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Ethnobotanical Uses, Phytochemistry and Pharmacology of Different *Rheum* Species (Polygonaceae): A Review

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Abstract

Today, there is an increased tendency to use herbal remedies. Rhubarb refers to several species of the genus *Rheum* L. in the Polygonaceae family. This species-rich genus is mainly distributed in Asian countries. Several medicinal effects have been attributed to the *Rheum* spp. in the traditional and modern medicine such as healing lungs, liver, kidney, womb and bladder diseases, cancer, diabetes, insect bites, relapsing fevers, diarrhea and constipation. Various *in vitro*, *in vivo* and clinical studies have investigated the therapeutic effect of extracts, fractions and pure compounds isolated from different species of this genus. Considering the positive findings, several pharmaceutical formulations contain-

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ing rhubarb extract like capsules, drops, mouthwashes and different topical formulations are now present in the market. However, there are other traditional therapeutic effects of rhubarb that have not been studied yet and it is of great importance to perform confirmatory experiments or clinical investigations. The current review summarizes general information regarding botany, phytochemistry, ethnobotany and pharmacological aspects of *Rheum* spp. It is hoped that the present review could motivate subsequent research on the other medicinal properties of these plants that have been neglected until today.

Keywords

Rhubarb · *Rheum* · Polygonaceae · Traditional medicine · Ethnobotany

22.1 Introduction

Rheum spp.(Polygonaceae) as one of the oldest and frequently used herbal medicines is mainly distributed in the Asian countries such as China, India, Nepal, Korea, Bhutan, Pakistan, Turkey, Iran, Russia and Tibet [1–3]. In the Islamic traditional medicine (ITM), various medicinal effects have been attributed to the *Rheum* genus such as healing liver, kidney, womb and bladder diseases, hiccups, diarrhea, constipation, insect bites and relapsing fevers [4, 5]. Several phytochemical studies have demonstrated that the main structures present in different species of this genus are anthraquinones, anthrones and different phenolic compounds such as stilbenes, flavonoids and tannins. These compounds have demonstrated a wide range of pharmacological activities including purgative [6], anti-cancer [7], anti-diabetes [8], anti-oxidative [9], hepatoprotective [10] and nephroprotective [11] in *in vitro*, *in vivo* and clinical studies. In the current chapter we present a general report on botany, phytochemistry, ethnobotany and pharmacological activities of *Rheum* genus.

22.2 Botany

22.2.1 Botanical Description

Rheum L. (Polygonaceae) is a species-rich genus, comprises a total of 44 accepted species (The Plant List, 2013). *Rheum* species, commonly called rhubarb, includes perennial, stout herbs with procumbent to erect basal leaves and heights range from the procumbent (*R. palaestinum*) to 2 m tall (*R. palmatum* and *R. webbianum*). The mountainous and desert regions of the Qinghai–Tibetan Plateau area (the highest and largest plateau in the world) and adjacent areas of central Asia are putatively centers of both origin and diversification of *Rheum*, owing to its extremely diversified morphology and high endemism at both species and section level [12]. It is suggested that the rich geological and ecological diversity of these regions, coupled with the habitat isolation due to oscillating climatic conditions during and after the uplifts of the plateau, might have caused the fast radiation and speciation of *Rheum* [13]. Furthermore, it seems that polyploidy have played an important role in driving diversification and speciation of this genus. More than 50% of taxonomically circumscribed species in *Rheum* taxa were involved in the polyploidy during their diversification histories [14]. The taxonomy of this genus remains complex, due to the convergent evolution and random fixation of unique morphological characters, which might explain the substantial inconsistencies among gross morphology, pollen exine pattern and trnL-F phylogeny within it [13]. The main habitats preferred by most *Rheum* taxa are cold and dry alpine meadow, steppe desert and dry slopes [15].

Rheum species are perennial plants, possess roots long, stout. Stem erect, hollow, sulcate, glabrous or strigose. Leaves basal and cauline, simple, sinuatedentate or palmate, the basal ones sparse, dense, or in a rosette, larger than the alternate cauline leaves, the latter sometimes lacking, ocrea usually large, membranous, margin entire, inflorescence simple or branched, usually paniculate, or spike-like or spherical, pedicel articulate, flowers bisexual or polygamo-monoecious, perianth persistent, tepals 6, stamens mostly 9

(6 + 3), rarely 7 or 8, styles 3, short, horizontal, stigmas inflated, recurved, achenes trigonous, winged [16].

According to the website 'TPL' (http://www.theplantlist.org.), there are 121 scientific plant names of species rank for the genus *Rheum*, of these 44 are accepted species names. Table 22.1 summarizes all synonyms of *Rheum* taxa.

22.2.2 Authentication and Detection of Adulteration

Because of some morphological similarities of the plants and their misidentification by the vendors and consumers, the crude medicinal plants are often substituted or adulterated in commerce which may lead to poor clinical efficacy and adverse effects. In Iran, a number of *Rheum* taxa are traded in traditional medicine markets and shops such as *R. palmatum, R. ribes* and *R. turkestanicum*. Taxonomic assessment revealed that some of them should be considered as adulterated and substituted samples. For instance, *R. ribes* are admixed with *R. turkestanicum* and are sold in the market which degrades its quality and efficacy [17, 18]. In various parts of India, *R. emodi* are adulterated with *R. webbianum* and *R. Spiciforme* [19]. In Chinese markets, many adulterants include *R. franzenbachii*, *R. undulatum*, *R. rhaponticum*, *Rumex crispus*, and *R. dentatus* are commonly admixed with official Da-huang (the dried rhizomes and roots of *R. palmatum*, *R. tanguticum*, and *R. officinale*), because of similar morphological traits. The results of several previous studies have shown significant differences in the chemical composition of rhubarbs, and it is recommended that clinical practice should be performed for each species individually [20]. Moreover, due to the increasing demand both domestically and internationally and the short supply of official rhubarb, some *Rheum* taxa, like *R. hotaoense* has also been used as commercial substitutes in certain regions [21]. Therefore, it is essential to provide an authentic tool for realizing the distinction between different *Rheum* species and their adulterants. **Authentication** of these crude medicinal plants

Table 22.1 Scientific names and synonym(s) of reported *Rheum* species worldwide [according to The Plant List (2013)]

No	*Rheum* species (Accepted names)	Synonyms
1	*Rheum acuminatum* Hook. f. & Thomson	*Rheum orientalixizangense* Y.K. Yang, J.K. Wu & Gasang.
2	*Rheum alexandrae* Batalin	–
3	*Rheum altaicum* Losinsk.	*Rheum rhaponticum* Herder
4	*Rheum australe* D. Don	*Rheum emodi* Wall. ex Meisn.
5	*Rheum compactum* L.	*Rheum nutans* Pall.
		Rheum orientale Losinsk.
6	*Rheum delavayi* Franch.	*Rheum strictum* Franch.
7	*Rheum forrestii* Diels	–
8	*Rheum glabricaule* Sam.	–
9	*Rheum globulosum* Gage	–
10	*Rheum hotaoense* C.Y. Cheng & T.C. Kao	–
11	*Rheum × hybridum* Murray	–
12	*Rheum inopinatum* Prain	–
13	*Rheum kialense* Franch.	*Rheum micranthum* Sam.
14	*Rheum laciniatum* Prain	
15	*Rheum lhasaense* A.J. Li & P.G. Xiao	
16	*Rheum likiangense* Sam.	*Rheum ovatum* C.Y. Cheng & T.C. Kao
17	*Rheum lucidum* Losinsk.	*Rheum korshinskyi* Titov ex Losinsk.
18	*Rheum macrocarpum* Losinsk.	*Rheum ferganense* Titov
		Rheum lobatum Litv. ex Losinsk.
		Rheum nuratavicum Titov
		Rheum plicatum Losinsk.
		Rheum vvedenskyi Sumner
		Rheum zergericum Titov
19	*Rheum maculatum* C.Y. Cheng & T.C. Kao	–

(continued)

Table 22.1 (continued)

No	*Rheum* species (Accepted names)	Synonyms
20	*Rheum moorcroftianum* Royle	–
21	*Rheum nanum* Siev. ex Pall**.**	*Rheum cruentum* Siev. ex Pall.
		Rheum leucorrhizum Pall.
22	*Rheum nobile* Hook. f. & Thomson	–
23	*Rheum officinale* Baill.	–
24	*Rheum palmatum* L.	*Rheum potaninii* Losinsk.
		Rheum qinlingense Y.K.Yang, D.K.Zhang & J.K.Wu
25	*Rheum przewalskyi* Losinsk.	–
26	*Rheum pumilum* Maxim.	–
27	*Rheum racemiferum* Maxim.	–
28	*Rheum reticulatum* Losinsk.	–
29	*Rheum rhabarbarum* L.	*Rheum franzenbachii* Münter
		Rheum franzenbachii var. *mongolicum* Münter
		Rheum undulalum L.
		Rheum undulatum var. *longifolium* C.Y. Cheng & T.C. Kao
30	*Rheum rhaponticum* **L.**	
31	*Rheum rhizostachyum* Schrenk	*Rheum aplostachyum* Kar. & Kir.
32	*Rheum rhomboideum* Losinsk.	–
33	*Rheum ribes* L.	–
34	*Rheum spiciforme* Royle	*Rheum scaberrimum* Lingelsh.
35	*Rheum subacaule* Sam.	–
36	*Rheum sublanceolatum* C.Y. Cheng & T.C. Kao	–

(continued)

Table 22.1 (continued)

No	*Rheum* species (Accepted names)	Synonyms
37	*Rheum tanguticum* Maxim. ex Balf.	*Rheum palmatum* subsp. *dissectum* Stapf
		Rheum palmatum f. *rubiflora* Stapf
		Rheum tanguticum var. *viridiflorum* Y.K. Yang & D.K. Zhang
38	*Rheum tataricum* L.f.	*Rheum caspicum* Pall.
		Rheum songaricum Schrenk
39	*Rheum tibeticum* Maxim. ex Hook. f.	–
40	*Rheum turkestanicum* Janisch.	*Rheum megalophyllum* Sumner
		Rheum renifolium Sumner
		Rheum rupestre Litv. ex Losinsk.
		Rheum turanicum Litv.
41	*Rheum uninerve* Maxim.	–
42	*Rheum webbianum* Royle	–
43	*Rheum wittrockii* C.E. Lundstr.	–
44	*Rheum yunnanense* Sam.	–

is very necessary since without correct identification, the efficacy and safety of products cannot be guaranteed.

22.2.3 Threat Categorization and Conservation Prioritization

Several ***Rheum*** species, particularly from Kashmir Himalaya are under tremendous risk and have been considered as “threatened” by several agencies such as International Union for Conservation of Nature (IUCN), United Nations Environment Programme (UNEP) and World Wide Fund for Nature (WWF) [22]. Multiple factors such as habitat loss and extensive collection from the wild have caused a significant decline in the natural resources of them. In India, various sub-endemic plant taxa belonging to the genus *Rheum*, were identified as threatened including *R. moorcroftianum* "critically endangered", *R. webbianum* "Endangered" and *R. australe* "vulnerable", due to a critical decrease in their population [23]. *R. wittrockii* is an endangered and rare species that grows in Kazakhstan. It is a very useful medicinal plant and is being used for cooking in a variety of dishes [24]. Some *Rheum* species, such as *R. alexandrae* and *R. nobile* are monocarpic perennial species, meaning that they only produce flowers once in a lifetime and are only reproduced through their seeds. These plants are "potentially endangered" and overexploitation of their wild resources should be forbidden [25]. Both of these rare noteworthy taxa-endemic to the high eastern Himalayas-are being used in traditional Tibetan medicine [26, 27]. Three other *Rheum* species including *R. tanguticum, R. officinale* and *R. palmatum* are endemic and "endangered" plant species that grow in China. In recent years, due to the overutilization and the loss of habitat of *R. tanguticum*, it has been named as "endangered" in the China higher plants endangered list [28, 29]. Moreover, *R. palmatum* and *R. officinale* wild resources have decreased due to a decrement in *R. tanguticum* natural resources, thus, both are considered as "threatened" taxa in China [30]. There is a strong need for conservation priorities and management strategies of such valuable *Rheum* gene pool through establishment of herbal gardens and medicinal plants nurseries for *ex situ* conservation, coupled with education and awareness programs for large-scale cultivation [23]. If overharvesting and habitat destruction of these valuable species continues, they may vanish from the area within a few years.

22.3 Phytochemical Constituents

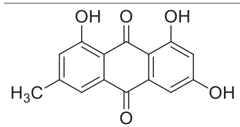
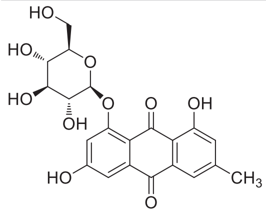
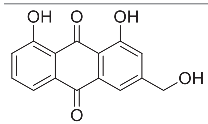
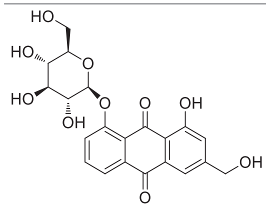
According to previous studies, the most important chemical structures from *Rheum* taxa are anthraquinones, anthrones and phenolic compounds (stilbenes, flavonoids, phenolic glycosides, phenolic acids, cinnamic acid derivatives and tannins). These compounds have been classified in Table 22.2.

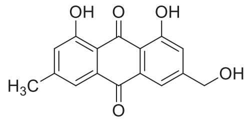
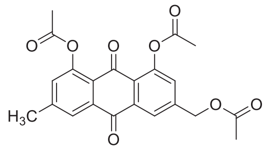
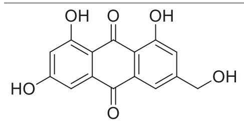
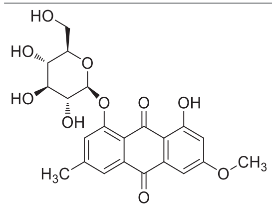
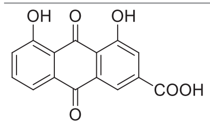
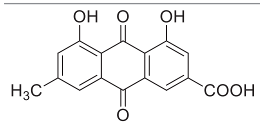
22.4 Ethnobotanical and Ethnomedicinal Knowledge

The traditional uses of *Rheum* species in **ethnomedicine** mainly originate from Asia and Europe. **25** species of *Rheum* have been reported to be beneficial among which *R. australe*, *R. palmatum*, *R. ribes* and *R. webbianum* have the highest number of citations in the world. Different parts of *Rheum* taxa including roots, petioles, fruits and seeds have been used as **ethnomedicine** for a long time. There are some reports on the traditional uses of *R. palmatum* and ***R. rhaponticum*** in European countries, particularly Bulgaria and Spain. In these countries, the roots are the most used part for treating fever, heart problems, stomachache and jaundice [60, 61]. Stems of *R. rhabarbarum* commonly known as "Rhabarber" have been recommended as depurative in Germany [62]. In Kazakhstan, *R. wittrockii* was used by Kazakhs against gastro-enteric and skin **ailments**. Moreover, *R. altaicum* was advised as an anti-inflammatory and for treating skin problems. Stalks of *R. compactum* and *R. wittrockii* were eaten by local people [63].

China represents most of the distribution range of the *Rheum* taxa in the world [16]. Many species of this genus are used in **traditional** Chinese **medicine** and many reports are found highlighting their traditional and ethnomedicinal applications. Among them, *R. officinale, R. palmatum* and *R. tanguticum* are the official rhubarbs. In Chinese markets, dried roots and rhizomes of *R. tanguticum* and *R. palmatum* are called "north rhubarb", while that of *R. officinale* are called "south rhubarb" [28, 29]. These taxa are known for their purgative, anti-bacterial, astringent, anti-carcinogenic, and stomachic properties [64]. Further, the roots and rhizomes of *R. palmatum*-commonly known as Zhang Ye Da Huang or Chinese rhubarb-have been recommended to treat abdominal distension, constipation and stomach pain [65]. Also, t**he roots of** *R. officinale,* known as Da Huang, have been recognized as a wound healing agent and purgative [66, 67]. Leaf petioles of *R. acuminatum, R. austral, R. globulosum, R. inopinatum, R. lhasaense,*

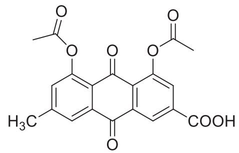
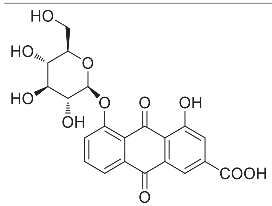
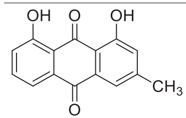
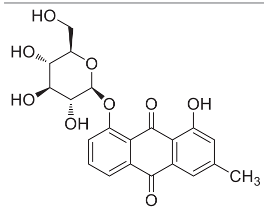
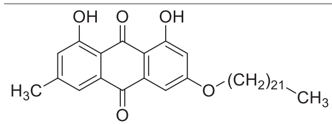
Table 22.2 The most important chemical structures isolated from different parts of *Rheum* spp.

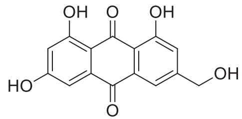
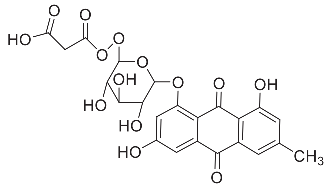
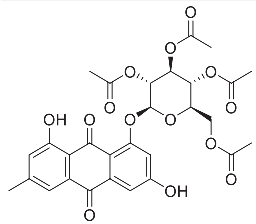
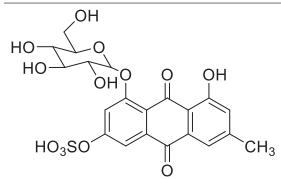
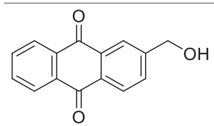
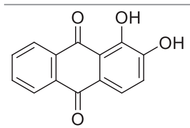
Structure	Name of compound	Species	Part used	References
Anthraquinone derivatives				
	Emodin	*R. nobile*	Rhizomes	[31]
		R. emodi	Roots and rhizomes	[32–34]
		R. acuminatum	Roots	[32]
		R. palmatum	Rhubarb powder	[32, 35]
		R. spiciforme	Different plant parts	[36]
		R. webbianum	Different plant parts	[36]
		R. tanguticum	–	[32]
	Emodin-8-O-*β*-D- glucopyranoside (emodin 8-glucoside)	*R. nobile*	Rhizomes	[31]
		R. emodi	Rhizomes, roots and rootstalks	[20, 33, 37–39]
		R. palmatum	Roots	[20]
		R. tanguticum	Roots	[20]
		R. officinale	Roots	[20]
		R. franzenbachii	Roots	[20]
		R. hotaoense	Roots	[20]
		R. emodi	Rhizomes	[33, 34]
		R. franzenbachii	Roots and rhizomes	[20, 40]
	Aloe-emodin	*R. emodi*	Rhizomes	[41]
		R. spiciforme	Different plant parts	[36]
		R. webbianum	Different plant parts	[36]
		R. rhabarbarum	Stalks	[42]
		R.palmatum	–	[32, 43]
		R. acuminatum	Roots	[32]
		R. tanguticum	–	[32]
	Aloe-emodin glucoside	–	Rhizomes	[40]

	6-Methyl-aloe-emodin	*R. emodi*	Rhizomes	[39]
	6-Methyl-aloe-emodin-triacetate	*R. emodi*	Rhizomes	[39]
	Physcion	*R. emodi*	Roots and rhizomes	[32, 33, 41]
		R. acuminatum	–	[32]
		R. officinale	Rhizomes, rhubarb samples	[32, 44, 45]
		R. tanguticum	–	[32]
		R. palmatum	–	[32, 43]
	Physcion-8-O-β-D-glucopyranoside	*R. nobile*	–	[31]
		R. emodi	Roots and rootstalks	[38]
	Rhein	*R.emodi*	Roots and rhizomes	[32, 41]
		R.officinale	Rhizomes, rhubarb samples	[32, 44, 45]
		R. tanguticum	–	[32]
		R. palmatum	–	[32, 43]
		R. spiciforme	Different plant parts	[36]
		R. webbianum	Different plant parts	[36]
	6-Methyl-rhein	*R. emodi*	Rhizomes	[39]

(continued)

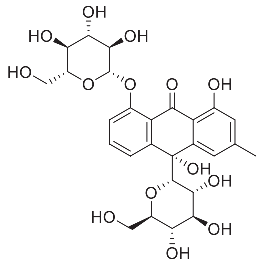
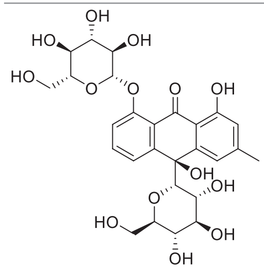
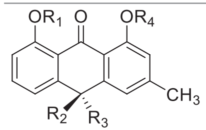
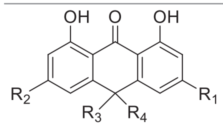
Table 22.2 (continued)

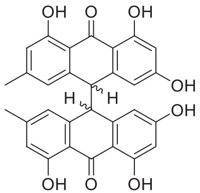
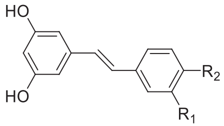
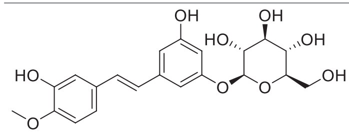
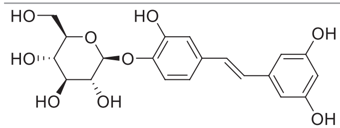
Structure	Name of compound	Species	Part used	References
	6-Methyl-rhein-diacetate	*R. emodi*	Rhizomes	[39]
	Rhein 8-O-glucoside	*R. officinale*	Roots	[20]
	Chrysophanol	*R. nobile*	Rhizomes	[31]
		R. emodi	Roots and rhizomes	[32–34]
		R. acuminatum	Roots	[32]
		R. officinale	Rhizomes, rhubarb samples	[32, 44, 45]
		R. palmatum	–	[32, 43]
		R. tanguticum	Rhizomes	[32, 44]
		–	Rhizomes, rhubarb samples	[40, 46]
	Chrysophanic acid (chrysophanol)	–	Rhubarb samples	[46]
	Chrysophanol glucoside	*R. emodi*	Roots and rhizomes	[20, 33, 34]
		R. officinale	Roots	[20]
		R. palmatum	Roots	[20]
		R. tanguticum	Roots	[20]
		R. franzenbachii	Roots	[20]
		R. hotaoense	Roots	[20]
	Chrysophanol-8-O-β-D-glucopyranoside	*R. nobile*	Rhizomes	[31]
	Revandchinone-3	*R. emodi*	Rhizomes	[47]

	Citreorosein	–	–	[48]
	Emodin 8-O-(6′-O-malonyl)-glucoside	*R. emodi*	Roots	[20]
		R. officinale	Roots	[20]
		R. palmatum	Roots	[20]
		R. tanguticum	Roots	[20]
		R. franzenbachii	Roots	[20]
		R. hotaoense	Roots	[20]
	Emodin 8-O-(2′, 3′, 4′, 6′-tetraacetyl)-glucoside	*R. emodi*	Roots	[49]
	Emodin 8-O-*β*-D-glucopyranosyl-6-O-sulfate	*R. emodi*	Roots	[49]
	2-Hydroxymethyl anthraquinone	*R. rhabarbarum*	Stalks	[42]
	Alizarin	*R. emodi*	Rhizomes	[50]

(continued)

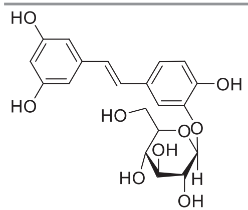
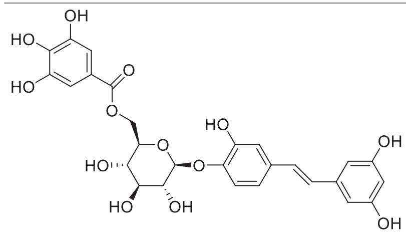
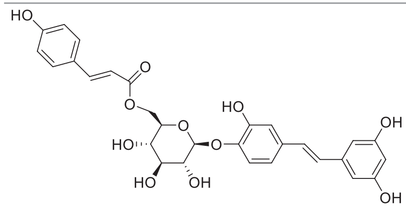
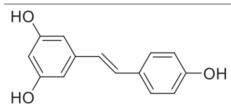
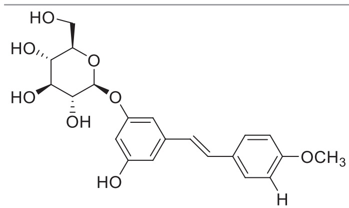
Table 22.2 (continued)

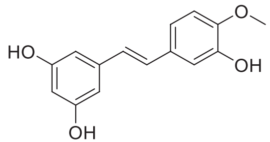
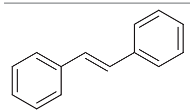
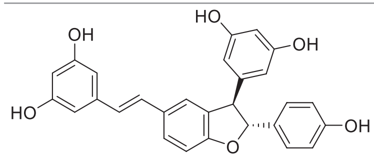
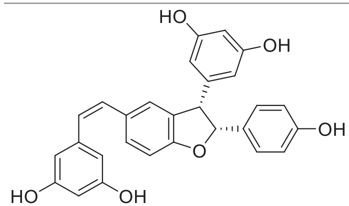
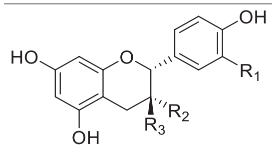
Structure	Name of compound	Species	Part used	References
Anthrone derivatives				
	10-Hydroxycascaroside C (anthrone C-glucosides)	*R. emodi*	Roots	[51]
	10-Hydroxycascaroside D	*R. emodi*	Roots	[51]
	10R-Chrysaloin1-O-β-D-glucopyranoside: R_1 = H, R_2 = H, R_3 = Glu, R_4 = Glu	*R. emodi*	Roots	[51]
	Cascaroside C: R_1 = Glu, R_2 = Glu, R_3 = H, R_4 = H	*R. emodi*	Roots	[51]
	Cascaroside D: R_1 = Glu, R_2 = H, R_3 = Glu, R_4 = H	*R. emodi*	Roots	[51]
	Cassialoin: R_1 = H, R_2 = OH, R_3 = Glu, R_4 = H	*R. emodi*	Roots	[51]
	Revandchinone-1: R_1 = CH_3, R_2 = OCH_3, R_3 = H, R_4 = O-CO-$(CH_2)_7$-CH=CH-$(CH_2)_7$-CH_3	*R. emodi*	Rhizomes	[47]
	Revandchinone-2: R_1 = CH_3, R_2 = H, R_3 = H, R_4 = O-CO-$(CH_2)_{26}$-CH_3	*R. emodi*	Rhizomes	[47]
	Revandchinone-4: R_1 = CH_2OH, R_2 = OH, R_3 = OH, R_4 = O-$(CH_2)_{17}$-CH_3	*R. emodi*	Rhizomes	[47]

	*trans*-Emodindianthrone: 10–10′ *trans* *cis*-Emodindianthrone: 10–10′ *cis*	*R. nobile*	Rhizomes	[31]
Stilbenes				
	Piceatannol: R_1 = OH, R_2 = OH	*R. emodi*	Roots	[32, 37, 38]
		R. acuminatum	Roots	[32]
	Piceatannol-4′-O-*β*-D-(6″-O-acetyl)-glucoside: R_1 = OH, R_2 = O-(6′-O-acetyl)-Glu	*R. nobile*	Rhizomes	[31]
	Piceatannol-4′-O-*β*-D-glucoside: R_1 = OH, R_2 = O-Glu	*R. nobile*	Rhizomes	[31]
	Resveratrol-4′-O-*β*-D-glucoside (resveratroloside): R_1 = H, R_2 = O-Glu	*R. nobile*	Rhizomes	[31]
		R. rhabarbarum R. rhaponticum	Leaves, petioles, rhizomes	[52]
	Desoxyrhaponticin: R_1 = H, R_2 = OCH_3	*R. emodi*	Rhizomes	[53]
		R. rhabarbarum R. rhaponticum	Leaves, petioles, rhizomes	[52]
	Rhaponticin	*R. rhabarbarum*	Stalks	[42]
		R. rhabarbarum R. rhaponticum	Leaves, petioles, rhizomes	[52]
	Piceatannol-4′-O-*β*-D-glucopyranoside	*R. emodi*	Roots, rhizomes, rootstalks	[37, 38]

(continued)

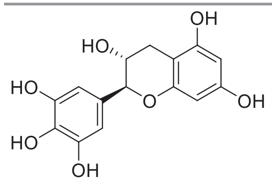
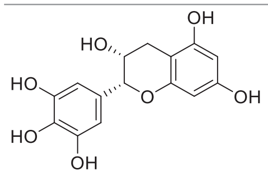
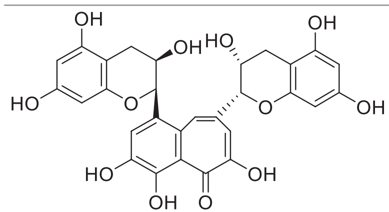
Table 22.2 (continued)

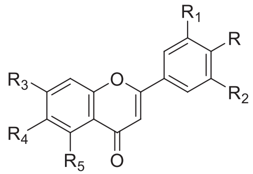
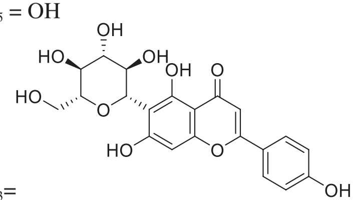
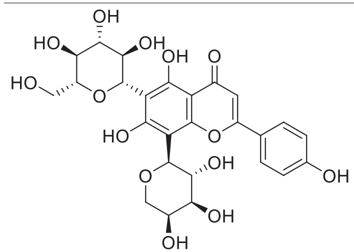
Structure	Name of compound	Species	Part used	References
	Piceatannol-3′-O-*β*-D-glucopyranoside	*R. emodi*	Roots and rootstalks	[38]
		R. rhabarbarum R. rhaponticum	Leaves, petioles, rhizomes	[52]
	Piceatannol-4′-O-*β*-D-(6″-O-galloyl)-glucopyranoside	*R. emodi*	Roots and rhizomes	[37]
	Piceatannol-4′-O-*β*-D-(6″-O-*p*-coumaroyl)-glucopyranoside	*R. emodi*	Roots and rootstalks	[38]
	Resveratrol	*R. australe*	Roots	[32]
		R. undulatum	Rhizomes	[54]
		R. acuminatum	Roots	[32]
	Desoxyrhapontigenin	*R. emodi*	Rhizomes	[53]
		R. rhabarbarum R. rhaponticum	Leaves, petioles, rhizomes	[52]

	Rhapontigenin	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]
	*trans*-Stilbene	*R. undulatum*	Rhizomes	[54]
	Maximol A	*R. maximowiczii*	Roots	[55]
	Maximol B	*R. maximowiczii*	Roots	[55]
Flavonoids (flavan-3-ols)				
	(+)-Catechin: R_1 = OH, R_2 = H, R_3 = OH	*R. nobile*	Rhizomes	[31]
		R. emodi	Roots and rhizomes	[37]
		R. rhabarbarum	Leaves, petioles, rhizomes	[52]
		R. rhaponticum	Leaves, petioles, rhizomes	[52]
	(−)-Epicatechin: R_1 = OH, R_2 = OH, R_3 = H	*R. nobile*	Rhizomes	[31]
		R. emodi	Rhizomes	[53]
	(−)-Epicatechin-3-O-gallate: R_1 = OH, R_2 = O-Glu, R_3 = H	*R. nobile*	Rhizomes	[31]
	(−)-Epiafzelechin: R_1 = H, R_2 = OH, R_3 = H	*R. nobile*	Rhizomes	[31]

(continued)

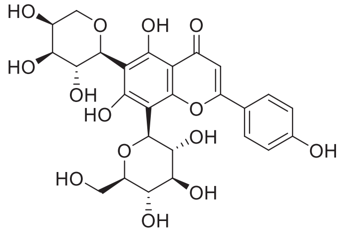
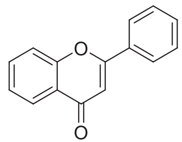
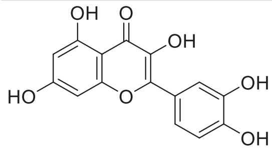
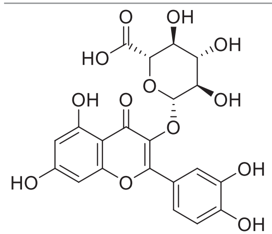
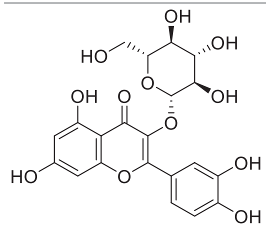
Table 22.2 (continued)

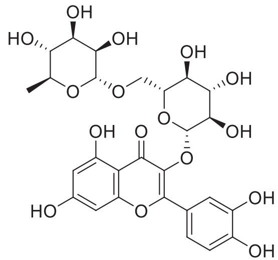
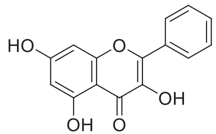
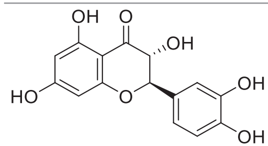
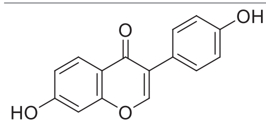
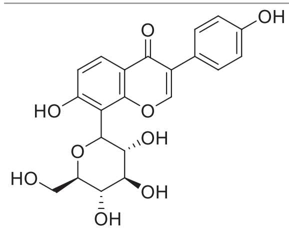
Structure	Name of compound	Species	Part used	References
	(−)-Gallocatechin	*R. emodi*	Rhizomes	[50]
	(-)-Epigallocatechin	*R. emodi*	Rhizomes	[50]
	Theaflavin	*R. emodi*	Rhizomes	[50]

Flavonoids (flavones)				
	7,4′-dihydroxyflavone: R = OH, R_1 = H, R_2 = H, R_3 = OH, R_4 = H, R_5 = H	*R. emodi*	Rhizomes	[50]
	Chrysin: R = OH, R_1 = OCH_3, R_2 = OCH_3, R_3 = OH, R_4 = H, R_5 = OH	*R. emodi*	Rhizomes	[50]
	Genkwanin: R = OH, R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = H, R_5 = OH	*R. emodi*	Rhizomes	[50]
	Luteolin: R = OH, R_1 = H, R_2 = OH, R_3 = OH, R_4 = H, R_5 = OH	*R. emodi*	Rhizomes	[50]
	Luteolin-3′, 7-di-O-glucoside: R = OH, R_1 = H, R_2 = O-D-Glu, R_3 = O-D-Glu, R_4 = H, R_5 = OH	*R. emodi*	Rhizomes	[50]
	Diosmetin-7-O-rhamnoside (diosmin): R = OCH_3, R_1 = H, R_2 = OH, R_4 = H, R_5 = OH  R_3=	*R. emodi*	Rhizomes	[50]
	Sinensetin: R = OCH_3, R_1 = H, R_2 = OCH_3, R_3 = OCH_3, R_4 = OCH_3, R_5 = OCH_3	*R. emodi*	Rhizomes	[50]
	Isovitexin	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]

(continued)

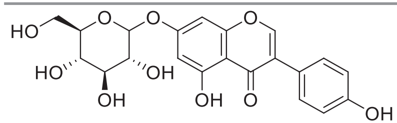
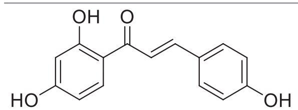
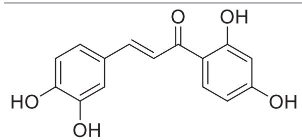
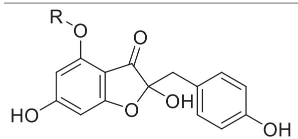
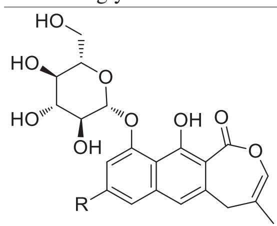
Table 22.2 (continued)

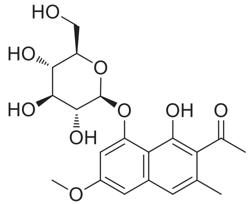
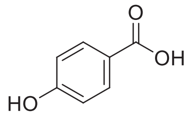
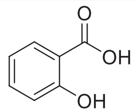
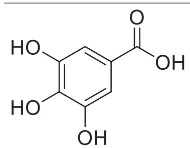
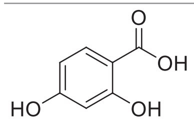
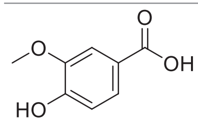
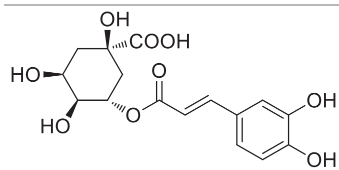
Structure	Name of compound	Species	Part used	References
	Schaftoside: 6-C-β-D-glucosyl-8-C-β-D-arabinosylapigenin	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]
	Isoschaftoside: 6- C-β-D-arabinosyl-8-C-β-D-glycosylapigenin	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]
Flavonoids (flavonols)				
	Flavonol	*R. emodi*	Rhizomes	[50, 56]
	Quercetin	*R. emodi*	Rhizomes	[56]
		R. tataricum	Leaves and seeds	[57]
	Miquelianin: (quercetin-3-O-glucuronide)	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]

	Isoquercitrin	*R. rhabarbarum*	–	[42]
	Rutin	*R. rhabarbarum R. rhaponticum*	Leaves, petioles, rhizomes	[52]
	Galangin	*R. emodi*	Rhizomes	[50]
Flavonoids (flavanonols)				
	(+)-Taxifolin	*R. emodi*	Rhizomes	[56]
Flavonoids (isoflavones)				
	Daidzein	*R. emodi*	Rhizomes	[56]
	Puerarin: daidzein-8-O-glucoside	*R. emodi*	Rhizomes	[50, 56]

(continued)

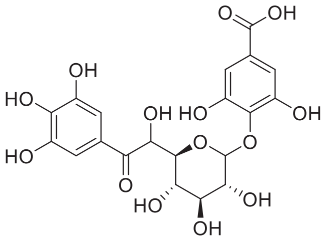
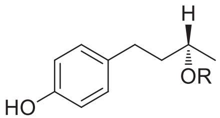
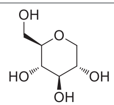
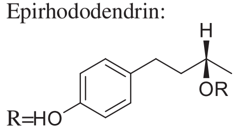
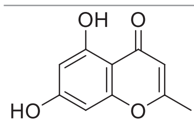
Table 22.2 (continued)

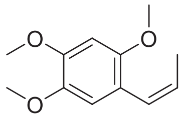
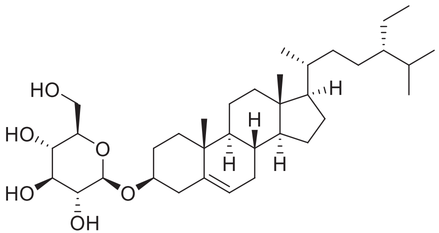
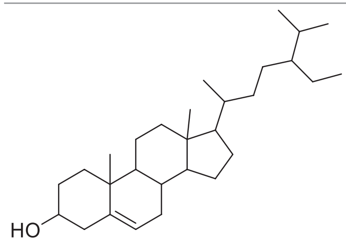
Structure	Name of compound	Species	Part used	References
	Genistin (genistein-7-O-glucoside)	*R. emodi*	Rhizomes	[50]
Flavonoids (chalcones)				
	Isoliquiritigenin	*R. emodi*	Rhizomes	[50]
	Butein	*R. emodi*	Rhizomes	[50]
Flavonoids (auronols)				
	Carpusin (marsupsin): R = CH_3	*R. emodi*	Roots	[49]
	Maesopsin: R = H	*R. emodi*	Roots	[49]
Phenolic glycosides				
	8-Methoxyl-rheumone A: R = OCH_3	*R. nobile*	Rhizomes	[31]
	Rheumone A: R = H	*R. nobile*	Rhizomes	[31]

	Torachrysone-8-O-*β*-D-glucopyranoside	*R. nobile*	Rhizomes	[31]
		R. emodi	Roots and rhizomes	[49, 53]
Phenolic acids				
	*p*-Hydroxybenzoic acid	*R. emodi*	Rhizomes	[50]
	*o*-Hydroxybenzoic acid	*R. emodi*	Rhizomes	[50]
	Gallic acid	*R. emodi*	Rhizomes	[50, 56]
	*β*-Resorcylic acid	*R. emodi*	Rhizomes	[56]
	Vanillic acid	*R. emodi*	Rhizomes	[50]
Cinnamic acid derivatives				
	Chlorogenic acid (caffeoylquinic acid)	*R. emodi*	Rhizomes	[50]

(continued)

Table 22.2 (continued)

Structure	Name of compound	Species	Part used	References
Tannins				
	Digalloyl glucose (gallic acid 4-O-(6-galloylglucoside))	–	Commercial rhubarb	[58]
Miscellaneous				
	(+)- Rhododendrol: R = H	*R. maximowiczii*	Roots and barks	[55, 59]
R= 	Epirhododendrin: 	*R. maximowiczii*	Roots and barks	[55, 59]
	(S)-4-(4-Hydroxyphenyl)-2-butanol 2-O-sulfate: R = SO_3H	*R. maximowiczii*	Roots	[55]
	(S)-4-(4-Hydroxyphenyl)-2-butanol 2-O-(6-O-galloyl)-D-glucopyranoside: R = 6-galloyl-β-D-Glcp	*R. maximowiczii*	Roots	[55]
	(S)-4-(4-Hydroxyphenyl)-2-butanol 2-O-(6-O-acetyl)-D-glucopyranoside: R = 6-O-acetyl-β-D-Glcp	*R. maximowiczii*	Roots	[55]
	(S)-4-(4-Hydroxyphenyl)-2-butanol 2-O-[6-O-(3,5-dimethoxy-4-O-L-rhamnopyranosyl galloyl)-D-glucopyranoside]: R = α-L-rhamnopyranosyl	*R. maximowiczii*	Roots	[55]
	Noreugenin	*R. emodi*	Rhizomes	[53]

Phenyl propanoids				
	*β*-Asarone	*R. emodi*	Rhizomes	[47]
Phytosterols				
	Daucosterol	*R. emodi*	Roots, rhizomes and rootstalks	[37, 38]
	*β*-Sitosterol	*R. emodi*	Roots, rhizomes and rootstalks	[37, 38]

R. palmatum, R. pumilum, R. rhomboideum and *R. tanguticum* are used as condiment in China [68].

In Nepal, the crushed and boiled roots of *R. acuminatum* and *R. australe* are used for indigestion, menstruation problems and blood purification. Besides, the roots paste is applied externally on fractured and broken bones. The petioles of *R. acuminatum* have been used to treat diarrhea, constipation, cold, cough and headache and also to make pickles [69].

In Iranian traditional medicine, people use the roots of *R. turkestanicum* to treat diabetes, hypertension and cancer [70]. The roots of *R. palmatum* are traditionally used for liver diseases, constipation, and backache and as cardiac tonic, appetizer and anti-lithiatic. Moreover, different parts of *R. ribes* (Persian name: Rivas) are used for various **ailments** of human and animals.

Fresh young stems of *R. tibeticum* -known as Sheepod in Pakistan- are being used as vegetable and mild laxative agent [71]. In the Pakistan folk medicine, the powdered rhizomes of *R. australe* are used topically for treating wounds and orally for curing constipation [72]. Furthermore, different parts of *R. spiciforme* have been recognized for curing digestive disorders and as blood purifier and tonic for livestock [73].

In India, *R. australe* has been used to treat abdominal pain and constipation, loss of appetite, asthma, bronchitis, fever, cuts, dysentery, eye disorders, sprains, swellings, ulcers and wounds. *R. moorcroftianum* has been recommended to treat colds and internal injuries. *Rheum webbianum* has been advised as an astringent agent and purgative and is used for curing wounds, abdominal disorders and boils [23]. The most frequent traditional uses of *Rheum* taxa in different countries is to treat gastrointestinal **diseases**, skin problems, abdominal complaints, kidney **ailments,** jaundice, diabetes, bronchitis, worms and boils. Apart from their medicinal applications, several species of *Rheum* are used as natural dyes. The roots of *R. acuminatum, R. austral, R. moorcroftianum* and *R. webbianum* are good sources to obtain yellow color which is used in cosmetics, textile industry or as a food colorant [68, 69, 74].

22.5 Nature of *Rheum* spp. Described in ITM

In Islamic Traditional Medicine (ITM) four genus of *Rheum* have been described including *R. palmatum* (Râvand Sini), *R. rhaponticum* (Râvand Shâmi), *R. turkestanicum* (Râvand Torki) and *R. ribes* (Ribâs). The temperament (Mizaj) of *R. palmatum, R. rhaponticum* and *R. turkestanicum* are mentioned as warm and dry in second degree, but *R. ribes* is described as cold and dry in second degree (Table 22.3). In different traditional references, Rivand is mentioned as resolving (moḥallel), cutting (moqaṭeʿ), deobstruent (mofaṭeḥ), purifying (monaqi), attenuating (molaṭef), and also astringent (qabeḍ). Ribas (*R. ribes*) is attenuating, astringent and gastrointestinal tonic [75].

22.6 Medicinal Uses of *Rheum* spp. in ITM

The different properties of *Rheum* spp. are categorized according to the organs of the body on which they exert their effects.

22.6.1 Respiratory System

One of the most important therapeutic applications of *R. palmatum* and *R. rhaponticum* in ITM is respiratory problems. These rhubarb species are considered as expectorant, corrosive moisture desiccant and anti-cold cough. They also improve asthma, hemoptysis and orthopnea [4, 5, 75]. In contrast, *R. ribes* is considered as a harmful plant for respiratory system in ITM [5].

Table 22.3 *Rheum* spp. used in ITM

Rheum taxa	Part used	Temperament
R. palmatum	Roots	Warm/Dry
R. rhaponticum	Roots	Warm/Dry
R. turkestanicum	Roots	Warm/Dry
R. ribes	Stems and leaves	Cold/Dry

22.6.2 Central and Peripheral Nervous System

Rheum palmatum and *R. rhaponticum* are known as good remedies for brain purgation, headache and memory [4]. It has been reported that *R. ribes* is deleterious for central and peripheral nervous system [5].

22.6.3 Liver, Kidney and Spleen

Avicenna, in his book (Canon), together with several other scientists such as Ibn Al-Baytâr have recommended rhubarb preparations as anti-weakness and analgesic of liver and kidney [4, 5]. It is liver deobstruent and is able to break kidney and bladder stones. It also removes rigidity and edema from spleen and is useful in treating dropsy [5, 75].

22.6.4 Gastrointestinal System

According to the studied texts, rhubarb is very useful for internal organs, especially stomach and liver. It is believed that all of the species can attenuate stomach problems [4, 5, 75]. A dense extract of *R. ribes* is used to reduce thirst and to cure nausea and hemorrhoids. The astringent property of *R. ribes* seeds can be effective in curing diarrhea. The other species of *Rheum* can be beneficial in treating flatulence, hiccups, diarrhea, constipation and intestinal ulcers [4, 76].

22.6.5 Skin

In ITM, rhubarbs have a good potential for eliminating skin freckles and lentigo as well as healing dermatitis and psoriasis [4, 75]. *Rheum ribes* is used for erysipelas, rosacea acne and herpes in a preparation with barely (*Hordeum vulgare* Linn) flour [75].

22.6.6 Reproductive Organs

Rheum taxa. Except *R. ribes*, reduce libido and remove the womb pain [75].

22.6.7 Joints and Muscles

Rheum spp. except *R. ribes* are used as anti-sciatic and analgesic. They also improve muscle weakness and nerve rupture [4, 75].

22.6.8 Heart

According to ITM, *R. ribes* can empower the principle organs of the body meaning heart, brain and liver. It can also improve tachycardia [4].

22.6.9 Mental Properties

Rheum ribes is anti-depressant and exhilarant. Moreover, it attenuates melancholia and misanthropy [76].

22.6.10 Bacterial Infections

Rhubarbs are mentioned as anti-recurrent fevers in ITM [5]. Also, *R. ribes* is considered as an anti-smallpox and anti-measles herb [4].

22.6.11 Other Properties

Topical use of *R. ribes* extract is useful for improving eyesight [5, 76].

22.7 Pharmacological Aspects

At present, various pharmacological activities of *Rheum* species including anti-cancer, anti-viral, anti-fungal, anti-bacterial, anti-oxidative, anti-dermatitis, hypoglycemic, hypolipidemic and kidney and liver protective have been shown in different *in vitro*, *ex vivo* and *in vivo* studies (Tables 22.4, 22.5, 22.6). The effect of different preparations of rhubarb in treating atherosclerosis, acute bleeding of the upper gastrointestinal tract, constipation, dysenteric diarrhea and depression has been demonstrated in some clinical trials as well (Table 22.7).

Table 22.4 *In vitro* studies of *Rheum* spp.

Pharmacological effect	Species	Part used	Constituents/Preparations	Tested pathogen/cell	Results	References
Anti-cancer	*R. officinale*	–	Aqueous extract	A549 (lung) MCF-7 (breast)	Decreasing cell number, DNA fragmentation and single DNA strand breakage IC_{50}[1] for A549: 620 ± 12.7μg/mL IC_{50} for MCF-7: 515 ± 10.1μg/mL	[77]
	R. emodi	Rhizomes	MeOH and aqueous extracts	MDA-MB-435S (breast) Hep3B (liver)	Demonstrating considerable cytotoxicity in both cell lines MeOH extract: IC_{50} for MDA-MB-435S: 8.50 ± 3.70μg/mL IC_{50} for Hep3B: 38.43 ± 6.00μg/mL Aqueous extract: IC_{50} for MDA-MB-435S: 33.00 ± 8.31μg/mL IC_{50} for Hep3B: 85.58 ± 3.60μg/mL	[56]
	R. turkestanicum	Roots	*n*-hexane, EtOAc and aqueous extracts	HeLa (cervix) MCF-7 Human blood lymphocytes (non-malignant control)	Decreasing cell viability in malignant cells but not in non-malignant cells by *n*-hexane and EtOAc extracts	[70]
	R. palmatum	–	Crude extract	LS1034 cells (human colon adenocarcinoma)	Inducing apoptosis and DNA damage Decreasing the percentage of viable cells in a dose-dependent manner	[78]
	R. emodi	Leaves and rhizomes	MeOH and EtOAc extracts Pure compounds (emodin, chrysophanol and their glycosides)	MIAPaCa-2 (pancreas) HCT-116 (colon) MCF-7 T47D (breast)	Reducing the viability of MIAPaCa-2 and HCT-116 cells by rhizomes MeOH extract and leaves EtOAc extract	[79]
Anti-metastatic	*R. palmatum*	Bark	Hydro-alcoholic extract	MDA-MB-231	Inhibiting migration, mobility and invasion at non-toxic concentrations	[80]
Anti-metastatic and anti-cancer	*R. palmatum*	–	Crude extract	U-2 OS human osteosarcoma cells	Inhibiting migration and invasion of the cells Decreasing the percentage of viable cells in a dose-dependent manner	[81]
	R. palmatum	–	Hydro-alcoholic extract	SCC-9 (squamous carcinoma of the tongue) SAS (oral)	Inhibiting motility, invasion and migration at non-toxic concentrations Decreasing the viability at concentrations>20μg/mL	[82]

Anti-HBV	*R. palmatum*	Roots	Aqueous extract	HepG2 2.2.15 (liver)	Reducing the level of extracellular HBV[2] virion DNA at 64–128µg/mL Preventing the secretion of HBsAg[3] dose dependently	[83]
	R. palmatum	Rhizomes	EtOH extract	HepAD38 (liver)	Preventing the production of HBV-DNA and HBsAg dose-dependently	[84]
	R. palmatum	Rhizomes	EtOH extract	HepG2 2.2.15 (liver)	Preventing the production of HBV-DNA and HBsAg expression dose-dependently	[85]
Anti-CVB_3	*R. palmatum*	Roots and rhizomes	EtOH extract	CVB_3[4] propagated in HEp-2 (human laryngeal carcinoma)	Inhibiting the activity of CVB_3 (IC_{50}: 4µg/mL)	[86]
Anti- JEV	*R. palmatum*	Crude extract powder	MeOH and aqueous extracts Pure compounds (chrysophanol and aloe-emodin)	BHK-21 (baby hamster kidney)	Reducing JEV[5] plaque Exhibiting virucidal activity Inhibiting residual infectivity compared to controls	[87]
Anti-HIV	*R. palmatum*	Roots	Aqueous MeOH extract	Jurkat (human T-lymphoblastoid cells) HEK293T (human embryonic kidney cells)	Preventing the HIV-1[6] RNase H activity (IC_{50}: 0.9µg/mL)	[88]
	R. officinale				Preventing the HIV-1 RNase H activity (IC_{50}: 0.25µg/mL)	
Anti-H1N1	*R. tanguticum*	Roots and rhizomes	EtOH extract	Influenza virus A (H1N1) (propagated in MDCK cells)	Inhibiting viral entry Preventing viral attachment and penetration into the host cells Blocking haemagglutinin-mediated fusion	[89]
Anti-fungal	*R. emodi*	Rhizomes	MeOH extract	*Candida albicans* *Cryptococcus neoformans* *Sporotrichum schenckii* *Trichophyton mentagrophytes* *Aspergillus fumigatus*	MIC[7]: *C. albicans*: 250µg/mL *C. neoformans*: - *S. schenckii*: - *T. mentagrophytes*: 250µg/mL *A. fumigatus*: 250µg/mL	[41]
	R. emodi	Rhizomes	MeOH extract	*Aspergillus niger* *C. albicans*	MIC: *A. niger*: 50 mg/mL *C. albicans*: 16.66 mg/mL	[90]
Anti-biofilm formation	*R. undulatum*	Roots	Extract	*C. albicans*	Blocking the adhesion of *C. albicans* biofilms to polystyrene surfaces Damaging the cell membrane integrity	[91]

(continued)

Table 22.4 (continued)

Pharmacological effect	Species	Part used	Constituents/Preparations	Tested pathogen/cell	Results	References
Anti-cariogenic	*R. undulatum*	Roots	Dichloromethane extract	*Streptococcus mutans* and *S. sobrinus*	Inhibiting the caries-inducing factors Preventing *in vitro* dental plaque formation	[92]
	R. undulatum	Roots	Dichloromethane extract	*S. mutans*	Reducing the initial rate of glycolytic acid production of *S. mutans* biofilms	[93]
Anti-bacterial	*R. palmatum* *R. undulatum* *R. rhaponticum*	Roots	EtOH extract	*Staphylococcus aureus* and *S. epidermidis* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis*	All the extracts were more active against *Staphylococcus* spp. in comparison to gram negative strains *R. undulatum* extract had the strongest inhibitory effect on *Staphylococcus* spp	[94]
	R. ribes	Roots, stalks and leaves	MeOH extract	1. *S. aureus* 2. *E. coli* 3. *K. pneumonia* 4. *Pseudomonas aeruginosa* 5. *Shigella flexneri*	All extracts had good anti-bacterial activity against test organisms All extracts were found to be more active against *S. flexneri* and *K. pneumonia*	[95]
	R. ribes	Roots and rhizomes	EtOH and aqueous extracts	*E. coli* *S. aureus* *P. aeruginosa* *P. mirabilis*	Both extracts showed significant zones of inhibition against all the tested microorganisms The EtOH extract showed a higher zone of inhibition range in comparison with the aqueous extract	[96]
	R. ribes	Flowers	*n*-hexane extract Essential oil (EO)	*S. aureus* and *S. epidermidis* *S. pneumoniae* *E. coli* *K. pneumonia* *Neisseria gonorrhoeae* *P. aeruginosa* *Salmonella typhimurium*	Moderate anti-bacterial activity of extract and EO on *S. pneumonia*, *S. epidermidis*, *K. pneumonia* and *S. typhimurium* *S. epidermidis* was the most sensitive organisms affected by the hexane extract and EO	[97]

Anti-oxidant	*R. ribes*	Roots and stems	Chloroform and aqueous MeOH extracts	–	All four extracts exhibited stronger activity than known standards (BHT[8] and α-tocopherol) Higher anti-oxidant activity of root extract than stem extract was observed	[98]
	R. ribes	Roots and stems of flowers (peels and flesh)	Ether, EtOH and aqueous extracts	–	All extracts showed radical and superoxide scavenging activity A significant difference between the control and extracts in linoleic acid peroxidation was observed	[99]
	R. emodi	Rhizomes	MeOH and aqueous extracts	–	MeOH extract was a stronger anti-oxidant in comparison with aqueous extract Aqueous extract showed efficiency in DNA protection	[56]
	R. emodi	Roots	MeOH, aqueous MeOH, acetone, aqueous acetone and aqueous extracts	–	Aqueous MeOH extract was the most active extract against radicals	[100]
	R. emodi	Roots	MeOH, chloroform and EtOAc extracts	–	All extracts showed radical scavenging activity MeOH extract was the most active radical scavenger	[101]
	R. officinale	Roots and tubers	EtOH extract	–	Demonstrating strong radical scavenging activity	[102]
Pancreatic insulin secretion	*R. ribes*	Roots and rhizomes	Aqueous extract	Pancreatic β-cells (MIN6)	Stimulating insulin secretion	[103]
α-glucosidase inhibitory effect	*R. emodi*	Rhizomes	MeOH extract	α-glucosidase from yeast and rat intestinal acetone powder	Inhibiting yeast and mammalian α-glucosidase activity	[53]
	R. rhabarbarum	Peels	MeOH extract	α-glucosidase from *Saccharomyces cerevisiae*	Inhibiting α-glucosidase activity with an IC_{50} value of 0.013 ± 0.002 mg/mL	[104]
	R. palmatum	Roots	MeOH extract	α-glucosidase from *Saccharomyces cerevisiae*	Inhibiting α-glucosidase activity with an IC_{50} value of 0.014 ± 0.0001 mg/mL	
	R. palmatum	Roots	EtOAc extract	α-glucosidase from *Saccharomyces cerevisiae*	Inhibiting α-glucosidase activity with an IC_{50} value of 0.016 ± 0.0002 mg/mL	
Hepatic stellate cells migration in liver fibrosis	*R. palmatum*	Roots and rhizomes	EtOH extract	HSC-T6 (hepatic stellate cells of rat)	Attenuating TGF-β1[9]-mediated migration of HSCs by possible interference in Smad2/3[10] phosphorylation, the MAPK[11] pathway, and MMP-2[12] activity	[105]

(continued)

Table 22.4 (continued)

Pharmacological effect	Species	Part used	Constituents/Preparations	Tested pathogen/cell	Results	References
Intestinal epithelial apoptosis	*R. tanguticum*	Roots	*R. tanguticum* Polysaccharides	HIEC cells (normal human intestinal epithelium)	Elevating cell survival Decreasing MDA[13] and LDH[14] activity Reducing cell apoptosis	[106]
Radiation-induced intestinal mucosal injury	*R. tanguticum*	Roots	*R. tanguticum* Polysaccharides	IEC-6 cells (rat intestinal crypt epithelial cells)	Inhibiting cell death Reducing the formation of intracellular ROS[15] Inhibiting apoptosis partially	[107]
Bone protection	*R. rhaponticum*	Roots	ERr 731® extract	U2OS-ERα[16] (osteosarcoma) U2OS-ERβ[17] (osteosarcoma)	Activating ERα significantly Stimulating the ERβ-dependent reporter gene activity	[108]
Tyrosinase and melanin biosynthesis inhibitory	*R. officinale*	Rhizomes	Aqueous MeOH, acetone, EtOAc and aqueous extracts Different fractions of EtOAc extract Pure compounds (2 glycosylated hydroxystilbenes)	Mushroom tyrosinase/B-16 mouse melanoma cells (for pure compounds)	Inhibiting tyrosinase activity by all the mentioned extracts, fractions and pure compounds Inhibiting melanin biosynthesis by the glycosylated hydroxystilbenes	[109]

Abbreviations: [1]Half maximal inhibitory concentration, [2]Hepatitis B virus, [3]The surface antigen of the hepatitis B virus, [4]Coxsackievirus B3, [5]Japanese encephalitis virus, [6]Human immunodeficiency virus, [7]Minimum inhibitory concentration, [8]Butylated hydroxytoluene, [9]Transforming growth factor beta 1, [10]A family of structurally similar proteins that are the main signal transducers for receptors of the TGF-β, [11]Mitogen-activated protein kinase, [12]Matrix metalloproteinase 2, [13]Malondialdehyde, [14]Lactate dehydrogenase, [15]Reactive oxygen species, [16]Estrogen receptor α, [17]Estrogen receptor β

Table 22.5 *Ex vivo* studies of *Rheum* spp.

Pharmacological effect	Species	Part used	Constituents/Preparations	Tested animal/tissue or cell	Results	References
Laxative	*R. palmatum*	Roots	EtOH extract	Sprague–Dawley rats/ileum	Affecting the Na^+-K^+-$2Cl^-$ cotransporter more directly than Na^+-K^+ ATPase on the serosal side of the intestinal epithelial cells	[110]
Hypotensive	*R. undulatum*	Rhizomes	Aqueous extract	Sprague–Dawley rats/thoracic aortae	Dilating vascular smooth muscles (vasorelaxation)	[111]
	R. undulatum	Rhizomes	MeOH extract	Sprague–Dawley rats/thoracic aortae	Dilating vascular smooth muscles (vasorelaxation)	[112]

Table 22.6 *In vivo* studies of *Rheum* spp.

Disease	Species	Part used	Constituents/Preparations	Animal	Study design	Results	References
CVB_3 infection	*R. palmatum*	Roots and rhizomes	EtOH extract in normal saline	BALB/c mice	i.p.[1] administration of the extract at 0.3 g/kg/d starting from 24 hours post-virus exposure	Alleviating clinical signs Increasing survival rate Decreasing viral titer	[86]
Hypoglycemic effect in healthy mice	*R. ribes*	Roots	Hydro-alcoholic extract, chloroform and water fractions of hydro-alcoholic extract in normal saline (containing Tween 80)	NMRI mice	Single dose oral administration of extracts at 50 mg/kg to healthy mice	Reducing blood glucose in healthy mice by water fraction	[113]
Glucose and starch tolerance test	*R. ribes*	Roots and rhizomes	Aqueous extract	Sprague-Dawley rats	Oral administration of extract at 125, 250 and 500 mg/kg	Improving glucose homeostasis through retarding carbohydrate digestion	[114]
Diabetes	*R. franzenbachii*	Roots and rhizomes	EtOH extract in NaCMC[2] solution	Wistar rats	Oral administration of the extract at 125, 250 and 500 mg/kg/d for 14 days	Reducing plasma glucose level and MDA Increasing catalase activity	[115]
	R. ribes	Rhizomes	Aqueous extract fractions in normal saline	Swiss-Webster mice	i.p. administration of fractions at 12.5, 25 and 50 mg/kg	Decreasing blood glucose Improving peripheral nerve function	[116]
	R. turkestanicum	Roots	Hydro-alcoholic extract in water	Wistar rats	Oral administration of extract at 100, 200 and 300 mg/kg/d for 4 weeks	Decreasing blood glucose, HbA1c[3], TG[4], total Chol[5], and LDL[6] Suppressing body weight loss Reducing ALT[7], AST[8] and LDH activity	[117]

Dyslipidemia in diabetes	*R. palmatum*	Rhizomes	Aqueous extract in saline	Wistar rats	Oral administration of extract at 150 and 300 mg/kg, and 300 mg/kg (plus 0.2 mg/kg atropine)	Decreasing postprandial hypertriglyceridemia at 150 and 300 mg/kg by promoting intestinal transit in a dose-dependent manner	[118]
	R. turkestanicum	Rhizomes	Water decoction	Wistar rats	Oral administration at 200, 400 and 600 mg/kg/d for 3 weeks.	Decreasing TG levels in comparison to untreated diabetic rats Reducing cholesterol levels at the doses of 400 and 600 mg/kg as compared to the control group	[119]
Dyslipidemia in high-fat diet	*R. rhabarbarum*	Rhizomes	EtOH extract in 0.8% CMC solution	C57BL/6 mice	Oral administration of extract at 100 mg/kg for 8 weeks	Blocking body weight gain Reducing feed efficiency, liver weight and total and LDL-cholesterol levels	[120]
Dyslipidemia	*R. emodi*	Rhizomes	EtOH extract and different fractions (hexane, chloroform, butanol-soluble and butanol-insoluble) of EtOH extract in 0.2% w/w aqueous gum acacia solution	Charles foster rats	Oral administration of the extract and fractions at 200 mg/kg	Decreasing total cholesterol, phospholipid, TG, VLDL[9] and LDL besides an increase in HDL[10] by EtOH extract and butanol-soluble fraction	[121]
Nephrotoxicity	*R. emodi*	Rhizomes	Water-soluble and insoluble fractions of MeOH extract in 1% CMC solution	Wistar albino rats	Oral administration of extracts at 350 mg/kg/d	Water-soluble fraction: protecting all the proximal tubule segments Water-insoluble fraction: protecting S2 segment of proximal tubule beside enhancing gentamicin nephrotoxicity	[122]
	R. palmatum	Roots and rhizomes	EtOH extract, total anthraquinones, total tannins and remaining compounds fractions in 0.5% CMC solution	Sprague-Dawley rats	Treatment with different fractions at different doses for 7 days.	Only total tannin fraction protected the kidney function in $K_2Cr_2O_7$-injured rats	[123]

(continued)

Table 22.6 (continued)

Disease	Species	Part used	Constituents/Preparations	Animal	Study design	Results	References
Chronic renal failure	*R. officinale*	Roots	Petroleum ether (PE), EtOAc, and butanol (BU) fractions	Sprague-Dawley rats	Oral administration of PE, EtOAc and BU fractions at 800, 200 and 600 mg/kg, respectively for 6 weeks	All of the fractions resulted in: Lowering creatinine and BUN[11] levels Enhancing creatinine clearance Improving renal tubulointerstitial injury	[124]
Diabetic nephropathy	*R. officinale*	Roots	Water decoction	Wistar rats	Oral administration of water extract at 125 mg/kg/d for 80 days	Ameliorating high blood and urinary glucose levels Improving hyperlipidemia and creatinine excretion	[125]
$HgCl_2$ renal toxicity	*R. turkestanicum*	Roots	Hydro-alcoholic extract in saline	Wistar rats	i.p. administration of extract at 100 and 200 mg/kg/d for 3 days	Improving necrosis and atrophy of the kidney Decreasing serum urea, creatinine and renal MDA	[126]
$HgCl_2$ hepatotoxicity	*R. turkestanicum*	Roots	Hydro-alcoholic extract in saline	Wistar rats	i.p. administration of extract at 100 and 200 mg/kg/d for 3 days	Improving liver function by reducing serum ALT and AST Decreasing MDA and inflammatory infiltration in the liver	[126]
Chronic liver injury	*R. palmatum*	Roots and rhizomes	Hydro-alcoholic extract in normal saline	Sprague-Dawley rats	Intragastric administration of rhubarb extract at 2, 5.40, 14.69 and 40 g/kg/d for 12 weeks	Hepatoprotection for injured rats at 2 and 5.4 g/kg/d Hepatic injury for normal rats at all the tested doses and injured rats at 14.69 and 40 g/kg/d	[127]
Acute liver failure	*R. palmatum*	Roots and rhizomes	–	ICR mice	i.p. administration of *R. palmatum* at 1.5 g/kg/d	Reducing ALT, AST and inflammatory factors Regulating the expression of apoptosis-related proteins	[128]

Nonalcoholic fatty liver disease	*R. palmatum*	Roots and rhizomes	Aqueous extract in normal saline	Sprague-Dawley rats	Oral administration of extract at 690 and 1300 mg/kg/d for 6 weeks	Reducing liver weight, blood glucose, ALT enzyme and liver steatosis	[129]
Hepatotoxicity	*R. emodi*	Roots and rhizomes	Flavonoid-containing fractions in normal saline	Wistar rats	Oral administration of different fractions every 6 hours	Decreasing ALT, AST, ALP[12] and bilirubin	[130]
Hepatocellular carcinoma	*R. palmtum*	Roots	MeOH extract	Wistar rats	Oral administration of extract at 100 mg/kg/d for 12 weeks	Reducing the elevated ALT and AST Increasing total proteins, albumin and globulin Reducing the tumor markers (AFP[13] and GGT[14]) levels	[131]
TNBS-induced colitis	*R. Tanguticum*	–	*R. tanguticum* polysaccharides	Sprague-Dawley rats	Oral administration of polysaccharides at 200 mg/kg/d for 5, 7, 10 and 14 days	Reducing diarrhea, mortality, colon mass and ulcer area	[132]
	R. tanguticum	–	*R. tanguticum* polysaccharides	Sprague-Dawley rats	Oral administration of extract alone or in combination with 5-ASA at 200 mg/kg/d for 5 days	Both groups resulted in: Attenuating histological signs Decreasing NF-κBp65[15] and TNF-α[16] expressions Inhibiting the overexpression of COX-2[17]	[133]
Gastric ulcer	*R. ribes*	Leaves	Aqueous and MeOH extracts in 0.5% acacia gum solution	Wistar rats	Oral administration of the extracts at 200 mg/kg/d for 5 days	MeOH extract increased the level of muco proteins and reduced ulcer scores	[134]

(continued)

Table 22.6 (continued)

Disease	Species	Part used	Constituents/Preparations	Animal	Study design	Results	References
Uterotrophy model	*R. rhaponticum*	Roots	ERr 731® extract in Caster oil	Wistar rats	s.c.[18] administration of estradiol at 0.5µg/kg/d alone or in combination with ERr 731® at 0.1, 1, 10 and 100 mg/kg/d for 3 days	Reducing the estradiol-induced uterine growth stimulation when combined with estradiol	[135]
					s.c. administration of estradiol at 4µg/kg/d and ERr 731® at 0.1, 1, 10 and 100 mg/kg/d, for 3 days		
Endometrial safety	*R. rhaponticum*	Roots	ERr 731® extract	Wistar rats	Oral administration of the extract at 1 mg/kg or 1 g/kg for 90 days	No stimulatory activity on proliferation in the uterus No effect on the bone mineral density	[136]
Experimental atopic dermatitis	*R. Tanguticum*	Rhizomes	Hydro-alcoholic extract	NC/Nga mice	Oral administration of the extract at 30–300 mg/kg/d for 5 weeks	Ameliorating skin leisons Inhibiting dermatitis	[137]
Pigmentation	*R. officinale*	Roots and rhizomes	Raspberry ketone (RK) in Vaseline	C57BL/6 J mice	Topical application of 0.2 or 2% RK twice daily for 3 weeks	Increasing the degree of skin whitening within 1 week of treatment	[138]
Irradiation-induced immune damage	*R. tanguticum*	–	A polysaccharide component in saline	Kunming mice	Oral administration of the component at 200, 400 and 800 mg/kg/d for 14 days before irradiation	Promoting the innate immune function by increasing spleen and thymus index, phagocytic function of macrophages, and rate of carbon clearance Improving humoral and cellular immune function by increasing serum hemolysin and NK cells[19] activity, respectively	[139]

Yeast-induced pyrexia	*R. palmatum*	Roots	MeOH extract in normal saline	Sprague-Dawley rats	Oral administration of extract at 3.5 g/kg 1 h before and 3 hrs after pyrexia induction	Decreasing rectal temperature from 4–12 hrs after yeast induction Inhibiting PGE_2[20] production	[140]
Alzheimer's disease	*R. ribes*	Roots and rhizomes	Hydro-alcoholic extract	Wistar rats	i.p. administration of extract at 250 and 500 mg/kg/d for 20 days	Improving memory deficits induced by bilateral nucleus basalis of Meynert lesions	[141]

Abbreviations: [1]Intraperitoneal, [2]Sodium carboxymethyl cellulose, [3]Hemoglobin A1c, [4]Triglyceride, [5]Cholesterol, [6]Low-density lipoprotein, [7]Alanine aminotransferase, [8]Aspartate aminotransferase, [9]Very low-density lipoprotein, [10]High-density lipoprotein, [11]Blood urea nitrogen, [12]Alkaline phosphatase, [13]α-fetoprotein, [14]Gamma-glutamyl transferase, [15]Nuclear factor κB, [16]Tumor necrosis factor α, [17]Cyclooxygenase 2, [18]Subcutaneous, [19]Natural killer cell, [20]Prostaglandin E_2

Table 22.7 Clinical studies of *Rheum* spp.

Disease	Species	Part used	Preparations	Study design	Participants	Dose	Results	References
Atherosclerosis	*R. officinale*	Roots	Capsules (from aqueous extract)	Randomized, double-Blind, placebo-controlled, clinical trial	103 patients aged between 45–65 years,	Trial group: routine medications plus rhubarb capsules at 50 mg/kg Control group: Routine medications (metoprolol and aspirin) plus placebo capsules containing starch	Improving endothelial function (which might be mainly due to its lipid-lowering effect)	[142]
Acute bleeding of the upper gastrointestinal tract	–	–	Raw rhubarb powder Raw rhubarb tablet Roasted rhubarb powder	–	400 patients aged between 13–81 years	3 g 2–4 times daily until occult blood ceased to occur in the stool	Ceasing the bleeding rapidly Decreasing the loss of blood and need for anti-coagulant drugs Disappearing the absorption fever Increasing appetite Correcting anemia	[143]
Constipation after operation for lumbar vertebral fracture	*R. officinale*	–	Gauze smeared by powder	–	74 patients aged between 28–66, failed to pass gas in 6 h after the internal fixation for lumbar vertebral fracture, coupled with abdominal distention and discomfort	Observation group: Ordinary treatment plus daily topical application of rhubarb at acupoint Shenque for 6 h for 3 days Control group: Ordinary treatment	Lowering the time to conduct the first flatulence and defecation	[144]

Dysenteric diarrhea in children	*R. ribes*	Dried fruits	Syrup (from aqueous extract)	Randomized, double-blind, placebo controlled and parallel-group clinical trial	150 children aged between 12–72 months with suspected *Shigella* dysentery	2.5 mL for children less than 15 kg, or 5 mL for children more than 15 kg, every 6 hrs. For 5 days+standard antibiotic treatment	Alleviating the severity of fever and diarrhea Reducing the duration of dysentery, fever and abdominal pain	[145]
Primary dysmenorrhea	*R. emodi*	Roots and rhizomes	Capsules (from roots and rhizomes powder)	Randomized, single-center, single-blind, standard controlled Trial	45 unmarried participants between ages of 15–25 years, having regular menstrual cycles with moderate to severe dysmenorrhea	Experimental group: 3 capsules of rhubarb twice a day starting from 2 days before menstruation and continuing until first 3 days of menstruation for 3 consecutive cycles Control group: 1 capsules of mefenamic acid 3 times a day after meal with the same protocol	Decreasing the menstrual pain by both treatments after three-cycle intervention	[146]
Major depressive disorder	*R. ribes*	Stalks	Capsules (from hydro-alcoholic extract)	Randomized, double blind, parallel-group trial	33 patients aged between 18–60 years, having mild to moderate major depressive disorder	Oral administration of 400 mg capsules 3 times daily for 6 weeks	Reducing depressive symptoms in week 4 and 6	[147]

22.8 Conclusion

Traditional medicine around the world plays an important role in exploring new drugs. Utilizing from accurate instructions of famous scientists, ITM texts are valuable sources for detecting new drugs. In this review, the applications and lucrative properties of *Rheum* spp. were investigated in ITM books, and adapted with the results reported in pharmacological studies.

Rhubarb is said to possess a wide range of therapeutic applications in the traditional and folklore medicine such as healing gastrointestinal, liver, kidney, womb and bladder diseases, diarrhea and constipation [4, 5], skin problems, diabetes, bronchitis and boils. The medicinal effects of rhubarb may owe to the several chemical compounds present in this plant specifically anthraquinones, anthrones and different phenolic compounds such as stilbenes, flavonoids and tannins. The effect of this herb in treating both constipation and diarrhea is due to anthraquinones and tannins, respectively. At low doses, rhubarb is said to act as anti-diarrheal, while at higher doses it is cathartic [148]. Many effects of rhubarb including anti-cancer, anti-microbial, anti-oxidant, anti-diabetic, anti-dyslipidemic, anti-pigmentation, nephroprotective, hepatoprotective and immunoprotective have been shown in *in vitro* and *in vivo* studies. In addition, some clinical trials have indicated the efficacy of this plant in treating atherosclerosis, gastrointestinal bleeding, diarrhea and dysmenorrhea which is in agreement with the traditional and folklore medical applications of rhubarb. The results of previous studies have shown significant differences in the chemical composition of *Rheum* genus, and it is recommended that clinical practice should be performed for each species individually [20]. Though many pharmacological activities of *Rheum* spp. have been investigated, further studies especially clinical trials are needed to fill the present gaps in our knowledge of different aspects of this plant. According to the potency of rhubarb in treating different diseases, the demand for this plant in international and domestic markets is growing leading to excessive exploration and a sharp drop in the wild resources of rhubarb as well as damage to the wildlife [149]. Several ***Rheum*** species are under immense risk and have been considered as “threatened” and it is of great importance to stop overharvesting and habitat destruction and establish rhubarb gardens in combination with education and awareness programs for large-scale cultivation and conservation of this genus [23].

Taken together, rhubarb is a valuable medicinal plant that has been useful in treating several diseases for centuries. Due to the different therapeutic effects mentioned in the ITM texts and folklore medicine as well as various pharmacological and clinical studies and notable phytochemicals isolated from *Rheum* spp., this genus is highly recommended to the herbal pharmaceutical industry for manufacturing several oral and topical formulations beside exploring new lead compounds and drugs for treating skin, gastrointestinal, metabolic and reproductive diseases.

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Conflict of Interest None.

References

1. Shimomura K, Yoshimatsu K, Jaziri M, Ishimaru K. Traditional medicinal plant genetic resources and biotechnology applications. In: Watanabe K, Pehu E, editors. Plant biotechnology and plant genetic resources for sustainability and productivity. Austin: RG Landes Company and Academic Press Inc; 1997. pp. 209–225
2. Barney DL, Hummer KE (2012) Rhubarb: botany, horticulture, and genetic resources. In: Janick J (ed) Horticultural reviews, vol 40. Wiley, New York, pp 147–182
3. Mozaffarian V (2013) Identification of medicinal and aromatic plants of Iran. Farhang Moaser Publishers, Tehran. (in Persian)
4. Al-Baytâr AA (1992) Al-Jâmeʿ le-Mofradât al-Adwiah wa al-Aghd̲iyah (comprehensive book in simple drugs and foods). Dâr al-Kotob al-Iʿlmiyah, Beirut
5. Ibn Sinâ HA (2015) Al-Qanun fi'l-Ṭibb (canon of medicine). In Masoudi A (ed). Almaʿee, Tehran
6. Zhang WS, Li F, Bao JQ, Wang SC, Shang GW, LI JC, et al. (2008) Regulative effects of emodin on

aquaporin 2 expression in intestinal epithelial cell line LoVo. Chin Tradit Herb Drug 39(5):718–723
7. Shi P, Huang Z, Chen G (2008) Rhein induces apoptosis and cell cycle arrest in human hepatocellular carcinoma BEL-7402 cells. Am J Chin Med 36(4):805–813
8. Chen J, Ma M, Lu Y, Wang L, Wu C, Duan H (2009) Rhaponticin from rhubarb rhizomes alleviates liver steatosis and improves blood glucose and lipid profiles in KK/Ay diabetic mice. Planta Med 75(05):472–477
9. Liu L, Mei Q, Li B, Zhou S, Cao Z (2001) Antioxidation of Tanguficum maxim polysaccharide on acute liver injury mice. J Fourth Military Med Univ 22(6):530–533
10. Zhao YL, Wang JB, Zhou GD, Shan LM, Xiao XH (2009) Investigations of free anthraquinones from rhubarb against α-naphthylisothiocyanate-induced cholestatic liver injury in rats. Basic Clin Pharmacol Toxicol 104(6):463–469
11. Gao Q, Qin WS, Jia ZH, Zheng JM, Zeng CH, Li LS et al (2010) Rhein improves renal lesion and ameliorates dyslipidemia in db/db mice with diabetic nephropathy. Planta Med 76(01):27–33
12. Li AR (1998) Flora Republicae popularis Sinicae. Science Press, Beijing
13. Wang A, Yang M, Liu J (2005) Molecular phylogeny, recent radiation and evolution of gross morphology of the rhubarb genus *Rheum* (Polygonaceae) inferred from chloroplast DNA trnL-F sequences. Ann Bot 96(3):489–498
14. Ruirui L, Wang A, Tian X, Wang D, Liu J (2010) Uniformity of karyotypes in *Rheum* (Polygonaceae), a species-rich genus in the Qinghai-Tibetan Plateau and adjacent regions. Caryologia 63(1):82–90
15. Shi YF, Li JJ, Li BY (1998) Uplift and environmental changes of Qinghai-Tibetan Plateau in the late Cenozoic. Guangdong Science and Technology Press, Guangzhou, 463 p
16. Bao B, Grabovskaya-Borodina AE (2003) *Rheum*. In: Li AR, Bao BJ (eds) Flora of China, vol 5. Science Press/Missouri Botanical Garden, Beijing/St. Louis, pp 341–350
17. Joharchi MR, Amiri MS (2012) Taxonomic evaluation of misidentification of crude herbal drugs marketed in Iran. Avicenna J Phytomed 2(2):105–112
18. Amiri MS, Joharchi MR (2013) Ethnobotanical investigation of traditional medicinal plants commercialized in the markets of Mashhad. Iran Avicenna J Phytomed 3(3):254–271
19. Srivastava TN, Rajasekharan S, Badola DP, Shah DC (1986) An index of the available medicinal plants, used in Indian system of medicine from Jammu and Kashmir state. Anc Sci Life 6(1):49–63
20. Ye M, Han J, Chen H, Zheng J, Guo D (2007) Analysis of phenolic compounds in rhubarbs using liquid chromatography coupled with electrospray ionization mass spectrometry. J Am Soc Mass Spectrom 18(1):82–91
21. Zheng JH, Guo DA (2007) Modern research on rhubarb. Peking University Medical Press, Beijing, pp 453–454
22. Kabir Dar A, Siddiqui MAA, Wahid-ul H, Lone AH, Manzoor N, Haji A (2015) Threat status of *Rheum emodi* – a study in selected cis-Himalayan regions of Kashmir valley Jammu & Kashmir India. Med Aromat Plants 4(1):183–186
23. Singh A, Lal M, Samant SS (2009) Diversity, indigenous uses and conservation prioritization of medicinal plants in Lahaul valley, proposed Cold Desert biosphere reserve. India Int J Biodivers Sci Manage 5(3):132–154
24. Dagarova SS, Sitpayeva GT (2017) Conservation of biodiversity of wild plant of *Rheum wittrockii* Lundstr of Kazakhstan. Biosci Biotech Res Asia 14(1):93–98
25. Amiri MS, Joharchi MR (2016) Ethnobotanical knowledge of Apiaceae family in Iran: a review. Avicenna J of Phytomed 6(6):621–635
26. Byg A, Salick J, Law W (2010) Medicinal plant knowledge among lay people in five Eastern Tibet villages. Hum Ecol 38(2):177–191
27. Song B, Zhang ZQ, Stöcklin J, Yang Y, Niu Y, Chen JG et al (2013) Multifunctional bracts enhance plant fitness during flowering and seed development in *Rheum nobile* (Polygonaceae), a giant herb endemic to the high Himalayas. Oecologia 172(2):359–370
28. Chen F, Wang A, Chen K, Wan D, Liu J (2009) Genetic diversity and population structure of the endangered and medically important *Rheum tanguticum* (Polygonaceae) revealed by SSR markers. Biochem Syst Ecol 37(5):613–621
29. Hu Y, Wang L, Xie X, Yang J, Li Y, Zhang H (2010) Genetic diversity of wild populations of *Rheum tanguticum* endemic to China as revealed by ISSR analysis. Biochem Syst Ecol 38(3):264–274
30. Yang X, Ma X, Yang L, Yu D, Qian Y, Ni H (2009) Efficacy of *Rheum officinale* liquid formulation on cucumber powdery mildew. Crop Prot 28(12):1031–1035
31. Fei Y, Wang J, Peng B, Peng J, Hu JH, Zeng ZP et al (2017) Phenolic constituents from *Rheum nobile* and their antioxidant activity. Nat Prod Res 31(24):2842–2849
32. Rokaya MB, Maršík P, Münzbergová Z (2012) Active constituents in *Rheum acuminatum* and *Rheum australe* (Polygonaceae) roots: a variation between cultivated and naturally growing plants. Biochem Syst Ecol 41:83–90
33. Verma SC, Singh NP, Sinha AK (2005) Determination and locational variations in the quantity of hydroxyanthraquinones and their glycosides in rhizomes of *Rheum emodi* using high-performance liquid chromatography. J Chromatogr A 1097(1):59–65
34. Malik S, Sharma N, Sharma UK, Singh NP, Bhushan S, Sharma M et al (2010) Qualitative and quantitative analysis of anthraquinone derivatives in rhizomes of tissue culture-raised *Rheum emodi* wall. Plants. J Plant Physiol 167(9):749–756

35. Shang X, Yuan Z (2003) Determination of active components in rhubarb and study of their hydrophobicity by micellar electrokinetic chromatography. Bioorganic Med Chem Lett 13(4):617–622
36. Tabin S, Gupta RC, Kamili AN, Bansal G (2016) Phytochemical analysis of wild and *in vitro* raised plants of *Rheum* species using HPLC. Biochem Pharmacol 5(4):215–221
37. Liu B, Yang J, Wang S (2007) The chemical constituents in rhubarb rhizomes and roots derived from *Rheum emodi* Wall. West Chin J Pharm Sci 22(1):33
38. Wang AQ, Li JL, Li JS (2010) Chemical constituents of *Rheum emodi*. Chin Tradit Herb Drug 41(3):343–347
39. Singh SS, Pandey SC, Singh R, Agarwal SK (2005) 1, 8-Dihydroxyanthraquinone derivatives from rhizomes of *Rheum emodi* Wall. Indian J Chem 44(7):1494–1496
40. Okabe H, Matsuo K, Nishioka I (1973) Studies on rhubarb (Rhei rhizoma). II. Anthraquinone glycosides. Chem Pharm Bull 21(6):1254–1260
41. Agarwal SK, Singh SS, Verma S, Kumar S (2000) Antifungal activity of anthraquinone derivatives from *Rheum emodi*. J Ethnopharmacol 72(1):43–46
42. Nizioł J, Sekuła J, Ruman T (2017) Visualizing spatial distribution of small molecules in the rhubarb stalk (*Rheum rhabarbarum*) by surface-transfer mass spectrometry imaging. Phytochemistry 139:72–80
43. Liu SY, Sporer F, Wink M, Jourdane J, Henning R, Li YL et al (1997) Anthraquinones in *Rheum palmatum* and *Rumex dentatus* (Polygonaceae), and phorbol esters in *Jatropha curcas* (Euphorbiaceae) with molluscicidal activity against the schistosome vector snails *Oncomelania*, *Biomphalaria*, and *Bulinus*. Tropical Med Int Health 2(2):179–188
44. Komatsu K, Nagayama Y, Tanaka K, Ling Y, Cai SQ, Omote T et al (2006) Comparative study of chemical constituents of rhubarb from different origins. Chem Pharm Bull 54(11):1491–1499
45. Komatsu K, Nagayama Y, Tanaka K, Ling Y, Basnet P, Meselhy MR (2006) Development of a high performance liquid chromatographic method for systematic quantitative analysis of chemical constituents in rhubarb. Chem Pharm Bull 54(7):941–947
46. He LY, Luo SR (1980) Studies on the analysis of anthraquinone derivatives of Chinese medicinal herbs. I. Separation and determination of constituents of Chinese rhubarb. Yao Xue Xue Bao 15(9):555–562. (In Chinese)
47. Babu KS, Srinivas PV, Praveen B, Kishore KH, Murty US, Rao JM (2003) Antimicrobial constituents from the rhizomes of *Rheum emodi*. Phytochemistry 62(2):203–207
48. Oshio H (1978) Investigation of rhubarbs (IV) isolation of sennoside D, citreorosein and laccaic acid. Shoyakugaku zassi 32(1):19–23
49. Krenn L, Presser A, Pradhan R, Bahr B, Paper DH, Mayer KK et al (2003) Sulfemodin 8-*O*-β-D-glucoside, a new sulfated anthraquinone glycoside, and antioxidant phenolic compounds from *Rheum emodi*. J Nat Prod 66(8):1107–1109
50. Kumar DRN, Shikha S, George VC, Suresh PK, Kumar RA (2012) Anticancer and anti-metastatic activities of *Rheum emodi* rhizome chloroform extracts. Asian J Pharm Clin Res 5(3):189–194
51. Krenn L, Pradhan R, Presser A, Reznicek G, Kopp B (2004) Anthrone C-glucosides from *Rheum emodi*. Chem Pharm Bull 52(4):391–393
52. Krafczyk N, Kötke M, Lehnert N, Glomb MA (2008) Phenolic composition of rhubarb. Eur Food Res Technol 228(2):187
53. Babu KS, Tiwari AK, Srinivas PV, Ali AZ, Raju BC, Rao JM (2004) Yeast and mammalian α-glucosidase inhibitory constituents from Himalayan rhubarb *Rheum emodi* Wall. ex Meisson. Bioorganic Med Chem Lett. 14(14):3841–3845
54. Matsuda H, Morikawa T, Toguchida I, Park JY, Harima S, Yoshikawa M (2001) Antioxidant constituents from rhubarb: structural requirements of stilbenes for the activity and structures of two new anthraquinone glucosides. Bioorg Med Chem 9(1):41–50
55. Shikishima Y, Takaishi Y, Honda G, Ito M, Takeda Y, Kodzhimatov OK et al (2001) Phenylbutanoids and stilbene derivatives of *Rheum maximowiczii*. Phytochemistry 56(4):377–381
56. Rajkumar V, Guha G, Ashok KR (2011) Antioxidant and anti-cancer potentials of *Rheum emodi* rhizome extracts. Evid Based Complement Alternat Med 2011:697986
57. Chumbalov PK, Nurgalieva GM (1967) Flavonoids of *Rheum tataricum*. V. Chem Nat Compd 3(5):291
58. Nonaka G, Nishioka I (1983) Tannins and related compounds. X. Rhubarb (2): isolation and structures of a glycerol gallate, gallic acid glucoside gallates, galloylglucoses and isolindleyin. Chem Pharm Bull 31(5):1652–1658
59. Pan H, Lundgren LN (1994) Rhododendrol glycosides and phenyl glucoside esters from inner bark of *Betula pubescens*. Phytochemistry 36(1):79–83
60. Morales R, Pardo-de-santayana M, Tardio J (2006) The perception of plants in the complete works of Cervantes, particularly “Don Quijote” In: Proceedings of the IVth International Congress of ethnobotany, pp 451–459
61. Nedelcheva A (2012) Medicinal plants from an old Bulgarian medical book. J Med Plant Res 6(12):2324–2339
62. Pieroni A, Gray C (2008) Herbal and food folk medicines of the Russlanddeutschen living in Künzelsau/Taläcker, South-Western Germany. Phytother Res 22(7):889–901
63. Ryabushkina N, Gemedjieva N, Kobaisy M, Cantrell CL (2008) Brief review of Kazakhstan flora and use of its wild species. Asian Australas J Plant Sci Biotechnol 2(2):64–71
64. Hsu H, Chen Y, Shen S, Hsu S, Chen C, Chang H (1986) Oriental Materia Medica: a concise guide. Oriental Healing Arts Inst, Taipei

65. Shang X, Tao C, Miao X, Wang D, Tangmuke D et al (2012) Ethno-veterinary survey of medicinal plants in Ruoergai region, Sichuan province, China. J Ethnopharmacol 142(2):390–400
66. Buntaine MT, Mullen RB, Lassoie JP (2007) Human use and conservation planning in Alpine areas of Northwestern Yunnan. China Environ Dev Sustain 9(3):305–324
67. Tang T, Yin L, Yang J, Shan G (2007) Emodin, an anthraquinone derivative from *Rheum officinale* Baill, enhances cutaneous wound healing in rats. Eur J Pharmacol 567(3):177–185
68. Malaisse F, Clause W, Drolkar P, Lopsang R, Wangdu L, Mathieu F (2012) Ü ethnomycology and ethnobotany (South Central Tibet). Diversity, with emphasis on two underrated targets: plants used for dyeing and incense. Geo Eco Trop 36:185–199
69. Rokaya MB, Münzbergová Z, Timsina B (2010) Ethnobotanical study of medicinal plants from the Humla district of Western Nepal. J Ethnopharmacol 130(3):485–504
70. Shiezadeh F, Mousavi SH, Amiri MS, Iranshahi M, Tayarani-Najaran Z, Karimi G (2013) Cytotoxic and apoptotic potential of *Rheum turkestanicum* Janisch root extract on human cancer and normal cells. Iran J Pharm Res 12(4):811–819
71. Khan B, Abdukadir A, Qureshi R, Mustafa G (2011) Medicinal uses of plants by the inhabitants of Khunjerab National Park, Gilgit, Pakistan. Pak J Bot 43(5):2301–2310
72. Shah GM, Ahmad M, Arshad M, Khan MA, Zafar M, Sultana S (2012) Ethno-phyto-veterinary medicines in northern Pakistan. J Anim Plant Sci 22:791–797
73. Khan KU, Shah M, Ahmad H, Ashraf M, Rahman IU, Iqbal Z et al (2015) Investigation of traditional veterinary phytomedicines used in Deosai plateau. Pakistan Global Vet 15(4):381–388
74. Kala CP (2002) Indigenous knowledge of Bhotiya tribal community on wool dyeing and its present status in the Garhwal Himalaya. India Curr Sci 83(7):814–817
75. Aqili Alawi Khorâsâni Shirâzi MH (2014) Makhzan al-Adwiyah (Drug Treasure). In Shams Ardakani MR, Rahimi R, Farjadmand F (eds) Sabz Arang Publisher, Tehran
76. Al-Anṭâki D (2000) Taḏkirat olo al-Albâb Wa al-Jâme le al-Aʿjb al-Uʿjâb (the reminder to wise people and the miraculous collector). Dâr-al-Kotob al- Iʿlmiyah, Beirut
77. Li WY, Chan SW, Guo DJ, Chung MK, Leung TY, Yu PH (2009) Water extract of *Rheum officinale* Baill. induces apoptosis in human lung adenocarcinoma A549 and human breast cancer MCF-7 cell lines. J Ethnopharmacol 124(2):251–256
78. Ma YS, Hsu SC, Weng SW, Yu CC, Yang JS, Lai KC et al (2013) Crude extract of *Rheum palmatum* L induced cell death in LS1034 human colon cancer cells acts through the caspase-dependent and -independent pathways. Environ Toxicol 29(9):969–980
79. Pandith SA, Hussain A, Bhat WW, Dhar N, Qazi AK, Rana S et al (2014) Evaluation of anthraquinones from Himalayan rhubarb (*Rheum emodi* Wall. ex Meissn.) as antiproliferative agents. S Afr J Bot 95:1–8
80. Nho KJ, Chun JM, Lee AY, Kim HK (2015) Anti-metastatic effects of *Rheum Palmatum* L. extract in human MDA-MB-231 breast cancer cells. Environ Toxicol Pharmacol 40(1):30–38
81. Hsu SC, Lin JW, Weng SW, Chueh FS, Yu CC, Lu KW et al (2013) Crude extract of *Rheum palmatum* inhibits migration and invasion of U-2 OS human osteosarcoma cells by suppression of matrix metalloproteinase-2 and -9. Biomedicine 3(3):120–129
82. Chen YY, Hsieh MJ, Hsieh YS, Chang YC, Chen PN, Yang SF et al (2017) Antimetastatic effects of *Rheum palmatum* L. extract on oral cancer cells. Environ Toxicol 32(10):2287–2294
83. Kim TG, Kang SY, Jung KK, Kang JH, Lee E, Han HM et al (2001) Antiviral activities of extracts isolated from *Terminalis chebula* Retz., *Sanguisorba officinalis* L., *Rubus coreanus* Miq. and *Rheum palmatum* L. against hepatitis B virus. Phytother Res 15(8):718–720
84. Sun Y, Li LJ, Li J, Li Z (2007) Inhibition of hepatitis B virus replication by *Rheum palmatum* L. ethanol extract in a stable HBV-producing cell line. Virol Sin 22(1):14–20
85. Li Z, Li LJ, Sun Y, Li J (2007) Identification of natural compounds with anti-hepatitis B virus activity from *Rheum palmatum* L. ethanol extract. Chemotherapy 53(5):320–326
86. Xiong HR, Shen YY, Lu L, Hou W, Luo F, Xiao H et al (2012) The inhibitory effect of *Rheum palmatum* against coxsackievirus B3 *in vitro* and *in vivo*. Am J Chin Med 40(4):801–812
87. Chang SJ, Huang SH, Lin YJ, Tsou YY, Lin CW (2014) Antiviral activity of *Rheum palmatum* methanol extract and chrysophanol against Japanese encephalitis virus. Arch Pharm Res 37(9):1117–1123
88. Esposito F, Carli I, Del Vecchio C, Xu L, Corona A, Grandi N et al (2016) Sennoside A, derived from the traditional chinese medicine plant *Rheum* L., is a new dual HIV-1 inhibitor effective on HIV-1 replication. Phytomedicine 23(12):1383–1391
89. Lin TJ, Lin CF, Chiu CH, Lee MC, Horng JT (2016) Inhibition of endosomal fusion activity of influenza virus by *Rheum tanguticum* (da-huang). Sci Rep 6:27768
90. Wani SA, Shah KW, Ahmad MA (2013) Antifungal activities of methanolic extracts of *Podophyllum hexandrum* and *Rheum emodi* against human pathogenic fungal strains. Int J Pharm Sci Rev Res 19(2):56–59
91. Lee HS, Kim Y (2014) Antifungal activity of *Rheum undulatum* on *Candida albicans* by the changes in membrane permeability. J Microbiol 50:360–367
92. Song JH, Yang TC, Chang KW, Han SK, Yi HK, Jeon JG (2006) *In vitro* anti-cariogenic activity of

dichloromethane fraction from *Rheum undulatum* L. root. Arch Pharm Res 29(6):490–496
93. Kim JE, Kim HJ, Pandit S, Chang KW, Jeon JG (2011) Inhibitory effect of a bioactivity-guided fraction from *Rheum undulatum* on the acid production of *Streptococcus mutans* biofilms at sub-MIC levels. Fitoterapia 82(3):352–356
94. Kosikowska U, Smolarz HD, Malm A (2010) Antimicrobial activity and total content of polyphenols of *Rheum* L. species growing in Poland. Cent Eur J Biol 5(6):814–820
95. Darsanaki R, Lisar M (2014) Antimicrobial potential of root, stalk and leaves extracts of *Rheum ribes*. J Rep Pharma Sci 3(1):10–13
96. Abdulla KK, Taha EM, Rahim SM (2015) Phenolic profile, antioxidant and antibacterial effects of ethanol and aqueous extracts of *Rheum ribes* L. roots. Der Pharmacia Lett 7:26–30
97. Amiri N, Shafaghat A, Salimi F (2015) Screening of the essential oil, hexane extract, chemical composition, antioxidant activity, and antimicrobial acitivity of the flower *Rheum ribes* L. from Iran. J Essent Oil Bear Pl 18(5):1108–1115
98. Öztürk M, Aydoğmuş-Öztürk F, Duru ME, Topçu G (2007) Antioxidant activity of stem and root extracts of rhubarb (*Rheum ribes*): an edible medicinal plant. Food Chem 103(2):623–630
99. Oktay M, Yildirim A, Bilaloglu V, Gülçin I (2007) Antioxidant activity of different parts of isgin (*Rheum ribes* L.). Asian J Chem 19(4):3047–3055
100. Singh PP (2013) Ambika, Chauhan SMS. Activity-guided isolation of antioxidants from the roots of *Rheum emodi*. Nat Prod Res 27(10):946–949
101. Tripathi B, Bhatia R, Pandey A, Gaur J, Chawala G, Walia S et al (2014) Potential antioxidant anthraquinones isolated from *Rheum emodi* showing nematicidal activity against *Meloidogyne incognita*. J Chem 2014:9
102. Li Q, Tu Y, Zhu C, Luo W, Huang W, Liu W et al (2017) Cholinesterase, β-amyloid aggregation inhibitory and antioxidant capacities of Chinese medicinal plants. Ind Crop Prod 108:512–519
103. Kasabri V, Abu-Dahab R, Afifi FU, Naffa R, Majdalawi L, Shawash H (2012) *In vitro* modulation of pancreatic MIN6 insulin secretion and proliferation and extrapancreatic glucose absorption by *Paronychia argentea*, *Rheum ribes* and *Teucrium polium* extracts. Jordan J Pharm Sci 5(3):203–219
104. Kongstad KT, Ozdemir C, Barzak A, Wubshet SG, Staerk D (2015) Combined use of high-resolution alpha-glucosidase inhibition profiling and high-performance liquid chromatography-high-resolution mass spectrometry-solid-phase extraction-nuclear magnetic resonance spectroscopy for investigation of antidiabetic principles in crude plant extracts. J Agric Food Chem 63(8):2257–2263
105. Lin YL, Wu CF, Huang YT (2009) Effects of rhubarb on migration of rat hepatic stellate cells. J Gastroenterol Hepatol 24(3):453–461
106. Liu LN, Mei QB, Liu L, Zhang F, Liu ZG, Wang ZP et al (2005) Protective effects of *Rheum tanguticum* polysaccharide against hydrogen peroxide-induced intestinal epithelial cell injury. World J Gastroenterol 11(10):1503–1507
107. Liu LN, Shi L, Li SC, Zhang WJ, Zhang Y, Zhang ZP (2015) Protective role of *Rheum tanguticum* polysaccharide 1 in radiation- induced intestinal mucosal injury. Iran J Pharm Res. 14(3):833–841
108. Möller F, Zierau O, Jandausch A, Rettenberger R, Kaszkin-Bettag M, Vollmer G (2007) Subtype-specific activation of estrogen receptors by a special extract of *Rheum rhaponticum* (ERr 731®), its aglycones and structurally related compounds in U2OS human osteosarcoma cells. Phytomedicine 14(11):716–726
109. Iida K, Hase K, Shimomura K, Sudo S, Kadota S, Namba T (1995) Potent inhibitors of tyrosinase activity and melanin biosynthesis from *Rheum officinale*. Planta Med 61(5):425–428
110. Tsai JC, Tsai S, Chang WC (2004) Effect of ethanol extracts of three Chinese medicinal plants with laxative properties on ion transport of the rat intestinal epithelia. Biol Pharm Bull 27(2):162–165
111. Moon MK, Kang DG, Lee JK, Kim JS, Lee HS (2006) Vasodilatory and anti-inflammatory effects of the aqueous extract of rhubarb via a NO-cGMP pathway. Life Sci 78(14):1550–1557
112. Yoo MY, Oh K-S, Lee JW, Seo HW, Yon GH, Kwon DY et al (2006) Vasorelaxant effect of stilbenes from rhizome extract of rhubarb (*Rheum undulatum*) on the contractility of rat aorta. Phytother Res 21(2):186–189
113. Naqishbandi AM, Josefsen K, Pedersen ME, Jäger AK (2009) Hypoglycemic activity of Iraqi *Rheum ribes* root extract. Pharm Biol 47(5):380–383
114. Kasabri V, Afifi FU, Hamdan I (2011) *In vitro* and *in vivo* acute antihyperglycemic effects of five selected indigenous plants from Jordan used in traditional medicine. J Ethnopharmacol 133(2):888–896
115. Chen ZQ, Wang JJ (2010) Hypoglycemic and antioxidant effects of *Rheum franzenbachii* extract in streptozotocin-induced diabetic rats. Pharm Biol 48(6):703–707
116. Raafat K, Aboul-Ela M, El-Lakany A (2014) Alloxan-induced diabetic thermal hyperalgesia, prophylaxis and phytotherapeutic effects of *Rheum ribes* L. in mouse model. Arch Pharmacal Res
117. Hosseini A, Mollazadeh H, Amiri MS, Sadeghnia HR, Ghorbani A (2017) Effects of a standardized extract of Rheum turkestanicum Janischew root on diabetic changes in the kidney, liver and heart of streptozotocin-induced diabetic rats. Biomed Pharmacother 86:605–611
118. Xie W, Xing D, Zhao Y, Su H, Meng Z, Chen Y et al (2005) A new tactic to treat postprandial hyperlipidemia in diabetic rats with gastroparesis by improving gastrointestinal transit. Eur J Pharmacol 510(1–2):113–120

119. Hadjzadeh MA, Rajaei Z, Khodaei E, Malek M, Ghanbari H (2017) *Rheum turkestanicum* rhizomes possess anti-hypertriglyceridemic, but not hypoglycemic or hepatoprotective effect in experimental diabetes. Avicenna J Phytomed 7(1):1–9
120. Lee W, Yoon G, Hwang YR, Kim YK, Kim SN (2012) Anti-obesity and hypolipidemic effects of *Rheum undulatum* in high-fat diet-fed C57BL/6 mice through protein tyrosine phosphatase 1B inhibition. BMB Rep 45(3):141–146
121. Mishra SK, Tiwari S, Shrivastava A, Srivastava S, Boudh GK, Chourasia SK et al (2014) Antidyslipidemic effect and antioxidant activity of anthraquinone derivatives from *Rheum emodi* rhizomes in dyslipidemic rats. J Nat Med 68(2):363–371
122. Alam MM, Javed K, Jafri MA (2005) Effect of *Rheum emodi* (Revand Hindi) on renal functions in rats. J Ethnopharmacol 96(1–2):121–125
123. Zeng LN, Ma ZJ, Zhao YL, Zhang LD, Li RS, Wang JB et al (2013) The protective and toxic effects of rhubarb tannins and anthraquinones in treating hexavalent chromium-injured rats: the Yin/Yang actions of rhubarb. J Hazard Mater 246-247:1–9
124. Zhang ZH, Vaziri ND, Wei F, Cheng XL, Bai X, Zhao YY (2016) An integrated lipidomics and metabolomics reveal nephroprotective effect and biochemical mechanism of *Rheum officinale* in chronic renal failure. Sci Rep 6:22151
125. Yokozawa T, He LQ, Muto Y, Nagasaki R, Hattori M, Oura H (1997) Effects of rhubarb extract in rats with diabetic nephropathy. Phytother Res 11(1):73–75
126. Hosseini A, Rajabian A, Fanoudi S, Farzadnia M, Boroushaki MT (2018) Protective effect of *Rheum turkestanicum* root against mercuric chloride-induced hepatorenal toxicity in rats. Avicenna J Phytomed 8(6):488–497
127. Wang JB, Zhao HP, Zhao YL, Jin C, Liu DJ, Kong WJ et al (2011) Hepatotoxicity or hepatoprotection? Pattern recognition for the paradoxical effect of the Chinese herb *Rheum palmatum* L. in treating rat liver injury. PLoS One 6(9):e24498
128. Zhang RZ, Qiu H, Wang N, Long FL, Mao DW (2015) Effect of *Rheum palmatum* L. on NF-κB signaling pathway of mice with acute liver failure. Asian Pac J Trop Med 8(10):841–847
129. Yang M, Li X, Zeng X, Ou Z, Xue M, Gao D et al (2016) Rheum palmatum L. attenuates high fat diet-induced hepatosteatosis by activating AMP-activated protein kinase. Am J Chin Med 44(3):551–564
130. Akhtar M, Habib A, Ali A, Bashir S (2016) Isolation, identification, and *in vivo* evaluation of flavonoid fractions of chloroform/methanol extracts of *Rheum emodi* roots for their hepatoprotective activity in Wistar rats. Int J Nutr Pharmacol Neurol Dis 6(1):28–34
131. El-Saied MA, Sobeh M, Abdo W, Badr OM, Youssif LT, Elsayed IH et al (2018) *Rheum palmatum* root extract inhibits hepatocellular carcinoma in rats treated with diethylnitrosamine. J Pharm Pharmacol 70(6):821–829
132. Liu L, Wang ZP, Xu CT, Pan BR, Mei QB, Long Y et al (2003) Effects of *Rheum tanguticum* polysaccharide on TNBS -induced colitis and CD4+T cells in rats. World J Gastroenterol 9(10):2284–2288
133. Liu L, Liu Z, Zhang T, Shi L, Zhang W, Zhang Y (2015) Combined therapy with *Rheum tanguticum* polysaccharide and low-dose 5-ASA ameliorates TNBS-induced colitis in rats by suppression of NF-κB. Planta Med 81(9):705–712
134. Sindhu RK, Kumar P, Kumar J, Kumar A, Arora S (2010) Investigations into the anti-ulcer activity of *Rheum ribes* Linn leaves extracts. Int J Pharm Pharm Sci 2:90–92
135. Papke A, Kretzschmar G, Zierau O, Kaszkin-Bettag M, Vollmer G (2009) Effects of the special extract ERr 731® from *Rheum rhaponticum* on estrogen-regulated targets in the uterotrophy model of ovariectomized rats. J Steroid Biochem Mol Biol 117(4):176–184
136. Keiler AM, Papke A, Kretzschmar G, Zierau O, Vollmer G (2012) Long-term effects of the rhapontic rhubarb extract ERr 731® on estrogen-regulated targets in the uterus and on the bone in ovariectomized rats. J Steroid Biochem Mol Biol 128(1):62–68
137. Jin JH, Ngoc TM, Bae KH, Kim YS, Kim HP (2011) Inhibition of experimental atopic dermatitis by rhubarb (rhizomes of *Rheum tanguticum*) and 5-lipoxygenase inhibition of its major constituent, emodin. Phytother Res 25(5):755–759
138. Lin CH, Ding HY, Kuo SY, Chin LW, Wu JY, Chang TS (2011) Evaluation of *in vitro* and *in vivo* depigmenting activity of raspberry ketone from *Rheum officinale*. Int J Mol Sci 12(8):4819–4835
139. Liu LN, Guo ZW, Zhang Y, Qin H, Han Y (2012) Polysaccharide extracted from *Rheum tanguticum* prevents irradiation-induced immune damage in mice. Asian Pac J Cancer Prev 13:1401–1405
140. Kong X, Wan H, Su X, Zhang C, Yang Y, Li X et al (2014) *Rheum palmatum* L. and *Coptis chinensis* Franch., exert antipyretic effect on yeast-induced pyrexia rats involving regulation of TRPV1 and TRPM8 expression. J Ethnopharmacol 153(1):160–168
141. Zahedi M, Hojjati MR, Fathpour H, Rabiei Z, Alibabaei Z, Basim A (2015) Effect of *Rheum ribes* hydro-alcoholic extract on memory impairments in rat model of Alzheimer's disease. Iran J Pharm Res. 14(4):1197–1206
142. Liu YF, Yu HM, Zhang C, Yan FF, Liu Y, Zhang Y et al (2007) Treatment with rhubarb improves brachial artery endothelial function in patients with atherosclerosis: a randomized, double-blind, placebo-controlled clinical trial. Am J Chin Med 35(4):583–595
143. Jiao DH, Ma YH, Chen SJ, Liu CT, Shu HN, Chu CM (1980) Résumé of 400 cases of acute upper digestive tract bleeding treated by rhubarb alone. Pharmacology 20(Suppl 1):128–130
144. Yu Y, Zhu X, Huang S (2015) Clinical observation of Da Huang (*Rheum officinale*) application

at Shenque (CV 8) for constipation after operation for lumbar vertebral fracture. J Acupunct Tuina Sci 13(6):373–376
145. Khiveh A, Hashempur MH, Shakiba M, Lotfi MH, Shakeri A, Kazemeini SK et al (2017) Effects of rhubarb (*Rheum ribes* L.) syrup on dysenteric diarrhea in children: a randomized, double-blind, placebo-controlled trial. J Integr Med 15(5):365–372
146. Rehman H, Begum W, Anjum F, Tabasum H, Zahid S (2015) Effect of rhubarb (*Rheum emodi*) in primary dysmenorrhoea: a single-blind randomized controlled trial. J Complement Integr Med 12(1):61–69
147. Sayyah M, Boostani H, Pakseresht S, Malayeri A (2009) Efficacy of hydroalcoholic extract of *Rheum ribes* L. in treatment of major depressive disorder. J Med Plants Res 3(8):573–575
148. Barnes J, Anderson LA, Phillipson JD (2007) Herbal medicines. Pharmaceutical Press, Chicago, p 507
149. Zheng QX, Wu HF, Guo J, Nan HJ, Chen SL, Yang JS et al (2013) Review of rhubarbs: chemistry and pharmacology. Chin Herb Med 5(1):9–32