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Rhaponticin as an anti-inflammatory component of rhubarb: a minireview of the current state of the art and prospects for future research

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Abstract Rhaponticin (3,3′,5-trihydroxy-4′-methoxystilbene 3-*O*-β-D-glucoside; synonym–rhapontin), is a stilbene compound, mainly found in various species of rhubarb (*Rheum* L.). The aglycone, rhapontigenin, is thought to be the biologically active form of rhaponticin. As a component of rhubarb, rhaponticin may be present in the human diet both in foods and dietary supplements. Although promising reports have been published on the various activities of rhaponticin (see: antioxidant, estrogenic, antithrombotic, anticancer and anti-inflammatory actions), no comprehensive review exists of its anti-inflammatory properties. Therefore, the aim of the present work is to summarize the existing evidence of the anti-inflammatory properties of rhaponticin and provide a prospective insight into research on this stilbenoid.

Keywords Rhaponticin · Rhapontin · Rhapontigenin · Rhubarb · Anti-inflammatory

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Introduction

The antioxidant properties of natural, plant-derived substances are widely believed to be of primary importance in the prevention of civilization diseases. The latest decade has provided new insights into the multifactorial pathophysiology of these disorders, and with them, some dose of criticism regarding the principal role played by the antioxidant activity of plant-derived compounds. The health-promoting and disease-preventive effects of antioxidants, observable at the level of the whole organism, may result from diverse molecular pathways, including not only reactions with oxidants, but also the ability to regulate gene transcription and modulate the adaptive response. The beneficial effects of many natural antioxidants and chemopreventive agents are also dependent on their anti-inflammatory actions (see Goszcz et al. 2015; Leopold 2015; Pashkow 2011). Disease-associated inflammation forms a complex network of interactions between pro-inflammatory mediators, oxidative stress and host immune response, as well as pathological changes in the physiology of organs and tissues. It is involved both in the pathogenesis and pathophysiology of numerous disorders, including malignant transformation and tumour progression, as well as the development of cardiovascular diseases and their complications (see Chang and Yang 2016; Moriya 2019; Yao and Narumiya 2019). For that reason, the anti-inflammatory activity of plant-derived

substances is a highly desirable biological property, widely regarded as being crucial for maintaining human health.

Rhaponticin (3,3′,5-trihydroxy-4′-methoxystilbene 3-*O*-β-D-glucoside; synonym–rhapontin) is a stilbene-type compound found in the human diet; its aglycone form is rhapontigenin (Fig. 1). The stilbenoids are a well-known group of bioactive phytochemicals, that are synthesized by various plant species and accumulated in aerial and underground plant organs. Although resveratrol still remains the best described stilbene (see Cheng et al. 2019; Ramírez-Garza et al. 2018), it should be noted that this class of polyphenols includes many other bioactive compounds, such as rhapontigenin and rhaponticin, which display a wide range of beneficial activities, including antioxidant, estrogenic, antithrombotic, anticancer and anti-inflammatory effects (see Czop et al. 2019; Kim and Ma 2018; Park et al. 2002; Sun et al. 2017; Wober et al. 2007; Zhang et al. 2007).

This short review summarizes the current literature concerning the anti-inflammatory activities of rhaponticin and its aglycone, and provides a prospective insight into research on these phytochemicals. The records were identified by a search of the PubMed/Medline, Science Direct, Springer Link, Google Scholar and Scopus databases (until June, 2019). Although recent years have provided a wealth of novel data on research trends and the bioactivity of rhaponticin and rhapontigenin, as with many other polyphenols, this research has not only yielded very promising results, but it has also revealed hitherto poorly-recognized aspects of its biological activity.

Sources of rhaponticin and its content in plant-derived preparations

Originally, rhaponticin was identified in *Rheum rhaponticum* L. (rhapontic rhubarb), and to date, it has been primarily listed as one of the most important bioactive substances of various rhubarb species. Its structural characteristics and chemical properties are summarized in a recent paper by Sun et al. (2017).

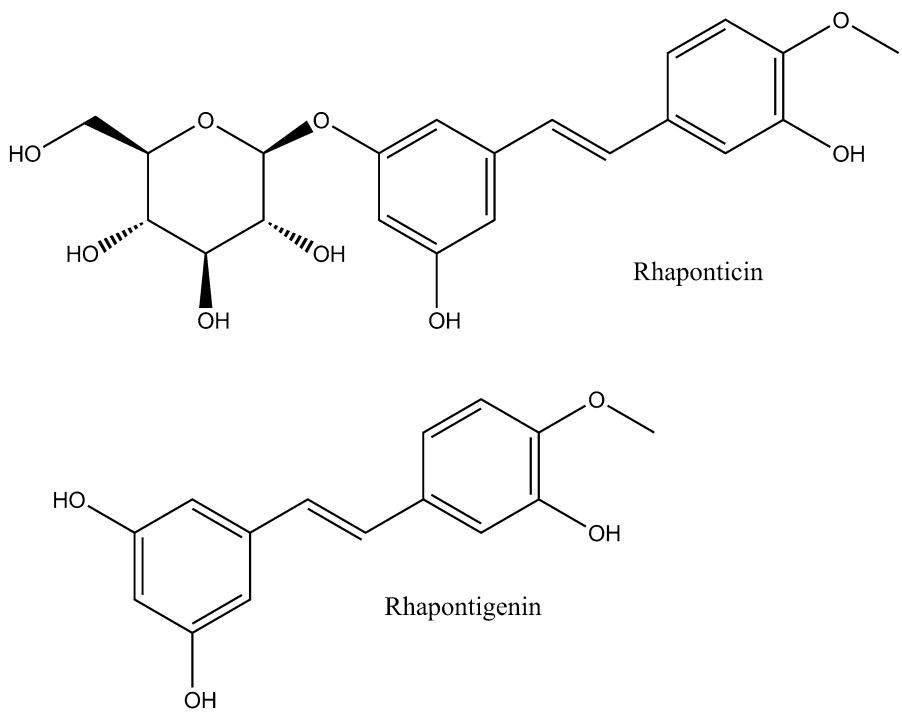

Fig. 1 Structures of rhaponticin (3,3′,5-trihydroxy-4′-methoxystilbene 3-*O*-β-D-glucoside; IUPAC name: (2S,3R,4S,5S,6R)-2-[3-hydroxy-5-[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]phenoxy]-6-(hydroxymethyl)oxane-3,4,5-triol) and its aglycone, rhapontigenin (IUPAC name: 5-[(E)-2-(3-hydroxy-4-methoxyphenyl)ethenyl]benzene-1,3-diol)

Quantitative analyses of rhaponticin content in plants include various advanced techniques such as ultra-performance liquid chromatography-diode array detection (UPLC-DAD), high-speed counter-current chromatography (HSCCC), β-cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC), zone electrophoresis with diode array detector (CZE-DAD), Fe_3O_4-based magnetic molecularly imprinted polymers (MMIPs) (Sun et al. 2017) as well as thin-layer chromatography (TLC) (Smolarz et al. 2013).

The rhaponticin content in *Rheum* species varies significantly depending on the type of the plant material and the mode of extraction, up to about 55 mg/g of dry weight (Table 1). A recent study employing a response surface methodology to improve the plant material extraction process, developed an optimal procedure based on the use of 57% EtOH, at 65 °C, for 24 h. This protocol yielded rhaponticin content of 13.17% in extract of *R. undulatum* roots (Kwak et al. 2019). Rhaponticin was also detected in other plants such as *Trigonella foenum-graecum* L. (fenugreek) (He et al. 2016; Li et al. 2018), *Guibourtia tessmannii* (Harms) J. Leonard (Nyemba et al. 1995), *Stuhlmannia moavi* Taub. (Liu et al. 2013), *Eucalyptus rubida* H. Deane & Maiden (Etoh et al. 1990) and *Baccharis grisebachii* Hieron (Gómez et al. 2019).

So far, the literature has provided very few reports dealing with quantitative estimation of rhaponticin and rhapontigenin in foods. Most works on the phytochemical profiling of dietary products contain a collective quantification of stilbene-type compounds and their derivatives or provide data on stilbenes other than rhapontigenin (mainly resveratrol). The total concentration of stilbene-type compounds in different wines (considered to be their most abundant source), can be as high as several mg/L of a product (El Khawand et al. 2018). Depending on the maceration times, *trans*-resveratrol and *trans*-piceid concentrations in wines were found to reach up to 1.75 and 4.48 mg/L, respectively (Kostadinović et al. 2012). In fresh wine grape skins, the resveratrol content may range from 19 to 508 μg/g, and that of *trans*-piceid could be as high as 196 μg/g (Vincenzi et al. 2013). Studies of edible berries found resveratrol to be present at levels up to 15.72 μg/g of fresh weight (f.w.) in red currant (*Ribes rubrum* L.), 19.29 μg/g f.w. in cranberry (*Vaccinium oxycoccos* L.) and 30 μg/g f.w. in cowberry (*Vaccinium vitis-idaea* L.) (Błaszczyk et al. 2019). In cocoa powders, the *trans*-resveratrol content was 1.85 ± 0.43 μg/g, and the *trans*-piceid content 7.14 ± 0.80 μg/g (Hurst et al. 2008). Isorhapontigenin was not detected in wine, but was found to be present at levels ranging from 0.55 to

Table 1 Exemplary data on rhaponticin content in different *Rheum* species

Rhubarb species	Rhaponticin content and the extraction mode	References
R. franzenbachii Münter	1.59 ± 0.077 mg/g of dried leaves (extracted with 80% EtOH, for 2 h)	Wang et al. (2014)
	4.36 ± 0.135 mg/g of dried roots (extracted with 80% EtOH, for 2 h)	
R. rhaponticum L.	38.07–40.83 mg/g of dried roots (in plant material collected from April till October), while the rhapontigenin content varied from 1.4 to 1.62 mg/g of dried roots (plant material macerated with 100% methanol, for 72 h)	Aaviksaar et al. (2003)
	25.5 ± 0.4 mg/g of dried roots (extracted with the boiled 80% methanol solution for 1 h)	Smolarz et al. (2013)
	0.3 ± 0.09 mg/g of dried petioles (extracted with the boiled 80% methanol solution for 1 h)	
R. tanguticum Maxim.	25.5 mg of *trans*-rhaponticin and 16.0 mg of *cis*-rhaponticin were isolated from 80 mg of crude sample (extracted from dried roots, using 70% ethanol under reflux, three times, each one for 2 h)	Zhao et al. (2013)
R. undulatum L.	31.5 ± 3.8 mg/g of dried roots (extracted with the boiled 80% methanol solution for 1 h)	Smolarz et al. (2013)
	0.8 ± 0.1 mg/g of dried petioles (extracted with the boiled 80% methanol solution for 1 h)	
	54.54 ± 24.59 mg/g of dried rhizome (ultrasonic extraction with 70% ethanol for 1 h)	VanMen et al. (2012)
	2.9 mg/100 mg of the 100% EtOH root extract (isolated at 60 °C, for 24 h)	Lee et al. (2018)
	14.66/100 mg of the 50% EtOH root extract (isolated at 100 °C, for 24 h)	
	15.44/100 mg of the 50% EtOH root extract (isolated at 60 °C, for 13 h)	

1.28 mg/kg f.w. in grape pomace (Fernández-Marín et al. 2014).

More detailed information on rhaponticin and rhapontigenin contents can be derived from studies on herbal material originating from rhubarb (Table 1). For instance, rhaponticin and rhapontigenin content in *R. rhaponticum* roots collected from April to October was found to demonstrate moderate variability depending on the plant growth stage. The total amount ranged from 36.48 to 43.20 mg/g of air-dried root for rhaponticin, and from 1.17 to 1.62 mg/g for rhapontigenin. In contrast, the content of resveratrol was more variable, ranging from 0.15 mg/g of air-dried root (in April) to 4.99 mg/g (in October) (Aaviksaar et al. 2003).

Studies on effects of different cooking regimes on the polyphenol content in rhubarb (*R. rhaponticum*) petioles found fast stewing, slow stewing and baking, to enhance both the total content of polyphenolic compounds and overall antioxidant capacity of the examined samples, compared to raw petioles; no such effect was observed for blanching. The highest polyphenolic content (in the filtrate of the homogenized pulp) was obtained by slow cooking for 30 min and baking for 20 min. This increase in polyphenolic content was most likely a result of thermal degradation of plant material and the ensuing release of these substances from plant cells and tissues (McDougall et al. 2010). However, no such information exists on changes in rhaponticin and rhapontigenin contents in rhubarb-containing foods or other dietary products, and as such, the above-mentioned results may constitute a basis for further studies, involving the quantitative analysis of stilbene content, especially rhaponticin and rhapontigenin, in rhubarb during thermal processing at low and high temperatures.

Besides rhubarb-containing foods, rhaponticin is a component of dietary supplements or herbal medicines, mainly recommended to alleviate menopausal complaints. The content of *R. rhaponticum* extract in such preparations usually ranges from 4 to 1000 mg; however, detailed information on the rhaponticin contents in plant extracts is not always available. According to data given by manufacturers, herbal medicines and dietary supplements typically provide milligram doses of rhaponticin: e.g. a preparation providing 4 mg of *R. rhaponticum* extract (ERr 731®)/ one tablet contains 2.2 mg of rhaponticin, another product contains 150 mg of rhubarb extract in one capsule (incl. 0.77% of rhaponticin), while a rhubarb-based dietary supplement provides 4 mg of *R. rhaponticum* extract per one tablet, standardized to ≥ 54% of rhaponticin.

Anti-inflammatory action of rhaponticin and rhapontigenin

In vitro data

Available evidence suggests that rhaponticin and rhapontigenin have moderate inhibitory effects on key enzymes of the arachidonic acid cascade (Table 2). In addition, these compounds not only inhibit COXs but also hyaluronidase (HYAL), belonging to another class of pro-inflammatory enzymes (Kim et al. 2000). Although both of the above-mentioned compounds were found to inhibit the cyclooxygenase enzyme isoforms 1 (COX-1) and 2 (COX-2) or lipoxygenase (LOX), in most cases their efficiency was weaker than that of resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) (Kutil et al. 2015; Ngoc et al. 2008; Park et al. 2016; Shin et al. 1998). Moreover, the fact that resveratrol and other applied reference substances are non-selective COX inhibitors significantly hinders reliable evaluation of the inhibitory potential of rhaponticin or rhapontigenin.

While rhapontigenin (the metabolite) is the active constituent of rhaponticin, the latter form (glycoside) evidently has lower activity. In a work of Kim et al. (2000), rhaponticin isolated from the rhizomes of *R. undulatum* was even designated as a prodrug—a source of the biologically active metabolite. Yamamoto et al. (2017) demonstrated that the nitric oxide (NO) production in macrophages declined by 34% upon treatment with rhapontigenin (30 μM), compared to only 23% inhibition by resveratrol. Elsewhere, NO production in macrophages was found to be partly decreased by both rhaponticin (IC_{50} < 100 μM) and rhapontigenin (IC_{50} = 48 μM), but more effective inhibition was observed for their naturally-occurring gallates, i.e. rhaponticin 2″-*O*-gallate and rhaponticin 6″-*O*-gallate (IC_{50} = 13 and 11 μM, respectively) (Kageura et al. 2001; Matsuda et al. 2000). Although neither rhaponticin nor rhapontigenin inhibited the activity of inducible nitric oxide synthase (iNOS) in the above-mentioned experiments,

Table 2 Inhibitory properties of rhaponticin and rhapontigenin towards pro-inflammatory enzymes in comparison to reference compounds

The examined enzyme	IC_{50} established for rhapontigenin and rhaponticin	IC_{50} established for reference compounds	References
COX-1	58 μM (rhapontigenin) > 100 μM (rhaponticin)	24 μM (resveratrol) 8 μM (indomethacin)	Shin et al. (1998)
	24.6 μM (rhapontigenin)	2.3 μM (resveratrol)	Kutil et al. (2015)
COX-2	36.1 μM (rhapontigenin)	3.4 μM (resveratrol)	Kutil et al. (2015)
LOX	10.7 (rhapontigenin)	3.4 μM (baicalein)	Ngoc et al. (2008), Park et al. (2016)
	34.3 μM (rhaponticin)	19.7 μM [(+)-catechin] 12.3 μM (resveratrol)	
	> 50 μM (rhapontigenin)	> 50 μM (resveratrol)	Kutil et al. (2015)
HYAL	> 2 mg/ml (rhaponticin) 0.14 mM (rhapontigenin)	15.2 mM (sodium cromoglycate)	Kim et al. (2000)

both compounds effectively inhibited iNOS expression in the investigated macrophages.

Some insight into the molecular basis of the anti-inflammatory actions of rhaponticin and rhapontigenin has been provided by cellular experimental systems (Fig. 2). However, due to the limited extent of in vitro studies and the substantial variation between studies with regard to experimental settings and conditions, the pharmacological significance of the anti-inflammatory actions of rhapontigenin and rhaponticin is still difficult to estimate. In addition, only the small number of reported results exists regarding reference anti-inflammatory clinically used drugs such as indomethacin. Most studies of the activities of rhaponticin and rhapontigenin compare them to resveratrol or other polyphenolics (Table 2). Hence, more detailed and advanced studies, including a variety of reference drugs and standardized experimental settings are needed to evaluate the safety of rhaponticin and rhapontigenin and their inhibitory efficiency towards inflammatory processes.

Despite sharing some biochemical pathways and molecular targets, the physiological effects of rhaponticin and rhapontigenin still remain poorly understood, when compared to the current knowledge of biological actions of resveratrol. Accumulating evidence from in vitro and in vivo investigations has indicated that resveratrol displays a wide range of beneficial properties such as antioxidant, cardioprotective, anticancer, neuroprotective and anti-inflammatory action (see Cheng et al. 2019; Ramírez-Garza et al. 2018). Resveratrol may interact with different targets and modulate the activities of numerous pro-inflammatory mediators through the inhibition of the nuclear factor kappa B (NF-κB) activation, reduction of inflammatory cytokine levels and iNOS activity as well as

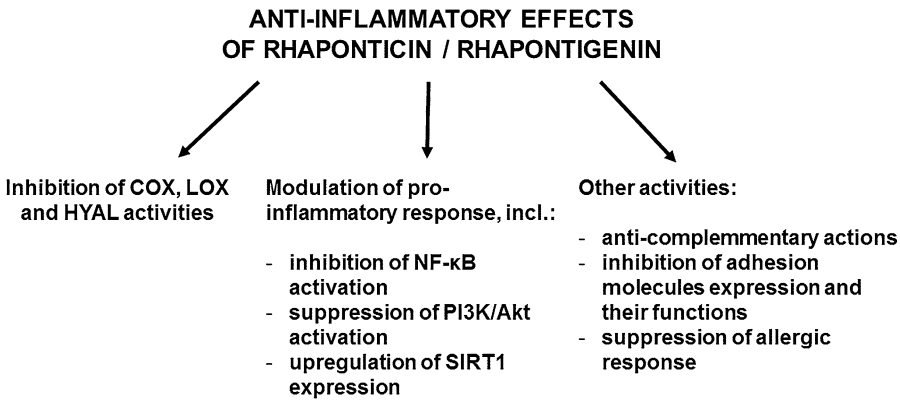

Fig. 2 Possible mechanisms of anti-inflammatory actions of rhaponticin and rhapontigenin

regulation of cell adhesion molecules and sirtuin 1 (SIRT1) expression (de Sá Coutinho et al. 2018). Similarly to resveratrol, the anti-inflammatory action of rhaponticin and rhapontigenin also involves the inhibition of the activation of NF-κB. Structure–activity relationship (SAR) studies indicated that the oxygen-containing functional groups such as –OH and $–OCH_3$ in the benzene ring might be essential for the activity of rhaponticin and rhapontigenin. The presence of a glucose moiety reduced this anti-inflammatory activity, while the α-, β-double bond had no effect (Kageura et al. 2001). Experiments on human myeloid cells confirmed the significance of hydroxyl groups for the anti-inflammatory activity of stilbenoids; however, the glycoside form (rhaponticin) was not found to have any inhibitory effect on NF-κB activation (Ashikawa et al. 2002). A recent study by Eräsalo et al. (2018) revealed that several aglycone stilbenoids (i.e. pinosylvin, monomethylpinosylvin, resveratrol, pterostilbene, piceatannol and rhapontigenin) have inhibitory effects on the pro-inflammatory response of macrophages. Simultaneously, it has also been found that the glycosides (astringin and rhaponticin) had weaker activity than their non-glycosylated forms (Eräsalo et al. 2018). Molecular pathways of anti-inflammatory actions of the examined stilbenoid aglycones have been shown to involve the suppression of PI3K/Akt activation. Furthermore, it has been suggested that the anticancer activity of rhapontigenin within the inflammatory microenvironment of a tumour may be based on the inhibition of TGF-β-mediated epithelial-mesenchymal transition depending on the PI3K/Akt/mTOR pathway (Yeh et al. 2016). Additionally, rhapontigenin was found to upregulate the expression of SIRT1 in the THP-1 human monocytic cell line (Kawakami et al. 2014). Since SIRT1 acts as an inhibitor of NF-κB activation (via deacetylation of the p65 subunit) (see Kauppinen et al. 2013), low activity of SIRT1 or its inhibition in cells results in an inflammatory response, triggered by the NF-κB-dependent activation of genes for cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). Conversely, compounds increasing SIRT1 level (such as rhapontigenin) might reduce the inflammatory response.

Other available evidence of biological activities of rhapontigenin possibly related to its anti-inflammatory properties includes anti-adhesive, immunomodulatory and anti-allergic effects (briefly summarized in Table 3).

Bioavailability of rhaponticin and limitations of its potential pharmacological use

Like many other polyphenols, rhaponticin and rhapontigenin also exist both in *cis* and *trans* isoforms in plant species and are photosensitive compounds (Fig. 3). Although the *trans* forms are primarily responsible for the biological actions of these compounds, susceptibility to UV-induced isomerization may result in their undesirable conversion into the less active *cis* form, leading to a significant decrease of bioactivity. Such isoforms have been identified in biological samples by analyses of the *cis–trans* isomerization kinetics of stilbenes, for example, by capillary electrophoresis and spectroscopic methods (Hui et al. 2011). This concept could be useful in evaluating of the content of photosensitive compounds, especially in the context of controlling the presence and stability of the biologically-active *trans* isomers in biological samples.

The pharmacokinetics of rhaponticin/rhapontigenin has been examined using various techniques, including UHPLC-Q-TOF/MS, UHPLC-DAD-MSn (Zhao et al. 2012), or analysis after complexation with cerium (Ce^{3+}) (Sun et al. 2013) and erbium (Er^{3+}) (Sun et al. 2016) ions. Since the metabolism of rhaponticin has recently been extensively discussed by Chen et al. (2019), these issues are only briefly mentioned here. Rhaponticin is quickly metabolized and distributed in vivo; its absolute bioavailability after oral administration was found to be 0.03% (Zhao et al. 2012). Molecular modelling of human serum albumin (HSA)-rhaponticin interactions demonstrated that rhaponticin binds to the sub-domain IIA hydrophobic cavity (site I) of HSA (Sun et al. 2012). The HSA protein binding rate (%) for rhapontigenin has recently been estimated as 79.99 ± 0.59% (Cao et al. 2019). The concentration of rhapontigenin in blood plasma declines rapidly: after an intravenous dose of 10 mg/kg of body weight (b.w.), its half-life in rat plasma was found to be 3.0 ± 1.35 h with a volume of distribution of 11.05 L kg^{-1}. The total plasma clearance and hepatic clearance of rhapontigenin were 1.18 L h^{-1} kg^{-1} and 1.165 L h^{-1} kg^{-1}, respectively. The mean area under the curve (AUC) was estimated to be 8.39 μg h mL^{-1} (Roupe et al. 2006). Rhaponticin has also been found to undergo

Table 3 Broader insight into anti-inflammatory properties of rhapontigenin and rhaponticin—brief data on other evidence that may be related to their anti-inflammatory actions

Experimental system	Main findings	References
Complement activation in vitro	Anti-complementary actions of rhapontigenin and rhaponticin (IC_{50} = 370 μM and 700 μM, respectively) in classical pathway	Oh et al. (1998)
Human monocytic cell line THP1 (cells stimulated by TNF-α)	Moderate inhibitory effect of rhapontigenin on the expression of intercellular adhesion molecule-1 (ICAM-1) on THP1 cells; no effects for rhaponticin were found	Ahn et al. (2000)
Rat peritoneal exudate cells, stimulated by the compound 48/80 or calcium ionophore A-23-187	In the compound 48/80 experiments: reduction of histamine release, with IC_{50} of 0.29 μM and 0.079 nM, for rhaponticin and rhapontigenin, respectively	Kim et al. (2000)
	In the calcium ionophore A-23-187 experiments: reduction of histamine release, with IC_{50} of 0.90 μM and 0.25 nM, for rhaponticin and rhapontigenin, respectively	
Chinese hamster lung fibroblasts (V79-4)	Inhibition of the activity of activator protein 1 (AP-1) transcription factor by rhapontigenin	Zhang et al. (2007)
THP1 cells	Inhibitory effects of rhapontigenin on direct binding between sICAM-1 and the lymphocyte function-associated antigen-1 (LFA-1) on the examined cells (IC_{50} = 25.4 μM); moderate inhibition (46% at a conc. of 100 μM) of the VLA-4 antigen of THP-1 cells and the vascular cell adhesion molecule (sVCAM-1)	Lee et al. (2012)
Antigen-stimulated rat basophilic leukaemia cells (RBL-2H3 cells)	Anti-allergic properties of rhapontigenin, i.e. inhibition of cell degranulation, measured as the antigen-induced release of β-hexosaminidase from RBL-2H3 cells (IC_{50} = 14 μM)	Matsuda et al. (2016)

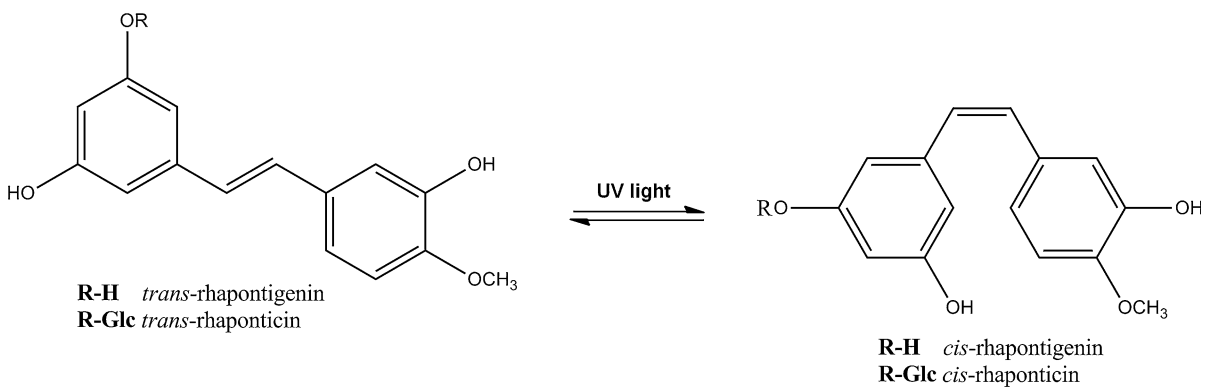

Fig. 3 The UV-induced *cis–trans* isomerization of rhaponticin and rhapontigenin (mechanism proposed by Hui et al. 2011)

rapid distribution and elimination from plasma. Pharmacokinetic analyses performed in a murine model following an oral dose of 100 mg/kg b.w. or injection with 10 mg/kg b.w. into the caudal vein revealed the presence of rhapontigenin in blood plasma 5 min after the injection, and its maximal concentration was 8.91 μg mL^{-1}. Oral administration of rhaponticin provided lower blood plasma concentrations of its metabolite with the maximal concentration of 1.71 μg mL^{-1}. The total clearance values for intravenous and oral administration of rhaponticin were 0.047 and 18.7 mL min^{-1} kg^{-1}, respectively, whereas their $AUC_{(0-t)}$ was 215.8 μg min mL^{-1} and 0.70 μg min mL^{-1} (Zhao et al. 2011, 2012).

The poor solubility of rhaponticin in an aqueous environment and its fast metabolism have been listed

as the main factors limiting further studies on its pharmacological actions. While several clinical examinations on rhubarb-based preparations have been registered, with 14 trials being recorded until June 2019 in the ClinicalTrials.gov NIH database (https://clinicaltrials.gov), no clinical trial has yet been performed on rhaponticin. Promising data suggests that both rhaponticin and rhapontigenin may possess considerable health-promoting or pharmacological potential; these findings may contribute to the development of new modes of drug delivery and accelerate pharmacological studies on these compounds. Therefore, some attempts have been undertaken in order to improve the bioavailability of rhaponticin. One of these strategies may be a construction of PEGylated liposomes containing rhaponticin (PEGL-RA). Preliminary tests suggested that these particles were effective delivery vehicles for rhaponticin, with a T_{max} approximately 4.5 times higher than that of rhaponticin alone. In addition, rhaponticin displayed a higher mean $T_{1/2}$ value (350.12 min) when delivered in PEGylated liposomes than alone (i.e. 180.02 min) (Sun and Zhao 2012).

Another way of improvement of rhaponticin bioavailability can be the synthesis of a folate receptor-targeted rhaponticin conjugate (Liang et al. 2013). This water-soluble conjugate was developed using a hydrophilic peptide spacer, linked to folic acid by a releasable disulfide linker, providing an amino-reactive derivative of rhaponticin. Although preliminary in vitro and in vivo examinations suggest that this formulation of rhaponticin may have considerable potential, especially as a chemotherapeutic agent, no further results have yet been published. In other examinations, rhaponticin was incorporated into phosphatidylcholine (PC-Chol) liposomes, designed for the delivery of cyclodextrin-bound drugs (Lim et al. 2008). The passage of PC-Chol liposomes with complexes of rhaponticin and β-cyclodextrin (HPβCD-Rh2 complexes) through guinea pig skin has also been established in preliminary studies.

In vivo evidence

So far, anti-inflammatory actions of rhaponticin and rhapontigenin have been evidenced in vivo in rodents (Table 4). Rhaponticin significantly reduced the development and expansion of pathological changes in an in vitro model of experimental pulmonary fibrosis, as well as in the bleomycin-induced pulmonary fibrosis in mice treated with daily doses of 25 mg and 100 mg/kg b.w. (Tao et al. 2017). At a daily dose of 100 mg/kg b.w., rhaponticin was also found to reduce colonic epithelial dysfunction in a mouse experimental model of colitis; the action involved SIRT1-dependent signalling (Wei et al. 2017). In other work, 50 and 100 mg/kg b.w. of rhapontigenin and 100 mg/kg b.w. of rhaponticin displayed anti-inflammatory effects in rats with carrageenan-induced edema (Ko et al. 2004). In mice, rhapontigenin (25 mg and 50 mg/kg b.w.) demonstrated greater anti-inflammatory and anti-allergic effects than disodium cromoglycate, an anti-allergic drug (100 mg/kg b.w.), in the treatment of passive cutaneous anaphylaxis (PCA) reaction. Similar results were obtained for analogous experiments conducted on rats, and complemented with in vitro studies on the anti-thrombotic effects of rhaponticin and rhapontigenin (Park et al. 2002). It has been suggested that such anti-inflammatory activity of rhapontigenin may constitute an important mechanism involved in its cardioprotective effect. In a murine model of isoproterenol-induced myocardial infarction, treatment with rhapontigenin (5.0 mg/kg b.w./day) ameliorated pathological changes in the heart and downregulated the expression of TNF-α, IL-6, p38 mitogen-activated protein kinase and iNOS in the examined animals (Fan 2019).

Conclusions

The currently available literature confirms that rhaponticin displays anti-inflammatory properties, which may enhance its health-promoting actions or pharmacological potential. However, most of this evidence is still derived from basic studies. Despite promising data from in vitro investigations, only six animal studies examining the anti-inflammatory action of rhaponticin have been described so far. When compared to resveratrol, the physiological effects and pharmacological significance of rhapontigenin still remain underestimated. As a promising natural medicine, resveratrol has been intensively examined, with over 120 clinical studies currently registered in the www.clinicaltrials.gov database. While the anti-inflammatory effects of resveratrol have been established in numerous in vitro and in vivo

Table 4 *In vivo* evidence of anti-inflammatory activities of rhaponticin and rhapontigenin

Experimental model	Results obtained for rhaponticin or rhapontigenin	Results for reference compounds	References
PCA reaction in mice	Rhaponticin (100 mg/kg b.w., orally)–53 ± 2% of PCA reaction inhibition rhaponticin (100 mg/kg b.w., intraperitoneally)–18 ± 3% of PCA reaction inhibition Rhapontigenin (25 mg/kg b.w., intraperitoneally)–48 ± 9% of PCA reaction inhibition Rhapontigenin (50 mg/kg b.w., intraperitoneally)–85 ± 4% of PCA reaction inhibition	Disodium cromoglycate (100 mg/kg b.w., administered orally)–38 ± 2% of PCA reaction inhibition	Kim et al. (2000)
Carrageenan-induced acute edema in rats	Rhapontigenin and rhaponticin (50 or 100 mg/kg) displayed the anti-edema effects	–	Ko et al. (2004)
Bleomycin-induced pulmonary fibrosis in mice	Rhaponticin (25, 50 or 100 mg/kg/day, administered orally for 14 days)–decrease of TGF-β1, IL-1β, IL-6 and TNF-α levels by about 36, 43, 50 and 33%, respectively	–	Tao et al. (2017)
Dextran sodium sulfate-induced acute colitis in mice	Rhaponticin (20, 50 or 100 mg/kg, administered by gavage, for 8 days)–decrease of TNF-α, IL-1β, IL-6, IL-8 levels by about 38, 32, 33 and 70%, respectively; the level of IL-10 (anti-inflammatory cytokine) was increased by about 2.5 fold	–	Wei et al. (2017)
Murine isoproterenol-induced myocardial infarction model	Rhapontigenin (1, 2.5 or 5 mg/kg b.w., for 8 days)–reduction of infarct size, the heart/body weight index, creatinine kinase, lactate dehydrogenase and cardiac troponin-T levels	–	Fan (2019)

studies (see de Sá Coutinho et al. 2018), the evaluation of pharmacological significance of rhaponticin and rhapontigenin remains mostly at the preliminary stage. In addition to their structural and chemical similarity, rhapontigenin and resveratrol also share some molecular mechanisms of their anti-inflammatory activity, at least in part; however, their physiological activities may be divergent.

The quick metabolism and low bioavailability of rhaponticin/rhapontigenin have hindered their experimental use and thus far prevented a full assessment of their properties; they have also limited current knowledge on their anti-inflammatory action. Nevertheless, several preliminary studies on new formulations of rhaponticin have been undertaken to increase its bioavailability. Therefore, detailed in vivo examinations are needed in order to more precisely elucidate the anti-inflammatory potential of rhaponticin and rhapontigenin, and to provide new data, which could allow for a more reliable evaluation of the pharmacological potential of these compounds.

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