Rheum rhaponticum and *Rheum rhabarbarum*: a review of phytochemistry, biological activities and therapeutic potential

Joanna Kolodziejczyk-Czepas · Oleksandra Liudvytska

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Abstract The *Rheum* genus (Polygonaceae) covers about 60 species of rhubarbs, including specimens with a long ethnomedicinal history in Asia, Europe and other regions of the world. The work reviews available literature (until March, 2020) on phytochemical profile, ethnomedicinal recommendations, biological activities, pharmacological uses and future prospects for therapeutic applications of *Rheum rhabarbarum* L. (garden rhubarb) and *Rheum rhaponticum* L. (rhapontic rhubarb). Although the above species are well-known vegetables, scientific interest in these plants is a relatively new issue; most of evidence of their biological activities and therapeutic potential derives from the last 15 years. Rhubarbs contain numerous bioactive substances, belonging to diverse groups of phytochemicals, e.g. stilbenes, anthraquinones and flavonoids. The registered special extract of *R. rhaponticum* (ERr731[®]) is administered to alleviate the menopause-related complaints. Furthermore, both ethnomedicinal surveys and recent studies on bioactive substances from rhubarbs indicate

that these plants may have significantly broader range of beneficial effects such as antioxidant, anti-inflammatory, antimicrobial and cardioprotective activities.

Keywords Rhubarb · Ethnomedicine · Biological activity · Bioactive substances

Introduction

The genus *Rheum* L. (rhubarb) covers about 60 species of perennial herbs, belonging to the Polygonaceae family. Rhubarbs have been known worldwide (in Asia, in particular) as medicinal and/or edible plants (Agarwal et al. 2001; Cao et al. 2017; He et al. 1992; Pourjabali et al. 2017; Rehman et al. 2014). Scientific interest in chemical composition and biological properties of two of the most popular rhubarb species, i.e. garden rhubarb (*Rheum rhabarbarum* L./syn. *R. undulatum* L.—according to www.theplantlist.org and <http://www.worldfloraonline.org>) and rhapontic rhubarb (*Rheum rhaponticum* L.; also called Siberian rhubarb) has significantly increased for the last 15 years. Despite the popularity of these species as foods, their phytochemical profiles, bioactive components and pharmacological relevance still remain partly elucidated. Their petioles (stalks) are commonly used for culinary purposes, and the leaves are toxic (Slaughter et al. 2012) due to a high content of oxalic

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J. Kolodziejczyk-Czepas · O. Liudvytska (✉)
Department of General Biochemistry, Faculty of Biology
and Environmental Protection, University of Lodz,
Pomorska, 141/143, 90-236 Lodz, Poland
e-mail: oleksandra.liudvytska@unilodz.eu

acid. However, contrary to the roots of *Rheum officinale* Baill., which are predominantly used as a laxative, underground parts of both the garden and rhapontic rhubarb have a broader range of applicability in traditional medicine and contemporary herbal therapies.

While the chemical profile and biological properties of other rhubarb species such as *R. australe* D. Don, *R. palmatum* L., *R. ribes* L., *R. officinale* Baill., *R. tanguticum* Maxim. ex Balf. or *R. emodi* L. have been extensively described and/or reviewed in the literature (Komatsu et al. 2006; Rashid et al. 2014; Rokaya et al. 2012; Wang et al. 2013; Zhang et al. 2015a), there is a lack of a comprehensive look at *R. rhabarbarum* and *R. rhaponticum*. The present work is based on a review of available literature dealing with ethnomedicinal data, phytochemical composition, biological activities and prospects for future pharmacological use of these rhubarb species. Since the evaluation of some of biological activities or pharmacological significance of rhubarb-derived compounds and extracts partly remain at the preliminary stage or available data are inconsistent, disputable issues have been critically presented in this work. Our review covers data (until March, 2020) originating from journals indexed in international databases such as Medline/Pubmed, Scopus, Science Direct/Elsevier and Springer Link/ICM. Additionally, local scientific publications, not indexed in the mentioned databases were also taken into consideration.

***Rheum rhaponticum* and *Rheum rhabarbarum* in traditional medicine**

Rhubarb is known in traditional medicine of Asian, European and other cultures (Agarwal et al. 2001; Pourjabali et al. 2017; Rehman et al. 2014), but a detailed appraisal of ethnomedicinal relevance of individual species or their biological actions is limited by the fact that in some cases, no precise botanical identification (including Latin names) of the used/described species is given. Even in recent literature, rhubarbs are frequently described generally, as “*Rheum* sp.” or just “rhubarb(s)”. Nevertheless, available data from ethnomedicinal and ethnobotanical surveys confirm the presence of *R. rhaponticum* and *R. rhabarbarum* in medicine from the Middle Ages (Nedelcheva 2009). According to data from one

of the oldest Polish books devoted to medicinal plants, i.e. *Herbarz Polski*” (Marcin z Urzędowa/Marcin of Urzędów 1595) roots of both these species were used in medicine of that time to cure a wide range of disorders. The author suggested using 1–2 or more “dragma” units (1 dragma corresponded to 1/8 of one ounce). Internally, *R. rhaponticum* (in wine, beer or mead) was used in therapy of gastrointestinal pain, gastritis, liver and spleen disorders, heartache and pain in pericardium, pulmonary system dysfunctions as well as disorders related to the reproductive system, including uterine and breast pains. Drinking of the *R. rhaponticum*-based mixtures or chewing its root was believed to alleviate indigestion. Externally, a vinegar macerate from this plant was applied to cure skin disorders such as itching and scratches; a water macerate was recommended in the therapy of ulcers. *R. rhabarbarum* was mainly administered as a purgative agent. Other recommendations for its use included liver, spleen and stomach dysfunctions as well as blood purification. Some fragments of this historical source indicated that this plant was also used to stop bleeding and to alleviate fever as well as to cure injuries, trauma after falls from a height and vein disorders.

Current literature devoted to ethnomedicinal issues also confirms that the roots of *R. rhaponticum* were an ingredient of different mixtures, administered to cure fever (a sugar syrup), to improve voice (roots boiled in red wine and sweetened with honey), to alleviate heart problems or stomachache (a brandy-based balsam), and a honey-based herbal paste was used in jaundice and distress (Nedelcheva 2012). Furthermore, underground parts of this rhubarb are an ingredient of Turkish folk food and the remedy, i.e. *Mesir* paste, having over 500 years history of use (Oskay et al. 2010). In Brazilian folk medicine, *R. rhaponticum* is used to treat gastrointestinal disorders (Cogo et al. 2010), while in Iran, it is one of the herbs traditionally used to treat hyperpigmentation (Ghafari et al. 2017). This rhubarb species has been also mentioned in different types of studies as one of medicinal plants in European and Asian countries (Debnath et al. 2006; Lachumy et al. 2013).

Similarly to *R. rhaponticum*, also the position of *R. rhabarbarum* in ethnomedicine of different cultures has been built for centuries. Both species are known in Central Asia and Russia as a natural demulcent, helpful in wound healing and relieving skin problems

(e.g. irritations, allergy and dermatitis) (Mamedov et al. 2008). *R. rhubarbarum* is known in Ayurvedic medicine (Dandekar and Deshpande 2016). In Chinese medicine, this plant has been administered to heal ulcers as well as to treat constipation, jaundice and gastrointestinal hemorrhage (State Pharmacopoeia Committee 2010), or as a natural anti-inflammatory ingredient of different formulations, useful in the therapy of appendicitis, cholecystitis and rheumatoid arthritis (Ma et al. 2009). Furthermore, *R. rhubarbarum* is a component of Yīn–Chén–Hāo decoction, a traditional Chinese herbal medicine used to treat damp-heat jaundice and hepatic disorders (Li et al. 2017). This rhubarb species was also listed in the Chilandar Medical Codex, a medieval Serbian manuscript, covering documents on European medical knowledge from the 12th to 15th century. Recommendations for the use of *R. rhubarbarum* included blood detoxification, gastrointestinal tract disorders, hydrops, melancholy as well as its administration as a mucolytic, purgative, sedative and antispasmodic preparation (Jarić et al. 2014). It is described as one of ethnomedicinal plants in Hungary (Babulka 1993), depurative herbal medicine in South-Western Germany (Pieroni and Gray 2008) and traditional Korean remedy for gastrointestinal disorders (Kim et al. 2014).

Phytochemical profile of *R. rhaponticum* and *R. rhubarbarum*

Studies on the phytochemical composition of different species of rhubarb were undertaken as early as at the beginning of the 20th century, and provided information on the presence of a variety of inorganic and organic acids (including tartaric, oxalic, citric, malic and ascorbic acid), anthraquinones (e.g. emodin, aloemodin and rhein) and stilbenes (Pucher et al. 1938; Tutin and Clewer 1911; Viehoever 1933). The last two decades have provided more detailed qualitative analyses of the chemical profile of *R. rhaponticum*, covering examinations of phenolic and non-phenolic components of this plant. Results of these studies, with names of the identified compounds, are summarized in the Table 1. Some information on methodological aspects of isolation of the individual components, e.g. rhaponticin and desoxyrhaponticin are also available (Smolarz et al. 2013a). For the first time, the

composition and content of flavonoids was investigated by German scientists who discovered rutin in leaves of *R. rhubarbarum* (0.7%) and *R. rhaponticum* (0.61%) (Hörhammer and Müller 1954). Later, glycosides of quercetin and kaempferol were found in the leaves and petioles of *R. rhubarbarum*, while in the flower petals, quercetin 3-rhamnoside and quercetin 3-rutinoside were identified (Vysochina 2012). In raw stalks of the rhapontic rhubarb, 42 components belonging to different groups of flavonoids as well as stilbenes, anthraquinones and naphthalene derivatives (for details, see the Table 1) were found. In the roots, derivatives of *trans*-piceatannol, *trans*-resveratrol, *trans*-rhapontigenin and *trans*-desoxyrhapontigenin, were identified (Fig. 1). Root samples contained pterostilbene acetylglucosides as well as hydroxyanthraquinones and their glycosides (Püssa et al. 2009). The presence of numerous organic compounds, representing various classes of (phyto)-chemicals and their distribution in *R. rhubarbarum* and hybrids of *R. rhubarbarum* and *R. rhaponticum* were described as well (Dregus and Engel 2003; Ha et al. 2020; Ko 2000; Krafczyk et al. 2008; Nizioł et al. 2017; Will and Dietrich 2013) (data collected in Table 2).

Different cooking regimes influence the content of polyphenols in rhubarb. Compared to raw petioles, both fast and slow stewing and baking were found to enhance the total content of polyphenolic compounds and overall antioxidant capacity of the examined rhubarb samples. This increase was attributed to thermal degradation of plant material, leading to a release of bioactive substances (McDougall et al. 2010). The literature provides reports dealing with quantitative data on different groups of metabolites in *R. rhaponticum* and *R. rhubarbarum*. A comparative examination of crude ethanol (96%; v/v) extracts, derived from the rhizomes and roots of *R. rhaponticum*, *R. palmatum* L. and *R. rhubarbarum* revealed that the rhapontic rhubarb had the lowest contents of total polyphenols, total anthracene derivatives, total anthraquinones and overall tannin concentration, attaining 46.11 ± 0.81 mg/g, 19.8 ± 0.60 mg/g, 16.6 ± 0.50 mg/g and 7.07 ± 0.25 mg/g of dry material, respectively (Kosikowska et al. 2010). The total concentrations of phenolic acids in *R. rhaponticum* rhizome amounted to 195.5 µg/g, with concentrations of individual acids ranging between 2.2 µg/g (*p*-hydroxybenzoic acid) and 77.7 µg/g (ferulic acid)

Table 1 Phytochemical composition of *R. rhaponticum*

Plant part/solvent	Identified substances	References
Air-dried roots/methanol (> 99.9%)	<i>Stilbene compounds</i> : piceatannol <i>O</i> -glucoside 1, piceatannol <i>O</i> -glucoside 2, resveratrol <i>O</i> -glucoside 1, resveratrol <i>O</i> -glucoside 2 (piceid), piceatannol <i>O</i> -galloylglucoside 1, piceatannol, piceatannol <i>O</i> -galloylglucoside 2, rhapontigenin <i>O</i> -glucoside (rhapontin), resveratrol <i>O</i> -galloylglucoside, rhapontigenin <i>O</i> -glucoside 2, <i>trans</i> -resveratrol, rhapontigenin <i>O</i> -galloylglucoside, rhapontigenin <i>O</i> -acetylglucoside 1, rhapontigenin, rhapontigenin <i>O</i> -acetylglucoside 2, desoxyrhapontigenin <i>O</i> -glucoside (desoxyrhapontin), desoxyrhapontigenin <i>O</i> -galloylglucoside, desoxyrhapontigenin <i>O</i> -acetylglucoside, pterostilbene <i>O</i> -acetylglucoside 1, resveratrol dimers 1-3, pterostilbene <i>O</i> -acetylglucoside 2, desoxyrhapontigenin <i>Hydroxyanthraquinones</i> : emodin, aloe-emodin <i>O</i> -glucoside, chrysophanol <i>O</i> -glucoside, emodin <i>O</i> -glucoside, emodin <i>O</i> -malonylglucoside, chrysophanol <i>O</i> -acetylglucoside 1, rhein <i>O</i> -glucoside, chrysophanol <i>O</i> -acetylglucoside 2 <i>Hydroxynaphthalenes</i> : torachryson <i>O</i> -glucoside, torachryson <i>O</i> -acetylglucoside	Püssa et al. (2009)
Air-dried petioles/methanol (> 99.9%)	Composition similar to the phytochemical profile of roots, with a few additional flavonoids, i.e. myricetin- <i>O</i> -rhamnoside, rutin, quercetin- <i>O</i> -glucuronide, quercetin- <i>O</i> -glucoside, quercetin- <i>O</i> -rhamnoside, quercetin	
Air-dried roots and rhizomes/ 80% methanol	<i>Phenolic acids</i> : ellagic acid, chlorogenic acid, gallic acid, protocatechuic acid, protocatechuic acid, caffeic acid, α -resorcylic acid, <i>p</i> -hydroxyphenylacetic acid, <i>p</i> -hydroxybenzoic acid, <i>p</i> -coumaric acid, syringic acid, vanillic acid, ferulic acid	Smolarz and Medyńska (2005)
Air-dried petioles/80% methanol	<i>Phenolic acids</i> : ellagic, gallic, protocatechuic, homoprotocatechuic, caffeic, <i>p</i> -hydroxybenzoic, <i>p</i> -coumaric, syringic, vanillic, ferulic, α -resorcylic and <i>p</i> -hydroxyphenylacetic acid <i>Hydroxyanthraquinone</i> : emodin	Smolarz et al. (2005)
Fresh petioles/50% acetonitrile with 0.1% formic acid	<i>Flavonoids</i> : cyanidin rutinoside, cyanidin hexose, proanthocyanidins, rutin, quercetin hexose/quercetin glucuronide, quercetin-rhamnose <i>Stilbene compounds</i> : rhapontigenin glycoside <i>Anthraquinones</i> : aloe-emodin, emodin glycosides and dimers, chrysophanol and its derivatives <i>Hydroxynaphthalenes</i> : torachryson and its derivatives	McDougall et al. (2010)
Fresh petioles/hexane	<i>Alcohols</i> : 3-methyl-3-pentanol, 3-hexanol, 2-hexanol, cyclopentanol, pentanol, 1-methylcyclopentanol and 2-methylcyclopentanol, 3-methylcyclopentanol, 1-octen-3-ol, octanol <i>Aldehydes and ketones</i> : acetone, butanal, pentanal, 3-methyl-2-pentanone, 3-hexanone, 2-hexanone, hexanal, 2-methylcyclopentanone, 3-methylcyclopentanone, octanal, nonanal, 3-octen-2-one, (E,E)-2,4-nonadienal <i>Acids and esters</i> : butyl acetate, pentanoic acid, hexanoic acid, 3-hydroxy-2,2,4-trimethylpentyl isobutanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutanoate, heptanoic acid, octanoic acid, nonanoic acid <i>Aromatic compounds</i> : benzaldehyde, acetophenone, benzyl alcohol, phenethyl alcohol, <i>p</i> -anisaldehyde; 2,5-dimethyl-tetra-hydrofuran, 5-methylfurfural, 2-acetylpyrrole, 2-(hydroxyacetyl)furan, pyrrole-2-carboxaldehyde, dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, 5-pentyl-2(5H)-furanone, 3-methyl-1H-pyrrole-2-carboxaldehyde, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one <i>Hydrocarbons</i> : cyclohexane, methylcyclohexane, tetradecane	Wu et al. (2017)

Stilbene compounds	R1	R2	R3	R4
	Desoxyrhapontigenin	OH	OH	H	OCH ₃
	Isorhapontigenin	OH	OH	OCH ₃	OH
	Piceatannol	OH	OH	OH	OH
	Pterostilbene	OCH ₃	OCH ₃	H	OH
	Rhapontigenin	OH	OH	OH	OCH ₃
	Resveratrol	OH	OH	H	OH

Anthraquinone compounds	R1	R2	R3	R4
	Aloe-emodin	H	CH ₂ OH	H	H
	Emodin	H	CH ₃	OH	H
	Chrysophanol	H	CH ₃	H	H
	Physcion	H	CH ₃	OCH ₃	H
	Rhein	H	COOH	H	H

Fig. 1 Main anthraquinone and stilbene compounds identified in *Rheum raphaniticum* and *Rheum rhabarbarum*

in the air-dried plant material (Smolarz and Medyńska 2005). Phenolic acids (at the total concentration of 198.16 µg/g) and emodin (at a concentration of 5.8 µg/g of dry weight) were also found in the petioles (Smolarz et al. 2005). Recent work on phytochemical profiles of two varieties of *R. rhabarbarum* demonstrated that the content of flavan-3-ols in rhubarb stalks was ranging between 86.6 and 196.0 mg/100 g (of dry mass), the flavonol content was 49.8–73.5 mg/100 g (d.m.), anthocyanins were present at the level of 4.3–96.2 mg/100 g (d.m.), and gallotannin content was 6.3–13.6 mg/100 g (d.m.). In general, the total phenolic content (TPC) was higher in samples collected in spring, than in those from autumn; in the “Red Malinowy” variety, TPC amounted up to 1270.3 mg/100 g d.m. (Kalisz et al. 2020).

Biological activities and pharmacological actions of *R. raphaniticum* and *R. rhabarbarum*

Menopausal complaints

To date, the terms “phytoestrogens” and “phytoestrogenic activity” have been mostly associated with isoflavones from the soya bean (*Glycine max* L.). On the other hand, the last two decades have brought better understanding of the hormone-like effects of different classes of phytochemicals and identification of various sources of phytoestrogens. Although the

soya bean is still considered the main source of phytoestrogens, it has been partly replaced by red clover (*Trifolium pratense* L.). Furthermore, following the discovery that not only isoflavones display estrogenic properties, the area of studies on hormonal effects of plant metabolites has been significantly extended (Dietz et al. 2016; Franco et al. 2016; Sirotkin and Harrath 2014; Schloss and Steel 2016). Scientific and medical interest in herbal preparations with estrogenic effects are additionally enhanced by data suggesting a beneficial role of phytoestrogens in prophylaxis of different women diseases, including osteoporosis and breast cancer (Obi et al. 2009).

Since the phytochemical profile of *R. raphaniticum* contains substances with estrogenic activities, this plant has gained scientific attention as a source of natural medicines, useful in the therapy of menopausal complaints or other hormone-related disorders (Chang et al. 2016; Hasper et al. 2009; Heger et al. 2006; Kaszkin-Bettag et al. 2008a, b, 2009; Keiler et al. 2012; Möller et al. 2007; Papke et al. 2009; Vollmer et al. 2010; Wober et al. 2007). The most important studies on molecular mechanisms of its biological action, pharmacological relevance and safety were summarized in the Table 3. The estrogenic action of *R. raphaniticum* is primarily attributed to the presence of hydroxystilbene compounds such as raphanticin, desoxyraphanticin, raphantigenin, desoxyraphantigenin, resveratrol and piceatannol. A preparation containing the *Rheum raphaniticum* extract ER731[®] was

Table 2 Phytochemical composition of *R. rhubarbarum* and hybrids of *R. rhubarbarum* and *R. rhaponticum*

Plant part/solvent	Identified substances	References
<i>R. rhubarbarum</i> rhizome/hot water extract	piceatannol-3, 4'- <i>O</i> - β -D-diglucoopyranoside, desoxyrhaponticin <i>Anthraquinone compounds</i> : emodin-1- <i>O</i> - β -D-glucoopyranoside, physcion-8- <i>O</i> - β -D-glucoopyranoside	Ko (2000)
<i>R. rhubarbarum</i> stalks/volatiles	<i>Alcohols</i> : 1-propanol, 2-methyl-1-propanol, 1-butanol, 2-methyl-1-butanol, 3-methyl-1-pentanol, 4-methyl-1-pentanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-penten-3-ol, (Z)-2-penten-1-ol, 4-methyl-3-penten-1-ol, hexanol, (E)-2-hexenol, (Z)-2-hexenol, (E)-3-hexen-1-ol, (Z)-3-hexen-1-ol, cyclohexanol, 4-methyl-1-hexanol, 2-ethyl-1-hexanol, hexadecanol, benzyl alcohol, 2-phenylethanol <i>Aldehydes</i> : (E)-2-pentenal, hexanal, (E)-2-hexenal, (Z)-2-hexenal, (Z)-3-hexenal, (E)-2-nonenal, (E,Z)-2,6-nonadienal, decanal <i>Esters</i> : ethyl formate, ethyl acetate, hexyl acetate, 2-methylbutyl 2-methylbutanoate, methyl (E)-2-hexenoate, ethyl (E)-2-hexenoate, (E)-2-hexenyl acetate, (E)-2-hexenyl butanoate, (E)-2-hexenyl hexanoate, (E)-3-hexenyl butanoate, (E)-2-hexenyl (E)-2-hexenoate, isopropyl myristate, diisobutyl phthalate, dibutyl phthalate, di(2-ethylhexyl) phthalate <i>Ketones</i> : 3-pentanone, 6-methyl-5-hepten-2-one, (E)-geranylacetone, 2,6,6-trimethyl-2-vinyltetrahydropyran-3-one <i>Acids</i> : acetic acid, 2-methylbutanoic acid, 4-methylpentanoic acid, hexanoic acid, 4-methylhexanoic acid, (E)-2-hexenoic acid, (E)-3-hexenoic acid, octanoic acid, nonanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, 9-hexadecenoic acid, octadecanoic acid <i>Other compounds</i> : limonene, linalool, sesquiterpenes, squalene, β -ionone, anethole, <i>p</i> -allylphenol, methyleugenol, 1,2-dimethoxybenzene, 1,4-dimethoxybenzene, indole	Dregus and Engel (2003)
<i>R. rhubarbarum</i> roots and rhizomes/80% methanol	Ellagic, chlorogenic, gallic, protocatechuic, protocatechuic, caffeic (3,4-dihydroxycinnamic), α -resorcylic, <i>p</i> -hydroxyphenylacetic, <i>p</i> -hydroxybenzoic, <i>p</i> -coumaric, syringic, vanillic and ferulic acid	Smolarz and Medyńska (2005)
<i>R. rhubarbarum</i> stalks fresh juice	Catechin, cyanidin-3-glucoside, cyanidin-3-rutinoside, 5-carboxypyranocyanidin-3-rutinoside, delphinidin-3-glucoside, delphinidin-3-rutinoside, myricetin-3-rutinoside, procyanidin B1, procyanidin B2, quercetin-3-galactoside, quercetin-3-rutinoside, quercetin-3-glucuronide, quercetin-3-glucoside, kaempferol-3-rutinoside, quercetin-3-rhamnoside <i>Acids</i> : ascorbic acid, citric acid, fumaric acid, lactic acid, malic acid, oxalic acid	Will and Dietrich (2013)
<i>R. rhubarbarum</i> rhizome/methanol	Rheundulin A <i>Stilbene compounds</i> : rheundulins B-D, δ -viniferin, rhapontigenin, rhaponticin, piceid <i>Anthraquinones</i> : chrysophanol-1- <i>O</i> - β -D-glucoopyranoside, chrysophanol-8- <i>O</i> - β -D-glucoopyranoside <i>Hydroxynaphthalenes</i> : torachrysone-8- <i>O</i> - β -D-glucoside <i>Naphthoquinone derivative</i> : 6-methoxy-2-acetyl-3-methyl-1,4-naphthoquinone-8- <i>O</i> - β -D-glucoopyranoside	Ha et al. (2020)

Table 2 continued

Plant part/solvent	Identified substances	References
<i>R. rhubarbarum</i> stalks/methanol acidified with 1% acetic acid	<i>Anthocyanins</i> : delphinidin-3- <i>O</i> -glucoside, delphinidin-3- <i>O</i> -rutinoside, cyanidin-3- <i>O</i> -glucoside, cyanidin-3- <i>O</i> -rutinoside <i>Flavan-3-ols</i> : procyanidin B1, (+)-catechin, procyanidin B2, (–)-epicatechin, procyanidin B dimer <i>Flavonols</i> : myreticin-3- <i>O</i> -glucuronide, myreticin-3- <i>O</i> -rutinoside, myreticin-3- <i>O</i> -ramnoside, quercetin-3- <i>O</i> -rutinoside, quercetin-3- <i>O</i> -glucuronide, quercetin-3- <i>O</i> -glucoside, quercetin-3- <i>O</i> -pentoside, quercetin-3- <i>O</i> -rhamnoside and isorhamnetin 3- <i>O</i> -rhamnoside <i>Phenolic acids</i> : galloyl- <i>O</i> -glucose, gallic acid, di- <i>O</i> -galloyl-glucose and derivatives of hydroxycinnamic acid	Kalisz et al. (2020)
<i>R. rhubarbarum</i> and <i>R. rhaponticum</i> hybrids leaves and petioles/ <i>n</i> -butanol	6,8-di-C- β -D-glucosylapigenin, 6-C- β -D-glucosyl-8-C- β -D-arabinosylapigenin, 6-C- β -D-arabinosyl-8-C- β -D-glucosylapigenin, rutin, isovitexin, quercetin-3- <i>O</i> - β -D-glucuronide	Krafczyk et al. (2008)
<i>R. rhubarbarum</i> and <i>R. rhaponticum</i> hybrids rhizome/ethyl acetate	(+)-catechin, <i>trans</i> -resveratrol-4'- <i>O</i> - β -D-glucopyranoside, <i>trans</i> -piceatannol-3'- <i>O</i> - β -D-glucopyranoside, <i>trans</i> -rhaponticin, <i>trans</i> -desoxyrhaponticin	Krafczyk et al. (2008)

registered as medicinal product in 1993 (Phytoestrol N, Chemisch-Pharmazeutische Fabrik Göppingen, Carl Müller, Apotheker, GmbH and Co KG, Göppingen, Germany), which was dedicated to alleviate menopausal complaints as an alternative for the hormonal replacement therapy (HRT). At doses ranging from 4 to 1000 mg, different extracts of *R. rhaponticum* are also present in other plant-based herbal products and dietary supplements.

Given the ample evidence that *R. rhaponticum* alleviates some menopause-related complaints, one would expect that also *R. rhubarbarum* possesses similar properties. However, so far, the estrogenic action of the latter has been confirmed only in basic studies. In human hepatoma (HepG2) cells, transiently transfected with ER α , ER β and ERE-reporter plasmid, some stilbene-derivatives such as piceatannol 3'-*O*- β -D-xylopyranoside, *cis*-rhaponticin and rhapontigenin 3'-*O*- β -D-glucopyranoside isolated from the roots of *R. rhubarbarum* (ethnomedicinal name: *Rhei undulati Rhizoma*) displayed a binding affinity to estrogen receptors (at concentrations of 1 and 10 μ M) (Park et al. 2018). The estrogenic activities of three other bioactive constituents of *R. rhubarbarum* roots (i.e. aloe-emodin, rhapontigenin and chrysophanol 1-*O*- β -D-glucopyranoside; 10–50 μ g/ml) were also demonstrated in an experimental model of breast cancer cells (MCF-7) (Lee et al. 2018).

Antioxidant properties

Due to a significant contribution of oxidative stress to the pathogenesis of a variety of disorders, antioxidant activity is one of the most investigated properties of natural, plant-derived extracts or individual substances. However, in the case of *R. rhaponticum* and *R. rhubarbarum*, this type of biological activity remains only partly described and evaluated. So far, antioxidant effects of *R. rhaponticum*-derived extracts have been examined in preliminary radical-scavenging assays (based on the DPPH $^{\bullet}$ and ABTS $^{\bullet+}$ radicals), mostly at concentrations that are significantly higher than physiologically achievable levels of natural substances and their metabolites (Joo et al. 2014; Kalisz et al. 2020; Park et al. 2008; Raudsepp et al. 2008, 2013; Won Jang et al. 2018; Wu et al. 2017; Zhang et al. 2007) (for details see the Table 5 in supplementary material). In addition to a limited number of studies, different laboratory protocols, diverse ways of data presentation (including a lack of EC₅₀ or IC₅₀ values) and modifications within the methodology significantly hinder unequivocal interpretation of the existing evidence.

What is the current knowledge of antioxidant effects of *R. rhubarbarum*? Analogously to *R. rhaponticum*, antioxidant assays of the garden rhubarb were preliminary assessed with the use of non-biological tests, but in this case, the literature offers more

Table 3 Studies on molecular mechanisms of biological action, pharmacological relevance and safety of the ERr731[®] *Rheum rhaponticum* extract

Study type	Study design/experimental system	Main findings	References
In vitro	Study in ER α -expressing yeast cells, ER α -responsive Ishikawa cells and human endometrial HEC-1B cells transiently transfected with the ER α or ER β	Activation of ER β ; lack of ER α activation in all used cell lines; no anti-estrogenic effects	Wober et al. (2007)
In vitro	Study in bone-derived U2OS cells, stably or transiently expressing the ER β	Estrogenic effects based on ER β -dependent activity; activation of the ER α in bone cells	Möller et al. (2007)
Animal	Examination of the safety in male and female beagle dogs, treated with 100, 300 and 1000 mg/kg body weight/day	No toxicity or pathological changes in organs; a slight decrease in glucose levels after a daily dose of 1000 mg/kg b.w.	Kaszkinn-Betttag et al. (2008a, b)
Animal	90-day study on the safety in terms of endometrial hyperplasia, in a murine experimental model	A stimulatory activity on proliferation in the uterus was excluded; no effects on the bone mineral density	Keiler et al. (2012)
Animal	Evaluation of dose-dependent effects of ERr731 [®] , alone or in combination with estradiol on growth and proliferation in the uterus of ovariectomized rats	No stimulatory effects on uterine proliferation by ERr731 [®] alone; ERr731 [®] reduced uterine growth induced by estradiol	Papke et al. (2009)
Randomized, double-blind, placebo-controlled prospective study	Clinical trial involving 109 women with menopausal complaints; participants were treated with a daily dose of either one enteric-coated tablet of ERr731 [®] (n = 54) or placebo (n = 55) for 12 weeks	No adverse effects; after 4 weeks; the number and intensity of hot flushes were reduced in the ERr731 [®] group; after 12 weeks both the Menopause Rating Scale II (MRS II) total score and each individual MRS II symptoms were alleviated in the ERr731 [®] group, compared to the placebo group	Heger et al. (2006)
Multicenter, prospective, 48-week observational study (OS) (OS I), followed by a 48-week OS II	Continuation of trial Heger et al. 2006. OS I involved 80 women of the earlier group of 109 participants; 39 were treated with ERr731 [®] and 41 women received placebo. OS II (51 women): 23 received ERr731 [®] and 28 received the placebo. The MRS II score was evaluated after 48 and 96 weeks	OS I: in women receiving the ERr 731 during previous RCT, a further reduction of climacteric symptoms was observed; in women from the placebo group of previous RCT who started the ERr731 [®] therapy, an alleviation of menopausal symptoms was found. OS II: in all women receiving the ERr731 [®] , a further decrease of menopausal symptom scores was found. The long-term use of ERr 731 [®] did not induce adverse effects	Hasper et al. (2009)
Multicenter, placebo-controlled, randomized clinical study	112 perimenopausal women with menopausal symptoms, treated for 12 weeks with ERr 731 (n = 56) or placebo (n = 56). The MRS total score, measured on days 0, 28, 56 and 84	In the study group, the MRS total score was significantly reduced (from 27.0 $\pm$ 4.7 points to 12.4 $\pm$ 5.3 points), when compared to the placebo group; the alleviation of menopausal symptoms included a reduction in individual MRS scores and hot flushes	Kaszkinn-Betttag et al. (2009)

Table 3 continued

Study type	Study design/experimental system	Main findings	References
6-month open observational study	363 menopausal women with climacteric symptoms, receiving one tablet of ERr731 [®] for 6 months. The MRS total score after 6 months	The treatment was well tolerated. In 252 women, an evident decrease (i.e. from 14.5 points to 6.5 points) of the MRS total score was found	Kaszkini-Bettag et al. (2008a, b)
Postmarketing report on data related to safety surveillance and consumer complaints	Research on available reports related to adverse effects in Germany (from 1993 to June 2014) as well as assessment of consumers' complaints in North America and South Africa (from the date of ERr731 [®] preparations launch, to June 2014)	124 reports on adverse effects were recorded in Germany per 140 million daily doses sold between 1993 and 2014. The most common complaints were hypersensitivity (74 reactions) and gastrointestinal symptoms (47 reactions). The sale in North America, from January 2009 to June 2014, attained 13 million tablets, providing 79 consumers' complaints to adverse effects, mostly related to gastrointestinal reactions (23 cases) or the lack of therapeutic/beneficial effects (22 cases). No consumers' complaints were recorded in South Africa, from February 2011 (the date of product implementation) to June 2014	Chang et al. (2016)

information derived from different bioassays (Table 5 in supplementary material). *R. rhabarbarum* contains natural antioxidants, capable of combating oxidative stress at different levels of the cellular antioxidant defense. Its bioactive constituents may act both as scavengers of reactive oxygen species (ROS, e.g. nitric oxide, superoxide anion and hydroxyl radical (Kalpana et al. 2012) and as modulators of cell signalling pathways and gene expression. Molecular mechanisms of these effects include the ability of stilbenes to up-regulate functions of the transcription factor Nrf2 (the nuclear factor (erythroid-derived 2)-like 2) and the Nrf2-mediated pathways. Six stilbenes (i.e. rhaponticin, rhapontigenin, isorhaponticin, desoxyrhaponticin, desoxyrhapontigenin and resveratrol), isolated from the rhizome of *R. rhabarbarum*, significantly reduced the intracellular generation of ROS in RAW 264.7 macrophages (Joo Choi et al. 2014). Furthermore, seven compounds from this plant (i.e. piceatannol, resveratrol, rhapontigenin, desoxyrhapontigenin, pterostilbene, (E)-3,5,4'-trimethoxystilbene and *trans*-stilbene) protected hepatocytes against the arachidonic acid- and iron ions-induced oxidative stress in vitro. Molecular mechanisms of this beneficial action involved the AMP-activated protein kinase (AMPK) pathway, an

important regulator of cellular metabolism and energy homeostasis (Dong et al. 2015).

Anti-inflammatory properties

Molecular mechanisms of the anti-inflammatory action of rhubarb-derived substances involve the inhibition of the nuclear factor kappa B (NFκB)-dependent pro-inflammatory pathways. In human umbilical vein endothelial cells (HUVECs), an aqueous extract from *R. rhabarbarum* suppressed the tumor necrosis factor α -induced activation of NF-κB-p65 as well as the expression of adhesion molecules (ICAM-1 and VCAM-1) and the monocyte chemoattractant protein-1 (MCP-1) (Moon et al. 2006). The rhizome-derived stilbenes (rhapontigenin, piceatannol and resveratrol), their derivatives (rhaponticin 2''-O-gallate, rhaponticin 6''-O-gallate) and a naphthalene glucoside (torachryson 8-O-β-D-glucopyranoside) were found to reduce NO production in macrophages (Matsuda et al. 2000). Other studies on macrophages demonstrated that also aloe-emodin was able to suppress the pro-inflammatory response (Hu et al. 2014). According to available reports, stilbenes isolated from rhizomes of this plant may impair an allergy-induced inflammatory response (Matsuda

Table 4 In vitro evidence of anti-inflammatory activities of *R. rhubarbarum*-derived substances

The examined substances	Experimental model of inflammatory response	Main findings	References
<i>R. rhubarbarum</i> -derived stilbenes	Antigen-stimulated RBL-2H3 cells	Inhibition of RBL-2H3 cell degranulation and secretion of TNF- α and IL-4; 3,5,4'-trimethylpiceatannol (IC ₅₀ = 2.1 μ M) and trimethylresveratrol (IC ₅₀ = 5.1 μ M) most effective. Piceatannol, 3,5,4'-trimethylpiceatannol, resveratrol, and trimethylresveratrol suppressed TNF- α and IL-4 release.	Matsuda et al. (2004)
Rhapontigenin, piceatannol, resveratrol, rhaponticin 2''-O-gallate, rhaponticin 6''-O-gallate, and torachrysone 8-O- β -D-glucopyranoside	Lipopolysaccharide-activated macrophages	Reduction of the NO generation	Matsuda et al. (2000)
Desoxyrhapontigenin	RAW 264.7 macrophages LPS-induced lung inflammation in mice (pre-treated with 2.5 or 10 mg/kg of desoxyrhapontigenin for 7 days, <i>i.p.</i>)	Stimulation of the DNA binding of Nrf2; increased expression of antioxidant proteins and enzymes (regulated by Nrf2) Reduction of the LPS-induced inflammation in lung tissue (biochemical and histological changes)	Joo Choi et al. (2014)
Rhapontigenin	HYAL inhibitory assay Experimental model of mast cells	Inhibition of HYAL activity: IC ₅₀ = 0.14 mM; IC ₅₀ for sodium cromoglycate was 15.2 mM Inhibition of histamine release and passive cutaneous anaphylaxis reaction	Kim et al. (2000)
Aloe-emodin	RAW 264.7 macrophages	Reduction of NO generation as well as interleukin-6 and -1 β (IL-6 and IL-1 β) synthesis and secretion	Hu et al. (2014)

et al. 2004). Rhapontigenin was described as an inhibitor of hyaluronidase (HYAL) activity, histamine release from mast cells and passive cutaneous anaphylaxis reaction (Kim et al. 2000). Desoxyrhapontigenin displayed anti-inflammatory properties in vitro and in vivo. It may be also a natural regulator/stimulator of activity of the hemeoxygenase-1 enzyme (HO-1), an important anti-inflammatory, antioxidant and cytoprotective enzyme (Joo Choi et al. 2014). It is believed that the anti-inflammatory and anti-osteoporosis effects of desoxyrhapontigenin are through its inhibitory action on the receptor activator of NF- κ B ligand (RANKL) (Tran et al. 2018).

Outcomes of in vitro examinations of anti-inflammatory properties of the isolated compounds (mainly stilbenes and their derivatives) and extracts from the *R. rhubarbarum* plant have been summarized in the

Table 4. Besides aforementioned works, anti-inflammatory properties of extracts derived from *R. rhubarbarum* have been also found in animal and clinical studies. The suppression of toll-like receptor 4 pathway by rhein (100 mg/kg b.w.) was demonstrated in an animal model of the lipopolysaccharide (LPS)-induced intestinal injury during sepsis (Zhang et al. 2015b). In a randomized clinical trial involving 120 patients with appendectomy, the therapy (twice a day) with an ointment containing 1 mg/g of *R. rhubarbarum* rhizome extract (methanol/water; 1:1, v/v) significantly reduced inflammation and improved the sutures healing process. Complementary experiments in this study indicated on HUVECs indicated on pro-angiogenic activity of the examined rhubarb extract (at concentrations of 5 and 10 mg/ml) (Li et al. 2016).

Cardioprotective properties

In most cases, cardioprotective effects of plant-derived substances are primarily attributed to their antioxidant and/or anti-inflammatory actions, even though, the biological activity of many natural substances evidently goes beyond these mechanisms. Due to a complex and multifactorial character of etiology and pathophysiology of cardiovascular disorders, research on modern prophylactic and therapeutic strategies encompasses a wide range of aspects related to these diseases. In addition to antioxidant and anti-inflammatory effects, the cardioprotective properties of natural substances include antiplatelet and anticoagulant effects, vasorelaxation and improvement of the blood lipid profile. A hypolipidemic activity of *R. rhaponticum* fibre was evidenced in animals maintained on the high-cholesterol diet (Basu et al. 1993) and in hypercholesterolemic human subjects in studies involving 10 hypercholesterolemic men, consuming a daily dose of 27 g of rhubarb stalk fibre, for 4 weeks. The fibre had also an ability to bind bile acids (Goel et al. 1997) and displayed stimulatory effects on the expression of the cholesterol 7 α -hydroxylase gene and excretion of bile acids in mice (Goel et al. 1999). Although the hypolipidemic action of rhubarb was originally attributed to the presence of pectins based on their well-known cholesterol-lowering properties (Fernandez 1995; Fernandez et al. 1992), later works demonstrated that also stilbene compounds, i.e. rhapontin and rhapontigenin might improve the lipid profile. In rats fed a high-cholesterol diet, an intake of these compounds (1–5 mg/kg/day) resulted in a dose-dependent decline of the serum lipid level and a considerable increase of the high-density lipoprotein (HDL) cholesterol level. Additionally, pathological changes in the degenerating fatty liver were significantly reduced by a treatment with either rhaponticin or rhapontigenin (Jo et al. 2014). However, no such promising effects of the rhubarb-fibre diet were found in an experimental model of diabetic rats (treated with 50 g of the rhapontic rhubarb stalk fibre/kg b.w.) (Cheema et al. 2003).

Similarly to lipid-lowering properties of rhapontic rhubarb, also *R. rhabarbarum* showed a cardioprotective potential. The current state of art in this field includes results from in vitro and animal studies, and most of the available data complement each other. It has been found that this plant contains natural

inhibitors of the soluble epoxide hydrolase (sEH) enzyme, which is one of the important molecular targets for the therapy of cardiovascular diseases. Preliminary analyses employing a recombinant human sEH demonstrated the following degrees of its inhibition: 49.8%, 107%, 30% and 39%, by the methanol extract, n-hexane, chloroform, and butanol fractions from *R. rhabarbarum* (at 25 μ g/ml), respectively. Further experiments revealed that the individual rhubarb-derived compounds modulated the sEH activity by diverse mechanisms. While piceatannol 3'-O- β -D-glucopyranoside was a competitive inhibitor of the enzyme, resveratrol, desoxyrhapontigenin, desoxyrhaponticin, rhaponticin, isorhapontin, astringin, chrysophanol-8-O- β -D-glucopyranoside and aloe-emodin acted as mixed-type inhibitors. Rhapontigenin and emodin were noncompetitive inhibitors of sEH. The strongest inhibitory effect was found for astringin ($IC_{50} = 2.5 \pm 0.5 \mu$ M), and the weakest one of the inhibitors was desoxyrhaponticin ($IC_{50} = 53.2 \pm 4.4 \mu$ M) (Jo et al. 2016). The anti-obesity and hypolipidemic effects of *R. rhabarbarum*-derived substances were found in vitro and in vivo. A hot water extract from this plant was found to inhibit protein tyrosine phosphatase 1B (PTP1B), an important regulator of the insulin signalling (Lee et al. 2010). Studies in high-fat diet-fed mice revealed the metabolism-regulatory activity of rhubarb extracts and its anthraquinone components, i.e. chrysophanol and physcion. The extract, at one daily dose of 100 mg/kg of b.w., administered for 8 weeks modulated the lipid metabolism in animals (including a stimulation of adiponectin synthesis) and significantly reduced the increase of body weight. In additional experiments, the isolated anthraquinones (30 μ M) inhibited PTP1B activity and enhanced the insulin sensitivity in serum-starved 3T3L1 cells (Lee et al. 2012b).

Some basic information on anti-thrombotic activity of *R. rhabarbarum* stilbenes is available as well. Desoxyrhapontigenin and rhapontigenin (100–200 μ M) inhibited the arachidonic acid- or collagen-induced aggregation of blood platelets in vitro, but no antiplatelet action was recorded for piceatannol (Ko et al. 1999). Besides the aforementioned effects, anti-diabetic and vasorelaxant activities of *R. rhabarbarum* are postulated. An in vitro screening of the α -glucosidase inhibitory activity of extracts from twenty four plants, suggests that aerial parts of *R. rhabarbarum* contain moderate inhibitors of this

enzyme. The methanol extracts from peel and the peeled stalks inhibited the enzyme with IC_{50} values of 0.013 and 4.94 mg/ml, whereas for the ethyl acetate extracts, the IC_{50} amounted 0.24 and 0.21 mg/ml, respectively. For a comparison, the strongest inhibitor in this study (i.e. the methanol extract from *Cinnamomum zeylanicum*) was characterized by the IC_{50} = 0.009 mg/ml (Kongstad et al. 2015). However, the latest study on α -glucosidase inhibitory activity of phytochemicals isolated from *R. rhubarbarum* has provided diverse results. The IC_{50} values for the most of the isolates exceeded 100 μ M; however, the inhibitory actions of δ -viniferin (IC_{50} = 0.5 μ M, i.e. 0.23 μ g/ml) and rhapontigenin (IC_{50} = 15.4 μ M, i.e. 3.97 μ g/ml) exceeded the efficiency of acarbose (IC_{50} = 126.8 μ M, i.e. 81.8 μ g/ml), a well-known inhibitor of this enzyme (Ha et al. 2020).

Desoxyrhapontigenin, emodin and chrysophanol isolated from rhizomes of *R. rhubarbarum* influenced the glucose metabolism in vivo. At oral doses of 0.21 (desoxyrhapontigenin), 0.45 (emodin) and 0.18 (chrysophanol) mg/kg b.w., these compounds reduced the postprandial hyperglycemia in animals by 35.8, 29.5, and 42.3%, respectively (Choi et al. 2005). Among seven stilbene-type compounds from the rhubarb rhizome (i.e. desoxyrhapontigenin, piceid, piceatannol, resveratrol, rhapontigenin, rhaponticin and ϵ -viniferin), the strongest vasorelaxation of the isolated rat aorta was observed after the treatment with piceatannol (EC_{50} = 2.4 μ M) (Yoo et al. 2007). It is suggested that molecular mechanisms of the piceatannol-induced vascular relaxation involve the endothelium-dependent nitric oxide signalling pathway, including the activation of the large conductance, Ca^{2+} -activated K^{+} channels (BKCa) (Oh et al. 2007). In vitro vasodilatory properties (also mediated by the endothelium-dependent NO/cGMP pathway) in rat aorta preparations were observed for an aqueous extract of *R. rhubarbarum* rhizomes (Moon et al. 2006). Moreover, both the vasorelaxant and anti-inflammatory effects of this extract were confirmed in vivo, in atherogenic diet-fed rats. The treatment with rhubarb extracts resulted in significant anti-atherogenic effects, including a reduction of low-density lipoprotein-cholesterol and an increase of the HDL-cholesterol in blood plasma. The extracts suppressed the atherogenic diet-induced expression of the vascular NF- κ B-p65, adhesion molecules (ICAM-1 and VCAM-1) and E-selectin in the examined animals

(Moon et al. 2008). Inhibitory effects of *R. rhubarbarum* stilbenes and their derivatives on functions of the cell adhesion molecules (CAMs) were also described in other papers, which hypothesized that the biological activity of rhubarb-derived substances may be a base for development for new therapeutic strategies (Lee et al. 2012a; Spelman et al. 2011).

Anticancer activity

Both the stilbene (Sirerol et al. 2016) and anthraquinone (Özenver et al. 2018) components of plant extracts display chemopreventive and antitumor properties; however, the anticancer action of the rhubarb-derived extracts has been evaluated hitherto only in vitro. A methanol extract from *R. rhubarbarum* (at concentrations of 70–350 μ g/ml) mediated cancer cell death through the activation of the intrinsic (mitochondria-dependent) apoptotic pathway in human adenocarcinoma gastric (AGS) cells (Hong et al. 2015). The exposure of these cells to aloe-emodin or chrysophanol 1-*O*- β -D-glucopyranoside increased the poly(ADP-ribose)polymerase (PARP) cleavage and induced downregulation of the anti-apoptotic protein, Bcl-2. Additionally, chrysophanol 1-*O*- β -D-glucopyranoside slightly stimulated the expression of pro-apoptotic proteins such as Bid and Bax (Trinh et al. 2019). In the MCF-7 human breast cell line, aloe-emodin and rhapontigenin induced the mitochondria-independent apoptosis (mediated by the caspase-8 pathway), while chrysophanol 1-*O*- β -D-glucopyranoside, acted by the mitochondria-dependent apoptotic pathway (Lee et al. 2018). In the same experimental model, the induction of cancer cell apoptosis was also found for desoxyrhapontigenin. Its anticancer effect was through a dilation of endoplasmic reticulum (ER) and up-regulation of the expression of ER stress markers such as a chaperone protein GRP78, inositol-requiring kinase 1 α (IRE1 α), eukaryotic translation initiation factor 2 (eIF2 α), C/EBP homologous protein (CHOP) as well as JNK and p38 kinases (Venkatesan et al. 2016). Furthermore, a hexane extract from *R. rhubarbarum* (20–60 μ g/ml) significantly decreased the growth and viability of cancer cells and induced apoptosis in the HN22 and SCC15 oral cancer cell lines (Choi et al. 2011).

In the case of *R. rhaponticum*, the available literature comprises a small number of reports strictly related to anticancer action of the extracts, including a

few mechanistic studies on this issue. The vast majority of data derives from studies on estrogenic properties of this plant; the hormone-like action is believed to be a molecular basis of cancer-preventive or anticancer effects of *R. rhaponticum*. A *R. rhaponticum* extract and its components were found to bind to ER β in various highly specific cancer cells such as human bone osteosarcoma (U2OS) and human endometrial adenocarcinoma (HEC-1B) cell lines (Kaszkin-Bettag et al. 2008a, b; Möller et al. 2007). In contrast, neither the extract nor its compounds and their metabolites (resveratrol and piceatannol) were able to activate the ER α receptor (Kaszkin-Bettag et al. 2008a, b; Möller et al. 2007). Additional source of data may be works on anticancer action of individual compounds (not isolated from *R. rhabarbarum*), but occurring also in these plants. Among others, such studies were described for piceatannol (Banik et al. 2020).

Antimicrobial and antiviral activities

It is assumed that *R. rhaponticum* and *R. rhabarbarum* contain antimicrobial substances that are active, at least, towards some pathogens (for details, see the Table 6 in supplementary material). The antiviral properties of rhubarbs have been described to a much lesser extent (Nurbaulina et al. 2009). However, despite some encouraging results, the pharmacological significance of antimicrobial action of rhubarbs is difficult to estimate, and main concerns are related to the lack of in vivo examinations. Furthermore, in many cases, beneficial effects were observed only at high, physiologically unachievable concentrations. On the other hand, it is known that various plant preparations are used externally, e.g. onto wounds, burns or ulcers. In these cases, also higher doses of bioactive substances may be clinically useful, if only, the necessary in vivo tests are done.

A comparative assessment of antibacterial actions of the rhizome and roots extracts, prepared from *R. rhaponticum*, *R. palmatum* and *R. rhabarbarum* demonstrated that all of the examined crude extracts (96% ethanol; v/v), were more efficient against the Gram-positive bacteria than those Gram-negative. The most effective one was the preparation from *R. rhabarbarum* (the minimum inhibitory concentration (MIC) = 125–250 $\mu\text{g/ml}$), but its activity was significantly weaker, compared to gentamicin and

cefuroxime. In the case of these antibiotics, the MIC values for reference strains of *Staphylococcus* spp. ranged from 0.12 to 0.49 $\mu\text{g/ml}$ and from 0.49 to 0.98 $\mu\text{g/ml}$, for gentamicin and cefuroxime, respectively (Kosikowska et al. 2010). Even an infusion from *R. rhaponticum* was found to display antimicrobial effects, though, its activity was weaker than chloramphenicol, a reference bacteriostatic agent (Raudsepp et al. 2013). A screening of antimycobacterial activities of *R. rhaponticum* root extract and its bioactive components such as rhaponticin, desoxyrhaponticin, resveratrol, barbaloin, aloe-emodin and chrysophanol revealed that the anthracene compounds were the most efficient (the MICs ranged between 32 and 64 $\mu\text{g/ml}$). However, no antimicrobial effects were found for the petiole extract (Smolarz et al. 2013b). Another study evidenced antibacterial properties of the crude, ethyl acetate and aqueous extracts originating from rhapontic rhubarb (Ziad et al. 2011).

Tests employing seventeen bacterial and one fungal strain (Table 6 in supplementary material) revealed antimicrobial activity of the ethanolic extract from the underground organs of *R. rhabarbarum* (Canli et al. 2016). An extract from the petioles was found to possess bacteriostatic, but not bactericidal properties against ATCC strains of *S. aureus*, *S. epidermidis*, *K. pneumoniae*, *P. aeruginosa* and *E. coli* (the MICs ranged from 700 to 900 $\mu\text{g/ml}$) (Pájaro et al. 2018). Surprisingly, in other comparative studies, based on antimicrobial actions of various extracts and freshly pressed plant juice from different species, the *R. rhabarbarum* preparations had moderate or weak antibacterial properties, except the water extract, which was an efficient inhibitor of growth of two Gram-positive bacteria, i.e. *Bacillus subtilis* and *Bacillus cereus* (Krisch et al. 2008).

Since the therapy of gastrointestinal disorders is one of the ethnomedicinal recommendations for use *R. rhaponticum*, extracts from this plant were tested in terms of anti-*Helicobacter pylori* activity. Nevertheless, literature dealing with antimicrobial properties of this plant has not confirmed its pharmacological efficiency in combating *H. pylori* (Cogo et al. 2010). It seems to that the use of rhubarb-derived substances for disease-preventive purposes, e.g. for maintaining oral hygiene and dental health, can be more promising. Traditionally, the *R. rhabarbarum* root-based preparations have been used for the treatment of dental diseases, and current studies on its inhibitory action on

the dental plaque formation or glycolytic acids production by *Streptococcus mutans* and *Streptococcus sobrinus* confirmed a protective effect of this plant in dental hygiene (Kim et al. 2011). Rhein, one of the anthraquinone components of *R. rhabarbarum* and *R. rhaponticum* roots, displays an ability to combat *Porphyromonas gingivalis*, a Gram-negative periodontopathogen, and thus, it is considered potentially useful in maintaining of oral health (Chinsembu 2016). Moreover, it has been demonstrated that rhein may act synergistically with a nitroimidazole antibiotic, metronidazole (Azemat et al. 2015).

Other biological activities

Hydroxystilbenes isolated from the roots of *R. rhaponticum* displayed hepatoprotective effects in mice exposed to ethanol inhalation. Animals were treated with *trans*-resveratrol (20 mg/kg b.w.) or received a hydroxystilbene-containing *R. rhaponticum* extract (air-dried root in ethanol, 1:10 w/v), administered to an equivalent of the *trans*-resveratrol dose of 20 mg/kg b.w. (Raal et al. 2009).

A methanolic extract from *R. rhaponticum* rhizome inhibited the tyrosinase activity in UV radiation-stimulated human epidermal melanocytes at very low concentrations. According to the authors, inhibitory effects of the examined rhubarb were comparable to the efficiency of kojic acid ($IC_{50} = 0.06 \mu\text{g/ml}$ and $0.02 \mu\text{g/ml}$, for the extract and kojic acid, respectively). Additionally, a significant reduction of both the UV-induced secretion of cytokines (IL-1 α and TNF- α) and the alpha-melanocyte stimulating hormone (α -MSH) synthesis was found (Silveira et al. 2013).

Advances in studies on *R. rhaponticum* and *R. rhabarbarum*: current state of art

The described rhubarb species contain bioactive phytochemicals with some health-promoting or therapeutic potential. However, only the estrogenic activity of *R. rhaponticum* has been well established in pre-clinical studies and clinical trials (data summarized in the Table 3), while other activities of this plant have been mainly evidenced by basic studies. Thus, most of the other curative uses of rhapontic rhubarb is still based on ethnomedicinal recommendations. Similar

concerns are related to *R. rhabarbarum*—also in this case, results from in vitro works prevail and are supported only by few animal studies. A cross-search in scientific sources and medical databases such as NIH U.S. National Library of Medicine (i.e. ClinicalTrials.gov and PubMed) and SpringerLink indicated that at least several clinical trials including a word “rhubarb” have been registered, but no records containing “rhababarum” or “undulatum” were found. In other scientific resources, only one clinical study on wound-healing and anti-inflammatory properties of *R. rhabarbarum* was found (Li et al. 2016).

One of recent trends in research on rhubarb extracts is their use as pharmacophores. Modern strategies are particularly focused on ecofriendly nanosize materials, produced during the *greener synthesis*/the *green chemistry* processes (Kharissova et al. 2019). Such attempts have been successfully undertaken with other substances of plant origin (Park et al. 2016; Saw et al. 2019). The *R. rhabarbarum*-based silver nanoparticles were found to possess significant antibacterial activity both against *E. coli* (CCM 4517) and *Staphylococcus aureus* (CCM 4516). Additionally, these particles displayed a dose-dependent anti-cancer effect in human epithelial carcinoma (HeLa) cell line (Palem et al. 2016, 2018).

Conclusions

Rheum rhaponticum and *Rheum rhabarbarum* are popular edible plants, commonly cultivated in different regions of the world. A wide range of biological activities of these species has been evidenced by numerous in vitro and several in vivo studies. Both of these species constitute interesting sources of biologically active compounds with health-promoting or therapeutic potential. However, the current knowledge of physiological effects and pharmacological efficacy of these rhubarbs remains incomplete. Therefore, further, more advanced studies (including clinical trials) on pharmacological activity of these rhubarb species are needed.

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