose, coumaroyl-O-galloyl-glucose, catechin trimers, catechin-glucopyranoside, and catechin gallate.[36]

Table 3 Main Tannins of Rhubarb

No.	Compounds	Substituent	Ref(s)
R100	(+)-Catechin	R_1=R_2=R_3=R_4=R_5=R_6=H	[24]
R101	(+)-Catechin 3-O-β-D-glucopyranoside	R_1=R_2=R_4=R_5=R_6=H R_3=Glc	[24]
R102	(+)-Catechin 7-O-β-D-glucopyranoside	R_1=R_2=R_3=R_4=R_6=H R_5=Glc	[24,35]
R103	(+)-Catechin 3'-O-β-D-glucopyranoside	R_1= Glc R_2=R_3=R_4=R_5=R_6=H	[24,35]
R104	(+)-Catechin 4'-O-β-D-glucopyranoside	R_1=R_3=R_4=R_5=R_6=H R_2=Glc	[10,24]
R105	(+)-Catechin 7,3'-di-O-β-D-glucopyranoside	R_1=R_5=Glc R_2=R_3=R_4=R_6=H	[10,24]
R106	(+)-Catechin 5,3'-di-O-β-D-glucopyranoside	R_1=R_3=Glc R_2=R_4=R_5=R_6=H	[10]
R107	(+)-Catechin 5,4'-di-O-β-D-glucopyranoside	R_1=R_4=R_5=R_6=H R_2=R_3=Glc	[10]
R108	(+)-Catechin 3',4'-di-O-β-D-glucopyranoside	R_1=R_2=Glc R_3=R_4=R_5=R_6=H	[10]
R109	(+)-Catechin 8-C-β-D-glucopyranoside	R_1=R_2=R_3=R_4=R_5=H R_6=Glc	[10]
R110	(+)-Catechin 6-C-β-D-glucopyranoside	R_1=R_2=R_3=R_5=R_6=H R_4=Glc	[10]
R111	Procyanidin B-1	R_1=R_4=OH R_2=R_3=R_5=R_6=H	[24]
R112	Procyanidin B-1 3-O-gallate	R_1=OG R_2=R_3=R_5=R_6=H, R_4=OH	[24]
R113	Procyanidin B-1 8-C-β-D-glucopyranoside	R_1=R_4=OH R_2=R_3=R_5=H R_6=Glc	[37]
R114	Procyanidin B-1 6-C-β-D-glucopyranoside	R_1=R_4=OH R_2=R_3=R_6=H R_5=Glc	[37]
R115	Procyanidin B-2	R_1=R_3=R_4=OH R_2=R_5=R_6=H	[37]
R116	Procyanidin B-2 3'-O-gallate	R_1=OH R_2=R_4=R_5=R_6=H R_3=OG	[37]
R117	Procyanidin B-2 3-3'-di-O-gallate	R_1=R_3=OG R_2=R_4=R_5=R_6=H	[24]
R118	Procyanidin B-2 8-C-β-D-glucopyranoside	R_1=R_3=OH R_2=R_4=R_5=H R_6=Glc	[37]
R119	Procyanidin B-2 6-C-β-D-glucopyranoside	R_1=R_3=OH R_2=R_4=R_6=H R_5=Glc	[37]
R120	Procyanidin C-1 3',3''-di-O-gallate	R_1=R_4=H R_2=G R_3=OG	[37]
R121	Procyanidin C-1 3,3',3''-tri-O-gallate	R_1=R_2=G R_3=OG R_4=H	[37]
R122	Epicatechin-(4β-8)-epicatechin-(4β-8)-catechin	R_1=R_2=R_3=H R_4=OH	[38]
R123	3-O-galloylepicatechin-(4β-8)-3-O-galloylepicatechin-(4β-8)-catechin	R_1=R_2=G R_3=H R_4=OH	[24]
R124	Procyanidin B-7	R_1=R_2=H	[37]
R125	Procyanidin B-7 3-O-gallate	R_1=G R_2=H	[24]
R126	Procyanidin B-5 3',3''-di-O-gallate	R_1=G R_2=OG	[24]
R127	Procyanidin B-5	R_1=R_3=H R_2=OH	[37]
R128	3-O-galloylepicatechin-(4β-6)-3-O-galloylepicatechin-(4β-8)-3-O-galloylepicatechin	R_1=G R_2=OG R_3=H	[24]
R129	Epicatechin-(4β-6)-epicatechin-(4β-8)-epicatechin	R_1=R_3=H R_2=OH	[38]
R130	3-O-galloylepicatechin-(4β-6)-3-O-galloylepicatechin-(4β-8)-catechin	R_1=G R_2=H R_3=OH	[24]
R131	Procyanidin B-3	R_1=R_3=H R_2=OH	[37]
R132	Procyanidin B-3 7-O-β-D-glucopyranoside	R_1=H R_2=OH R_3=Glc	[37]
R133	Procyanidin B-4	R_1=OH R_2=R_3=H	[37]
R134	Procyanidin B-4 3'-O-gallate	R_1=OG R_2=R_3=H	[37]
R135	3-O-galloylepicatechin-(4β-6)-3-O-galloylepicatechin-(4β-6)-3-O-galloylepicatechin	R_1=G	[24]
R136	Epicatechin-(4β-6)-epicatechin-(4β-6)-epicatechin	R_1=H	[38]
R137	3-O-galloylepicatechin-(4β-8)-3-O-galloylepicatechin-(4β-6)-catechin	R_1=G	[24]
R138	Epicatechin-(4β-8)-epicatechin-(4β-6)-catechin		[38]

Abbreviations: Glc, glucose; OG, O-gallate.

Table 4 Main Butyrophenones and Chromones of Rhubarb

No.	Compounds	Substituent	Ref(s)
R139	lindleyin	R_1= H R_2=G	[24]
R140	Isolindleyin	R_1=G R_2=H	[24]
R141	4-(4′-hydroxyphenyl)-2-butanone-4′-O-β-D-glucopyranoside	R_1=R_2=H	[24]
R142	4-(4′-hydroxyphenyl)-2-butanone-4′-O-β-D-(2″,6″-O-cinnamoyl)-glucopyranoside	R_1= R_2=G	[24]
R143	4-(4′-hydroxyphenyl)-2-butanone-4′-O-β-D-(2″-O-galloyl-6″-O-cinnamoyl)-glucopyranoside	R_1=G R_2=cin	[24]
R144	4-(4′-hydroxyphenyl)-2-butanone-4′-O-β-D-(2″-O-galloyl-6″-O-p-coumaryl)-glucopyranoside	R_1=G R_2=p-coum	[24]
R145	4-(4′-O-β-D-glucopyranoside-3’-methoxyphenyl)-2-butanone		[24]
R146	4-(4′- O-β-D-glucopyranoside-3’,5′-dimethoxyphenyl)-2-butanone		[24]
R147	2,5-dimethyl-7-hydroxychromone		[24]
R148	2-methyl-5-acetonyl-7-hydroxychromone		[24]
R149	2-methyl-5-carboxymethyl-7-hydroxychromone		[24]
R150	2-(2’-hydroxypropyl)-5-mehyl-7-hydroxychromone		[24]
R151	2-(2’-hydroxypropyl)-5-mehyl-7-hydroxychromone-7-O-β-D-glucopyranoside		[24]
R152	2-methyl-5-carboxymethyl-7-methoxychromone		[24]
R153	Aloesone-7-O-β-D-glucopyranoside		[24]
R154	2-methyl-5-(2’-oxo-4’-hydroxypentyl)-7-hydroxychromone-7-O-β-D-glucopyranoside		[24]

Abbreviations: cin, cinnamoyl; p-coum, p-coumaroyl.

Butyrophenone and Chromone

Butyrophenones such as lotus palmatin, isobarmatin, and phenylbutadione glucoside have been reported to exhibit analgesic and anti-inflammatory activities. Eight phenylbutanones have been isolated to date (Table 4 and Figure 1).[24] Chromones exhibit multiple pharmacological properties, including coronary vasodilation, cholesterol-lowering, antihypertensive, and antibacterial effects. A total of 26 chromone compounds have been identified in rhubarb,[39] of which eight representative compounds are listed in this review (Table 4 and Figure 1).

Other Isolated Components

Other phytochemicals identified in rhubarb include naphthalene glucosides, such as torachrysone 8-O-β-D-glucopyranoside.[22] Additionally, flavonoids, such as kaempferol, quercetin, and apigenin-8-O-β-glucopyranoside have been reported. A recent study has identified 31 acyl glucosides, including 3-O-cinnamoyl-1-O-galloyl-β-D-glucopyranoside, 2-O-cinnamoyl-1-O-galloyl-β-D-glucopyranoside, 2-O-cinnamoyl-1,6-di-O-galloyl-β-D-glucopyranoside, and 6-O-cinnamoyl-1-O-galloyl-β-D-glucopyranoside.[40] Previous reviews have shown that polysaccharides isolated from rhubarb exert immunomodulatory, lipid-lowering, antioxidant, and anticancer effects.[41]

Pharmacological Properties

Substantial evidence indicates that rhubarb and its constituents exhibit a wide spectrum of biological activities. These include anticardiovascular, anticancer, hepatoprotective, renoprotective, reproductive protective, pulmoprotective, cerebral protective, antidiabetic, anticolitis, and antibacterial effects. These therapeutic actions have been shown to be mediated through the regulation of various molecular mechanisms.

Several novel mechanisms, revealed through multiomics approaches, have been suggested. These include the modulation of microbial dysbiosis, dysregulation of noncoding RNAs (ncRNAs), such as long noncoding RNAs (lncRNAs) and microRNAs, as well as metabolic disturbances (Figures 3 and 4). Furthermore, rhubarb and its components have been found to activate or inhibit multiple signaling molecules and pathways, including phosphoinositide 3-kinases (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR), phosphatase and tensin homolog (PTEN), peroxisome proliferator-activated receptor γ (PPARγ), Janus kinase 2 (JAK2), signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), myeloid differentiation factor 88 (MyD88), toll-like receptor 4 (TLR4), transforming growth factor-β (TGF-β)/suppressor of Mothers against Decapentaplegic (Smad),

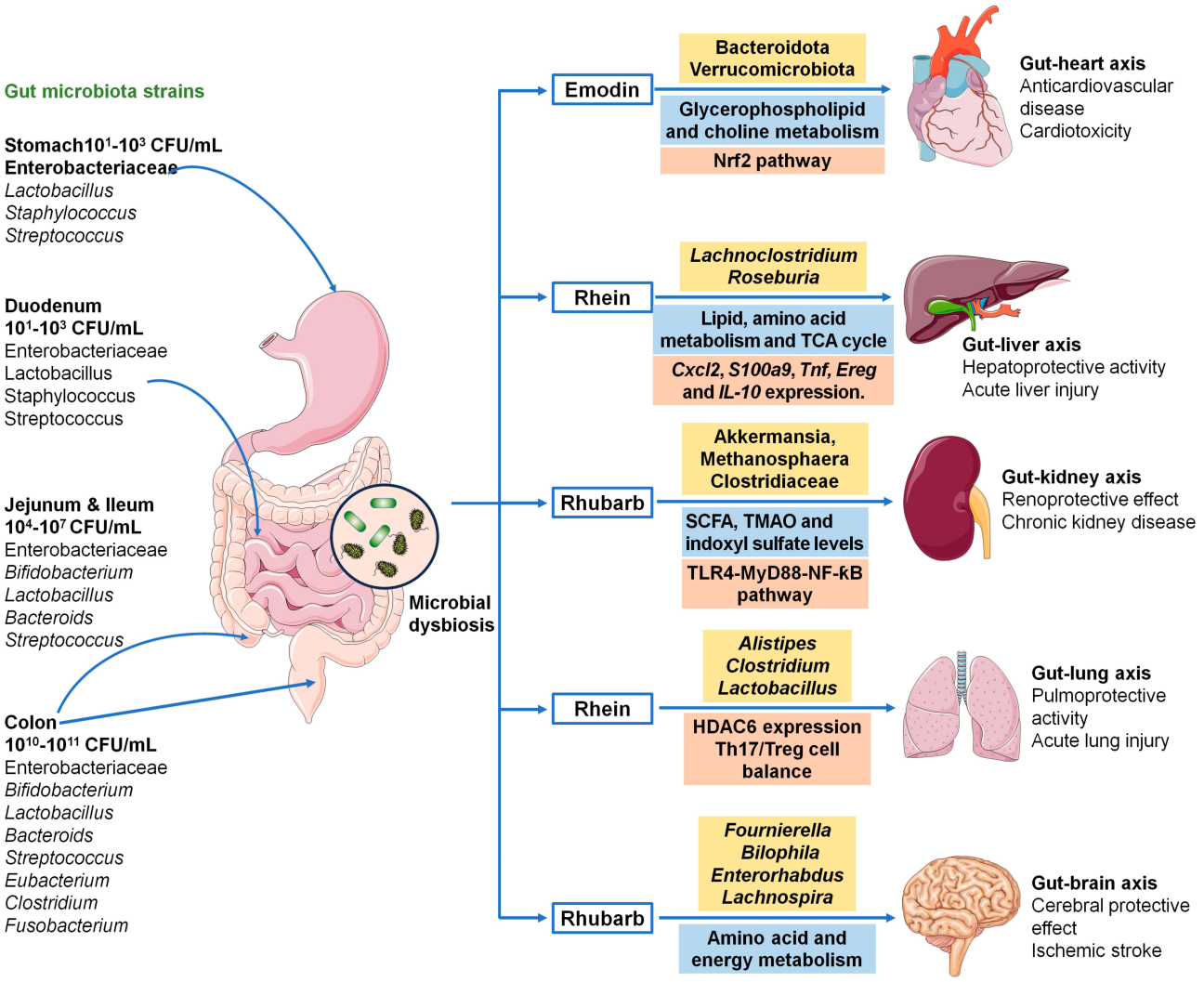

Figure 3 Rhubarb exerts its multi-organ protective effect by reshaping microbial dysbiosis and improving microbial-derived metabolite-mediated molecular mechanisms. The gut is the most abundant reservoir for human microbial ecosystems. Spatial composition and distribution of various types of bacteria in the human gastrointestinal tract. The healthy microbial ecosystem contributes to maintaining the normal physiological functions of the host. Dysbiosis of gut microbiota is involved in diverse diseases. Rhubarb exerts its anticardiovascular, hepatoprotective, renoprotective, pulmoprotective, and cerebral protective effects by regulating gut–heart axis, gut–liver axis, gut–kidney axis, gut–lung axis, and gut–brain axis by restoring metabolic disorders and underlying molecular mechanisms.

inhibitor of kappa B (IκB)/nuclear factor kappa B (NF-κB) and Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2).

Anticardiovascular Disease

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, posing a significant burden on public health and healthcare systems. Recent reviews have suggested that rhubarb extracts possess cardioprotective properties and may serve as potential therapeutic options for CVD management.[6,42,43] Among the chemical constituents of rhubarb, anthraquinones are considered the primary bioactive components, with emodin being the most extensively studied owing to its anticardiovascular effects. Several reviews have emphasized the beneficial roles of emodin, its underlying mechanisms, and therapeutic targets in the context of CVD.[44–46] Recent studies have demonstrated that emodin improves cardiac function and alleviates chronic heart failure and myocardial fibrosis by inhibiting the PI3K/Akt/mTOR signaling axis and modulating the miR-26b-5p/PTEN pathway[47,48] (Figure 4). Furthermore, cardiomyocyte pyroptosis induced by doxorubicin has been shown to be suppressed by emodin through direct binding to gasdermin D.[49] Emodin has also been reported to inhibit cardiac hypertrophy by attenuating angiotensin-induced hypertension and

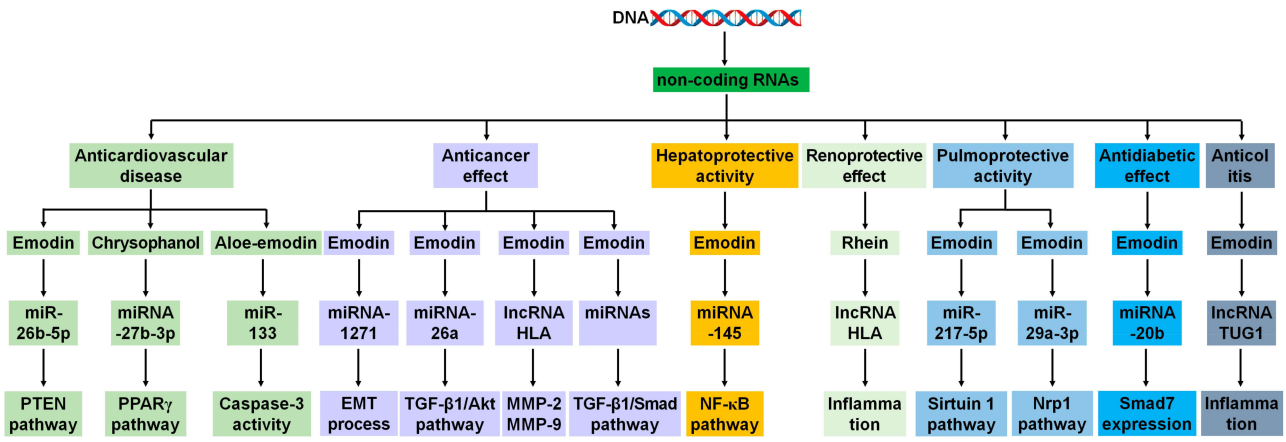

Figure 4 Rhubarb exerts multi-organ protective effects by regulating the underlying molecular mechanisms of non-coding RNAs. Aberrant ncRNAs, including miRNAs and lncRNAs, are associated with various diseases. Rhubarb exerts its anticardiovascular disease, anticancer, hepatoprotective, renoprotective, pulmoprotective, antidiabetic, and anti-colitis effects by improving the dysregulation of non-coding RNAs that mediate the underlying molecular mechanisms.

modulating the gut microbiome.[50] One study revealed that emodin restored the gut microbial balance in doxorubicin-induced mice by increasing *Bacteroidetes* and decreasing *Verrucomicrobiota*, which contributed to improved cardiac outcomes (Figure 3).[51] Additionally, fecal microbiota transplantation (FMT) of emodin-treated mice led to changes in serum metabolite profiles and improved cardiac function in recipient mice, including a reduction in ferroptosis. However, these protective effects were not observed in *Nfe2l2*$^{-/-}$ mice, suggesting that Keap1/Nrf2 pathway may be essential for the cardioprotective activity[51] (Figure 3).

Chrysophanol, the second most widely studied anthraquinone in rhubarb, has also shown significant cardioprotective potential.[52] It has been reported to attenuate arrhythmia, cardiac injury, chronic heart failure, and cardiac fibrosis by inhibiting endoplasmic reticulum stress, pyroptosis, and inflammation.[53–55] Additionally, chrysophanol has been shown to reduces sepsis-induced acute myocardial injury by modulating the miRNA-27b-3p/PPARγ axis[56] (Figure 4), alleviates doxorubicin-induced cardiotoxicity by inhibiting cellular poly(adenosine diphosphate-ribosyl)ation[57] and mitigates isoproterenol-induced cardiac hypertrophy by suppressing the JAK2/STAT3 pathway.[58]

Rhein attenuates myocardial injury by inhibiting mitochondrial fission, activating mitophagy, and suppressing apoptosis via the dynamin-related protein 1/PTEN-induced kinase 1/Parkin and p38 MAPK/heat shock protein 90/c-Jun/c-Fos signaling pathways.[59,60] Rhein has also been reported to ameliorate diabetic cardiomyopathy by suppressing inflammatory injury, mitochondrial dynamics dysfunction, apoptosis, and cardiac hypertrophy.[61,62] Recent studies have demonstrated that aloe-emodin mitigates radiation-induced heart disease by inhibiting P4HB lactylation and restoring kynurenine metabolism. It has also been shown to improve post-myocardial infarction cardiac remodeling by upregulating Smad7 and thereby blocking TGF-β/Smad signaling.[63] In addition, aloe-emodin was found to protect against myocardial infarction and apoptosis by upregulating miR-133 expression[64] (Figure 4). These findings support the potential use of rhubarb and its anthraquinone constituents as promising agents for the prevention and treatment of CVD.

Anticancer Effect

Cancer is a long-term disease involving aberrant cellular and immune functions. It is the second leading cause of death after CVD. Several studies have demonstrated that rhubarb extracts protect against lung, hepatocellular, colon, and breast cancers.[6] An earlier clinical study showed that rhubarb extract ameliorated radiation-mediated lung toxicity and enhanced pulmonary function, probably by reducing serum levels of TGF-β1 and interleukin (IL)-6 in lung cancer patients.[65] A recent analysis showed that rhubarb affects non-small cell lung cancer.[66] Previous studies have reported that extracts of *Rheum palmatum* and rhubarb suppress hepatocellular carcinoma by inhibiting the expression of STAT3 and β-catenin.[67–69] In addition, crude extracts of *Rheum palmatum* were found to inhibit migration and invasion by repressing matrix metalloproteinase-2/matrix metalloproteinase-9 via the MAPK and caspase signaling pathways in human colon cancer cells.[70,71] Moreover, *Rheum palmatum* extracts exhibit antimetastatic effects in human breast cancer cells.[72]

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Several recent reviews have demonstrated that rhubarb components, such as emodin, rhein, physcion, chrysophanol, aloe-emodin, and physcion 8-O-β-D-glucopyranoside, protect against various cancers, including liver, lung, and colon cancers.[73–75] The ncRNAs that do not encode proteins have emerged as regulators of various cellular processes. A recent study revealed that emodin suppresses colorectal cancer cells by targeting the lncRNA human leukocyte antigen complex P5[76] (Figure 4). Moreover, emodin inhibited hepatocellular carcinoma growth by modulating macrophage polarization via the miRNA-26a/TGF-β1/Akt axis[77] (Figure 4). Emodin suppressed the epithelial–mesenchymal transition and invasion of pancreatic cancer cells by upregulating miRNA-1271[78] (Figure 4). Furthermore, emodin blocked angiogenesis in pancreatic cancer by regulating the TGF-β1/Smad pathway and microRNAs[79] (Figure 4). Therefore, published data suggests that rhubarb and its components have beneficial effects on cancer suppression.

Hepatoprotective Activity

Liver diseases, including acute liver failure and chronic liver disease, are major global health problems. Liver fibrosis is a major risk factor for the development of liver cancer. An earlier study reported that rhubarb ameliorated TGF-β1-induced expression of α-smooth muscle actin and collagen and attenuated hepatic stellate cell (HSC) activity, which was associated with the downregulation of Smad2/3 and c-Jun N-terminal kinase phosphorylation and a reduction in matrix metalloproteinase-2 activity.[80] Metabolic disorders are a major global health concern. A recent study showed that rhubarb affects metabolic pathways such as fatty acid biosynthesis, bile acid biosynthesis, and the pentose phosphate pathway in high-fat diet-induced rats with nonalcoholic fatty liver disease.[81] Gong et al demonstrated that rhubarb anthraquinone attenuated acute liver injury and reversed aberrant metabolite levels associated with the biosynthesis and metabolism of tryptophan, tyrosine, phenylalanine, nucleotide sugars, amino sugars, pyrimidines, and steroid hormone biosynthesis in carbon tetrachloride-induced rats.[82]

Chrysophanol is the most extensively studied component of rhubarb for the treatment of liver disease. Several studies have suggested that chrysophanol ameliorated liver injury by regulating oxidative stress, endoplasmic reticulum stress, ferroptosis, and apoptosis.[83,84] In addition, chrysophanol-8-O-glucoside ameliorates acute liver injury and hepatic fibrosis by inhibiting HSC autophagy, liver-resident macrophage-mediated inflammation, and the STAT3 signaling pathway.[85,86] Several recent reviews have reported that emodin and aloe-emodin ameliorate liver diseases.[87,88] Emodin has been shown to promote HSC senescence, inhibit HSC activation, and attenuate liver fibrosis through nuclear receptor-mediated epigenetic regulation of glutaminase 1, as well as through the p38 MAPK and Smad signaling pathways.[89,90]

Lipopolysaccharide-induced liver inflammatory injury was mitigated by emodin via the upregulation of miRNA-145[91] (Figure 4). Gong et al found that rhein reshaped microbial dysbiosis, reducing the relative abundance of *Lachnoclostridium* and *Roseburia* and reversing L-α-amino acids, ofloxacin-N-oxide, 1-hydroxy-1,3-diphenylpropan-2-one, and L-4-hydroxyglutamate semialdehyde to normal levels. Additionally, the expression of *C-X-C motif chemokine ligand 2, S100 calcium binding protein A9, tumor necrosis factor, Epiregulin*, and *IL-10* was downregulated, whereas *Mfsd2a* and *Bhlhe41* was upregulated in mice with acute liver injury[92] (Figure 3). These findings demonstrate the therapeutic potential of rhubarb for the treatment of liver injury.

Renoprotective and Reproductive Protective Effects

Chronic kidney disease (CKD) is globally recognized as a public health problem, affecting 10–16% of the adult population.[93,94] Renal fibrosis is considered the final manifestation of CKD,[95–98] and is associated with activation of the renin-angiotensin system, oxidative stress, inflammation, aryl hydrocarbon receptor and Wnt1/β-catenin pathways, microbial dysbiosis, and metabolic disorders.[99–104] Increasing evidence has shown that natural products are widely demonstrated as an important therapy for CKD and renal fibrosis through the regulation of various mechanisms, including the pathways mentioned above.[105–111] An earlier study demonstrated that petroleum ether, ethyl acetate, and n-butanol extracts of rhubarb reduced the expression of alpha-smooth muscle actin, fibronectin, collagen I, collagen III, vimentin, and fibroblast-specific protein 1 in kidney tissues of adenine-induced CKD rats.[112] This reduction was accompanied by downregulation of the protein expression of TGF-β1, TGF-β receptor I, TGF-β receptor II, Smad2, phosphorylated Smad2, Smad3, phosphorylated Smad3, and Smad4 as well as upregulation of Smad7 protein

expression.[112] Moreover, rhein has been shown to blunt uric acid nephropathy in rats by suppressing lncRNA antisense non-coding RNA in the INK4 locus-induced inflammation.[113]

Accumulating evidence has highlighted the roles of gut microbiota dysbiosis and dysregulated microbial-derived metabolites in CKD pathogenesis.[114–118] Several studies have demonstrated that natural products and TCMs can improve kidney function and attenuate renal fibrosis by reshaping microbial dysbiosis.[108] Ji et al demonstrated that rhubarb enema treatment reduced the relative abundance of *Akkermansia, Methanosphaera*, and *Clostridiaceae* in CKD rats, which was associated with inhibition of the TLR4–MyD88–NF-κB signaling pathway and reduction of systemic inflammation[119] (Figure 3). The same research group further reported that rhubarb enema improved renal fibrosis by increasing serum levels of short-chain fatty acids (SCFAs), decreasing circulating trimethylamine N-oxide and indoxyl sulfate, and correcting microbial dysbiosis in 5/6 nephrectomized rats[120–122] (Figure 3).

As a powerful analytical platform, metabolomics has recently been used extensively for novel biomarker discovery,[101,123] disease diagnosis and prognosis,[124–127] disease mechanism identification,[128–131] pharmaceutical discovery and development,[132,133] and drug efficacy and toxicity evaluation.[134,135] An increasing number of studies have indicated that TCMs improve CKD and renal fibrosis by restoring metabolic disorders.[102] A previous study showed that rhubarb extract restored the levels of 40 metabolites, including indoleacetaldehyde, docosahexaenoic acid, kynurenic acid, hypotaurine, and arachidonic acid, which are associated with tryptophan, taurine, hypotaurine, purine, pyrimidine, fatty acid, glycerophospholipid metabolism, and the tricarboxylic acid (TCA) cycle, in the kidney tissues of adenine-induced CKD rats.[112] Another study showed that rhein restored the plasma concentrations of three aberrant biomarkers, arachidonic acid, indoxyl sulfate, and lysoPC(20:5), in rats with unilateral ureteral obstruction.[136] A more recent study revealed that rhein ameliorated renal fibrosis by activating the fatty acid oxidation pathway and correcting aberrant lipid metabolism.[137] Additionally, rhein attenuates renal fibrosis by enhancing Cpt1a-mediated fatty acid oxidation via the Sirtuin 1/STAT3/Twist1 pathway.[138] In chronic glomerulonephritis, glomerular inflammation and injury are caused by immune-mediated mechanisms. Rhein was shown to restore normal levels of 16 metabolites involved in amino acid metabolism, arachidonic acid metabolism, and the TCA cycle, thereby inhibiting oxidative stress, inflammation, and immune dysregulation.[139] These findings demonstrate that metabolomics provides profound insights into the therapeutic mechanisms of rhubarb.

Testicular torsion, a urological emergency in adolescents, is characterized by testicular ischemia due to an inadequate local blood supply, resulting in impaired testicular function.[140] A previous study showed that pyroptosis and inflammation were activated following testicular ischemia–reperfusion injury, whereas emodin attenuated the injury by inhibiting the NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) signaling pathway and pyroptosis.[140] The ameliorative effect of emodin on pyroptosis has been attributed to suppression of NLRP3 inflammasome activation.[140] The testes, which are the primary reproductive organs, are responsible for the production of androgens such as spermatozoa and testosterone. Wang et al reported that emodin improved sperm function and increased the levels of testosterone, follicle-stimulating hormone, and luteinizing hormone in cyclophosphamide-induced rats.[141] Emodin also inhibits testicular oxidative stress and the expression of pro-inflammatory markers, including malondialdehyde (MDA), interleukin-6, and tumor necrosis factor-α (TNF-α). At the same time, it increased the levels of testicular antioxidant enzymes, such as catalase, glutathione peroxidase, glutathione, and superoxide dismutase (SOD).[141] These findings indicate that emodin mitigates chemotherapy-induced testicular toxicity and provides protective effects in cyclophosphamide-induced rats by suppressing oxidative stress and inflammation.[141] Moreover, a thermosensitive hydrogel loaded with emodin-loaded triple-targeted nanoparticles was found to improve chronic nonbacterial prostatitis by inhibiting inflammation and fibrosis.[142] Therefore, emodin is a promising alternative treatment for reproductive diseases.

Pulmoprotective Activity

Acute lung injury (ALI) is a severe respiratory condition characterized by high morbidity and mortality rates.[143] Hu et al reported that rhubarb abrogated hyperoxia-mediated lung lesions by suppressing inflammation in neonatal rats with bronchopulmonary dysplasia.[144] Tang et al demonstrated that patients with ALI and lipopolysaccharide-induced ALI mice exhibited gut microbiota dysbiosis, which caused a Th17/Treg cell imbalance. In their study, rhubarb ameliorated ALI by increasing the relative abundance of *Alistipes, Clostridium*, and *Lactobacillus*, upregulating histone deacetylase 6

(HDAC6) expression, and restoring Th17/Treg cell balance[145] (Figure 3). Rhubarb anthraquinones were found to mitigate lung injury by increasing alveolar epithelial tight junction protein expression via the Ras homolog family member A/Rho-associated coiled coil-containing protein kinase 1 pathway.[146] Among the anthraquinone components, emodin has been identified as the most extensively studied compound with pulmoprotective effects.[147] Emodin alleviates intestinal ischemia/reperfusion-induced lung injury by upregulating heme oxygenase-1 expression through the PI3K/Akt pathway.[148] Additionally, ozone-mediated lung damage is attenuated by emodin via inhibition of the TLR4/MYD88/NF-κB pathway.[149] Given the high mortality rate of ALI in severe acute pancreatitis (SAP), a growing body of research has demonstrated that emodin alleviates SAP-associated ALI by activation of the Keap1/Nrf2 pathway, inhibition of ferroptosis, and regulation of the miR-217-5p/Sirtuin 1 axis[150–152] (Figure 4). Furthermore, emodin was found to modulate the miRNA expression profiles of exosomes in both the plasma and bronchoalveolar lavage fluid in rats with SAP-associated ALI. Among these, NOVEL-rno-miR-29a-3p in bronchoalveolar lavage fluid was identified to be specific to exosomes and played a key role in the therapeutic effects of emodin (Figure 4). Moreover, emodin was shown to ameliorate SAP-induced ALI by regulating lncRNA–mRNA interaction networks in rats[153] (Figure 4). These findings suggest that rhubarb ameliorates acute lung injury by modulating the expression of non-coding RNAs and targeting inflammatory and oxidative stress pathways.

Cerebral Protective Effect

Recent studies have shown that rhubarb extract prevents ischemic stroke by regulating gut microbiota and metabolic pathways through the microbiota–gut–brain axis.[154,155] Microbiome and metabolome analyses demonstrated that the aqueous extract of rhubarb reduced the abundance of *Fournierella* and *Bilophila* while increasing the abundance of *Defluviitaleaceae, Christensenellaceae, Enterorhabdus*, and *Lachnospira*. Altered levels of metabolites, including isoleucine, valine, methionine, 3-aminoisobutyric acid, trimethylamine N-oxide, betaine, choline, glucose, and lactate, were also observed, indicating their regulatory effects on amino acid and energy metabolism[154] (Figure 3). Similar findings have indicated that treatment with raw rhubarb confers protection against ischemic stroke via the microbiota–gut–brain axis.[155] Mao et al revealed that rhubarb mitigated cerebral ischemia–reperfusion injury by reducing harmful bacteria, correcting metabolic disturbances, restoring intestinal barrier function, attenuating blood–brain barrier dysfunction, and improving neurological outcomes.[156]

A recent review highlighted the cerebral protective effects of emodin and its molecular mechanisms in Alzheimer's disease.[157,158] Wang et al reported that emodin relieved neuropathic pain by inhibiting inflammation and increasing the abundance of beneficial bacteria and metabolites.[159] Additionally, emodin was found to alleviate hypoxia-induced neuronal injury by increasing miRNA-25 expression in PC-12 cells[160] (Figure 4). Based on a proteomic analysis identifying 1356 proteins, early studies indicated that rhubarb regulates the expression of neuron projection proteins involved in drug response and nervous system development. These proteins are associated with oxidative stress, calcium-binding protein regulation, vascularization, and energy metabolism.[161] These findings suggest that the cerebral protective effects of rhubarb are mediated by the regulation of inflammation, microbial dysbiosis, and metabolic dysfunction.

Antidiabetic Effect

A previous study showed that rhubarb extract inhibits α-glucosidase activity in the small intestine of rats with type 1 diabetes.[162] In another study, intestinal α-glucosidase activity was suppressed by rhubarb in rats with type 1 diabetes.[163] Several recent reviews have emphasized that rhein and emodin exert antidiabetic effects by improving insulin resistance, oxidative stress, inflammation, microbial dysbiosis, dyslipidemia, mitochondrial dysfunction, and β-cell failure.[164,165] An earlier study demonstrated that β-cells were protected by emodin from diabetogenic insults through inhibition of the IκB/NF-κB signaling pathway.[166] In addition, multiple studies have shown that anthraquinones, such as emodin and aloe-emodin, mitigate diabetic cardiomyopathy by inhibiting the Akt/glycogen synthase kinase-3β and NLRP3 inflammasome signaling pathways.[167,168] Moreover, glucose metabolism was improved by emodin by targeting miRNA-20b in insulin-resistant skeletal muscles[169] (Figure 4). These findings demonstrated the antidiabetic properties of rhubarb and its constituents.

Anticolitis

Accumulating evidence has indicated that polysaccharides have multiple pharmacological effects. Rheum tanguticum polysaccharide (RTP) ameliorated colitis injury, reduced the levels of IL-1β, IL-6, and TNF-α, and downregulated MDA and myeloperoxidase levels in dextran sulfate sodium salt-induced colitis mice.[170] These effects were accompanied by the regulation of Notch and NF-κB p65 mRNA expression as well as the restoration of gut microbiota dysregulation in colitis mice.[170] Several earlier studies have demonstrated that RTP attenuates colitis in 2,4,6-trinitrobenzene sulfonic acid-induced rats by inhibiting the NF-κB signaling pathway.[171] In addition, RTP was shown to improve intestinal bacterial balance, suppress TLR4 and NF-κB activation, and modulate Th1/Th2 cytokine production balance.[172] Furthermore, targeting the mannose receptor by RTP and the subsequent reduction in the Th1-polarized immune response have been suggested as potential mechanisms underlying its effect in the treatment of colitis.[173] Moreover, emodin suppressed acute pancreatitis by regulating lncRNA taurine upregulated 1 (TUG1) and exosomal lncRNA TUG1[174] (Figure 4). These findings suggest that rhubarb components, particularly RTP, have promising therapeutic potential for the treatment of colitis.

Antibacterial Effect

Rhubarb has been shown to exhibit inhibitory effects against a variety of bacteria, including *Escherichia coli, Staphylococcus aureus, Typhoid bacillus, Pseudomonas aeruginosa*, and *Dysentery bacillus*.[175] Mechanistically, the growth of *S. aureus* is inhibited by rhubarb through disruption of the bacterial cell wall structure and alteration of cell membrane permeability.[4] Additionally, higher antibacterial activity against *E. coli, S. aureus*, and *Klebsiella pneumoniae*, as well as against fungi such as *Candida albicans* MTCC 277 and ATCC 90028, has been demonstrated by the chloroform subcomponents of rhubarb.[176] Recent studies have highlighted the antibacterial properties of anthraquinones, particularly against *Aeromonas hydrophila*, suggesting potential applications of anthraquinones in the development of antibacterial agents. Previous findings have indicated that different substituents at the C3 and C6 positions of the anthraquinone benzene ring influence antibacterial activity. Specifically, the hydroxyl, hydroxymethyl, and carboxyl groups of hydroxyanthraquinones have been shown to enhance the antibacterial potency. Inhibitory effects against *S. aureus* have been reported for five types of free anthraquinones found in rhubarb, with rhein and emodin exhibiting stronger antibacterial activity than the other three hydroxyanthraquinones.[177] Moreover, rhubarb extract has been shown to inhibit the growth of *Helicobacter pylori*. An in vivo study further confirmed its high efficiency in terms of dosage, tolerability, and eradication of active H. pylori infection.[178] These findings indicated that rhubarb possesses broad-spectrum antibacterial activity.

Taken together, these findings suggest that Rheum and its components of anthraquinones such as emodin and chrysophanol display diverse pharmacological effects through anti-inflammatory and antifibrotic mechanisms, thereby suggesting their potential as multi-target therapeutics.

Rhubarb Toxicology

Although a wide range of pharmacological effects has been attributed to rhubarb, increasing evidence has demonstrated its potential toxicity, including hepatotoxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity. A recent study reported that accumulated rhein is associated with the induction of apoptosis and autophagy.[13] In earlier studies, emodin was shown to induce toxicity in mouse blastocysts and zebrafish embryos via apoptosis.[179,180] Therefore, apoptosis has been implicated in rhubarb-induced toxicity.

Hepatotoxicity

Increasing studies have suggested that rhubarb hepatotoxicity was mediated by a variety of underlying molecular mechanisms, such as the aberrant expression of uridine 5′-diphospho-glucuronosyltransferase 2B7 (UGT2B7), multidrug resistance-associated protein 2 (MRP2) and cytochrome P450 family 2 subfamily C member 19 (CYP2C19) as well as oxidative stress, mitochondrial injury and metabolic disorders.[181–185]

Hepatotoxicity of Rhubarb Extract

In an earlier study, liver damage induced by rhubarb extract was primarily caused by increased liver fibrosis in normal rats, suggesting that the hepatotoxicity of rhubarb could be attributed to liver cell fibrosis.[186] Metabolomic analyses showed that rhubarb-induced hepatotoxicity was associated with increased levels of lysoPE (18:2), cervonoyl ethanolamide, dynorphin B (10–13), and 3-hydroxyphenyl 2-hydroxybenzoate as well as decreased levels of dopamine, biopterin, choline, coenzyme Q9, and P1, P4-bis (5′-uridyl) tetraphosphate.[187]

Hepatotoxicity of Emodin Mediated by UGT2B7 and MRP2 Expression

Increasing publications have suggested that multiomics has been used to reveal emodin-mediated hepatotoxicity. In a recent genome-wide association study, four nucleotide polymorphisms (*rs6093966, rs2868094, rs2071197*, and *rs6073433*) located in the hepatocyte nuclear factor 4α gene were identified and found to be associated with emodin glucuronidation. Emodin has been emodin inhibited hepatocyte nuclear factor 4α expression, leading to downregulation of uridine UGT2B7 expression and subsequent hepatotoxicity.[188] In an earlier study, higher hepatotoxicity was observed in female rats than in male rats.[181] Metabolic and transcriptomic data from human liver and kidney tissues showed that *UGT2B7* serves as the primary enzyme responsible for emodin glucuronidation.[181] A genome-wide association study further identified *rs11726899*, located in *UGT2B*, as a variant that affects emodin metabolism. In HepG2 cells, the knockdown of *UGT2B7* results in decreased emodin glucuronidation and increased cytotoxicity.[181] In HepG2 cells treated with emodin, gene expression and protein levels of UGT2B7 were decreased, whereas those of MRP2 were increased.[181] Long-term administration of emodin was shown to reduce intrinsic clearance in liver microsomes from both male and female rats, thereby contributing to emodin accumulation.[181] However, higher self-induced MRP2 expression and lower hepatotoxicity have been observed in male rats than in females following emodin treatment.[181] Moreover, emodin-induced hepatotoxicity was alleviated by probenecid, which suppressed the expression of uridine 5′-diphosphoglucuronosyltransferase and MRP2.[182] Therefore, emodin hepatotoxicity has been shown to be mediated by the expression of UGT2B7 and MRP2.

Hepatotoxicity of Emodin Mediated by Mitochondrial Injury and Metabolic Disorders

Proteomic analyses have revealed that emodin-induced hepatotoxicity is associated with increased ROS and caspase-3 levels, decreased mitochondrial membrane potential, and impaired ATP synthesis, leading to mitochondrial damage and hepatocyte apoptosis.[183] Metabolomic studies have further demonstrated that emodin-induced hepatotoxicity is related to disrupted hepatic antioxidant homeostasis, particularly involving glutathione and xanthine metabolism.[184] Similarly, in human liver L-02 cells, emodin has been shown to exerts toxic effects by disturbing fatty acid and glutathione metabolism.[189] Moreover, both in vitro and in vivo studies have shown that 3-methylcholanthrene enhances emodin-induced hepatotoxicity by activating the aryl hydrocarbon receptor and inducing cytochrome P450 family 1 subfamily A member 1 expression.[185] These findings indicate that emodin hepatotoxicity is mediated by mitochondrial injury and metabolic disturbances.

Hepatotoxicity of Rhein Mediated by Oxidative Stress and CYP2C19 Expression

In a recent acute and subchronic toxicity study, no mortality was observed in immature mice, whereas mortality occurred in aged mice administered rhein.[190] Biochemical parameters, including serum aspartate transaminase, alanine aminotransferase, IL-6, and TNF-α, along with pathological liver alterations, demonstrated rhein-induced liver injury. This hepatotoxicity is associated with increased ROS production, Nrf2, and MDA levels, along with decreased SOD levels, indicating that rhein-induced oxidative stress leads to mitochondrial dysfunction and apoptosis.[190] However, MRP expression in the liver was not significantly altered.[190] Rhein-induced hepatotoxicity involves altered levels of metabolites through the CYP2C19 expression.[191] These findings suggest that rhein hepatotoxicity is mediated by oxidative stress and CYP2C19-related metabolic activation.

Hepatotoxicity of Aloe-Emodin Mediated by Oxidative Stress and MRP2 Expression

MRP2 is a key efflux transporter for substances involved in oxidative stress. In a recent study, aloe-emodin was shown to inhibit the transport activity of ATP-binding cassette subfamily C member 2 (ABCC2), downregulate ABCC2

expression, and disrupt intracellular redox balance, resulting in reduced intracellular glutathione levels, mitochondrial dysfunction, and apoptosis. Conversely, overexpression of ABCC2 attenuated aloe-emodin-induced oxidative stress and cell death, whereas ABCC2 knockdown enhanced these effects.[192] Additionally, aloe-emodin was found to induce autophagy-mediated degradation of ABCC2, thereby exacerbating hepatotoxicity in mice.[192] Another study demonstrated that aloe-emodin induced hepatic lesions in zebrafish, which was accompanied by upregulated expression of NF-κB and p53 at both the mRNA and protein levels, indicating that NF-κB and p53 signaling pathways contribute to aloe-emodin-induced hepatotoxicity.[193]

Nephrotoxicity of Rhubarb Mediated by Oxidative Stress

Chronic toxicity of rhubarb extract has been shown to primarily target the kidneys, with renal tubular epithelial cells identified as the most affected cell type in rats.[194] In a subchronic toxicity study, increases in both spleen and kidney weights were observed along with renal swelling, dark discoloration, and hydronephrosis. Extensive pigment deposition has been detected in the renal tubular epithelial cells.[195] Furthermore, total anthraquinones and emodin have both been shown to induce injury in HK-2 cells, with total anthraquinones causing more pronounced damage than emodin.[196] The impact of emodin on glomerular endothelial cells was also assessed, which revealed that emodin compromised glomerular filtration barrier integrity and increased barrier permeability. These effects were associated with elevated levels of TNF-α, TGF-β1, IL-6, and monocyte chemoattractant protein-1 (MCP-1), suggesting that oxidative stress–mediated inflammation may underlie emodin-induced nephrotoxicity.[197]

Reproductive Toxicity of Emodin

Emodin impairs the function of human sperm. A study by Luo et al demonstrated that total motility, linear velocity, and progressive motility of human sperm were significantly decreased following emodin exposure. Additionally, the ability of sperm to penetrate viscous medium and undergo progesterone-induced capacitation and acrosome reaction was inhibited. These effects were associated with reduced intracellular Ca^{2+} levels and suppressed tyrosine phosphorylation, indicating that emodin impairs sperm function by inhibiting intracellular calcium signaling and phosphorylation processes.[198] Furthermore, testicular toxicity was found to be mediated through insulin-like growth factor 1 receptor-dependent apoptosis. Additional effects involve alterations in casein kinase II, spermatogenesis, and sperm motility, which are modulated via four signaling pathways, including the tumor necrosis factor receptor 1 signaling pathway.[199]

Cardiotoxicity of Rhein Mediated by Fas Pathway

The cardiotoxic effects of rhein have been demonstrated both in vitro and in vivo. In H9c2 cells, reduced cell counts, cell atrophy, rounding, and detachment from the culture surface were observed following rhein treatment.[200] Proliferation of H9c2 cells is inhibited through S phase arrest, accompanied by increased levels of ROS and lactate dehydrogenase (LDH), decreased mitochondrial membrane potential, and downregulated SOD expression.[200] Rhein impaired cardiac function in vivo, as evidenced by reductions in the left ventricular ejection fraction and fractional shortening. Concurrently, elevated serum Ca^{2+}, cardiac troponin T, creatine kinase, and LDH levels were observed. These changes were associated with the activation of the Fas-induced apoptotic pathway.[200] These findings indicate that rhein-induced cardiotoxicity is mediated by Fas pathway–dependent apoptosis.

Neurotoxicity of Emodin Mediated by Autophagy

The role of autophagy in Alzheimer's disease (AD) pathogenesis is being increasingly recognized. Emodin has been shown to reduce cell viability and LC3-I/LC3-II conversion ratio while decreasing LDH levels in amyloid-β protein precursor/presenilin 1 mice and PC12 cells.[201] Both emodin and 3-methyladenine decreased the number of LC3-II–positive cells in the cortex, increased B-cell lymphoma 2 (Bcl-2) expression, and reduced the expression of Beclin-1 and human vacuolar protein sorting 34 (hVps34), particularly under amyloid-β 25–35 exposure, as confirmed by small interfering RNA silencing of Beclin-1 and Bcl-2.[201] Additionally, it was found that the PI3K inhibitor LY294002 blocked LC3-I/LC3-II conversion and increased Bcl-2 expression while reducing hVps34 and Beclin-1 expression.[201] These

findings suggest that emodin-induced neurotoxicity is associated with the modulation of the PI3K/Beclin-1/Bcl-2 signaling pathway.

Pharmacokinetic Studies

Anthraquinones are the primary active components of rhubarb. These compounds are predominantly absorbed in the intestine and are largely distributed in tissues and organs with high blood flow.[202] Among the free forms of anthraquinones, including rhein, aloe-emodin, and chrysophanol, the highest distribution was observed in the kidney, followed by the liver, with the lowest levels detected in the lungs.[88] The metabolism of aloe-emodin, emodin, chrysophanol, and physcion has been reported to occur rapidly, with rhein identified as the final metabolic product. Glucuronidation has been shown to be the most efficient metabolic pathway for anthraquinones.[203] However, most previous studies have concentrated on aglycones and their glycosides as naturally occurring in herbs, revealing that the oral bioavailability of anthraquinones is low due to the extensive conjugation of aglycones.

Emodin has been found to possess several limitations as a therapeutic agent, including poor water solubility, low oral bioavailability, hepatotoxicity, and nephrotoxicity. Rhein has been recognized as the major absorbable anthraquinone present in systemic circulation following oral administration. A previous study demonstrated a correlation between plasma rhein concentrations and three biomarkers directly associated with renal fibrosis.[136] Furthermore, the pharmacokinetics of aloe-emodin, emodin, rhein, and chrysophanol were investigated in rats with CKD induced through 5/6 nephrectomy, adenine, and advanced oxidation protein products (AOPP).[204] In these models, increased pharmacokinetic parameters for the four anthraquinones were observed, and these changes were positively correlated with AOPP levels in both 5/6 nephrectomized and adenine-treated rats.[204] Elevated AOPP levels and the corresponding increases in pharmacokinetic parameters have also been reported in AOPP-induced rats.[204]

Collectively, the above-mentioned findings show that rhubarb has dual roles of multiple biological activities and toxic effects and further anthraquinones are not only the bioactive components of rhubarb, but also the toxicity components of rhubarb. These structural features underlie their role as the anti-inflammatory and antifibrotic effects of rhubarb.

Conclusion, Limitations and Future Directions

The unique multi-target efficacy of natural medicines in treating various diseases has been increasingly recognized worldwide over the past several decades. This summarizes traditional use, chemical diversity, broad pharmacological effects, mechanistic insights, toxicity and pharmacokinetics. Rhubarb is widely distributed across East Asia, Europe, and North America. However, its species have varied significantly owing to differences in origin, as revealed by chemical fingerprinting and metabolomic analyses. Traditionally, rhubarb is bitter and cold in nature, with the effects of removing stagnation, detoxifying, purging fire, and promoting blood circulation and menstruation, reducing swelling and relieving pain. Anthraquinones have been identified as the principal components of rhubarb. This review suggests that anthraquinones are not only the bioactive components that exert a broad spectrum of pharmacological effects but also the primary contributor to rhubarb-induced multi-organ toxicity. The anticardiovascular, anticancer, hepatoprotective and renoprotective effects are pharmacological activities of rhubarb and its anthraquinone components. The antiinflammatory and antifibrotic mechanisms are common molecular mechanisms by which rhubarb and its anthraquinone components exert their various pharmacological effects. Intriguingly, based on the studies of genomics, transcriptomics and metabolomics, emerging multiomics studies reveal that pharmacological effects including antiinflammatory and antifibrotic mechanisms of rhubarb and its anthraquinone components are closely associated with reshaping microbial dysbiosis, restoring aberrant expression of ncRNAs and regulating maladaptive metabolite disorder. The latest mounting publications show that targeting gut microbiota, ncRNAs and endogenous metabolites are a promising therapeutic strategy in a myriad of diseases. Therefore, the underlying molecular mechanism by which rhubarb and its anthraquinone components improve various diseases by reshaping microbial dysbiosis, restoring aberrant expression of ncRNAs and regulating maladaptive metabolite disorder may provide new therapeutic targets for treatment of various diseases of rhubarb. Similarly, the antiinflammatory mechanism is common toxicological mechanisms of rhubarb-induced multi-organ toxicity that are also demonstrated to be associated with the dysregulation of genomics, proteomics, and metabolomics. Thus, multiomics is also a powerful tool for uncovering rhubarb's toxicological mechanisms. Although considerable progress has been made

regarding the therapeutic use of rhubarb in various diseases and in elucidating novel multilayered mechanisms, several key issues regarding its application remain unresolved. Integrated with multiomics strategies will offer a new perspective for dissecting and improving the therapy of rhubarb in various diseases.[205]

According to previous reports, the clinical use of rhubarb has primarily relied on the experience of TCM practitioners and lacks standardized application guidelines. Furthermore, the species and origins of rhubarb have not been clearly specified in many studies. Essential patient characteristics, such as age, body weight, and race, have not been adequately addressed in rhubarb treatment protocols. Therefore, large-scale and scientifically rigorous clinical trials should be conducted to re-evaluate the clinical efficacy of rhubarb using advanced technologies, including metagenomics, proteomics, metabolomics, and phenomics.

Cardiorenal syndrome, a complex clinical condition characterized by the interplay between cardiac and renal dysfunction, is associated with high global morbidity and mortality.[206] To date, only one study has reported that emodin attenuates mitochondrial injury in cardiorenal syndrome type 4 by activating PPARγ coactivator 1-alpha signaling.[207] Additional experimental and clinical investigations are warranted to assess the pharmacological effects of rhubarb on cardiorenal syndrome. With the growing appreciation and understanding of pathophysiological interrelatedness of metabolic risk factors such as diabetes, obesity, CKD, and CVD, cardiovascular-kidney-metabolic (CKM) syndrome is a new construct recently defined by the American Heart Association.[208] CKM syndrome reflects the interplay among metabolic risk factors, CKD, and CVD and has high morbidity and mortality. No report demonstrates that rhubarb is applied to treat CKM syndrome via multiomics-associated molecular mechanism. Therefore, the intervention study of rhubarb on CKM syndrome will provide a new avenue for the discovery of agents targeting CKM syndrome in the future.

Several critical concerns must be addressed based on prior studies. First, whether long-term rhubarb use contributes to carcinogenesis remains controversial. Second, sex-based differences may influence hepatotoxicity, nephrotoxicity, and reproductive toxicity of rhubarb. Therefore, the molecular mechanisms underlying rhubarb-induced toxicity remain unclear and require further investigation. Previous studies have suggested that rhubarb hepatotoxicity may be linked to emodin accumulation in the liver or interference with the oxidative phosphorylation pathway. A deeper understanding of rhubarb-related toxicity is essential for safe clinical application. The multiorgan toxicity of rhubarb must be comprehensively evaluated to ensure its safety and effectiveness in clinical practice.

Abbreviations

ABCC2, ATP-binding cassette subfamily C member 2; AD, Alzheimer's disease; ALI, Acute lung injury; AOPP, advanced oxidation protein products; Bcl-2, B-cell lymphoma 2; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CYP2C19, cytochrome P450 family 2 subfamily C member 19; FMT, fecal microbiota transplantation; HDAC6, histone deacetylase 6; HSC, hepatic stellate cell; hVps34, human vacuolar protein sorting 34; IL, interleukin; IκB, inhibitor of kappa B; JAK2, Janus kinase 2; Keap1, Kelch-like ECH-associated protein 1; MCP-1, monocyte chemoattractant protein-1; MRP2, multidrug resistance-associated protein 2; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor thermal protein domain-associated protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinases; PPARγ, peroxisome proliferator-activated receptor γ; RTP, Rheum tanguticum polysaccharide; SAP, severe acute pancreatitis; SCFAs, short-chain fatty acids; Smad, suppressor of Mothers against Decapentaplegic; SOD, superoxide dismutase; TCA, tricarboxylic acid; TGF-β, transforming growth factor-β; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TUG1, taurine upregulated 1; UGT2B7, uridine 5′-diphospho-glucuronosyltransferase 2B7.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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