

# Tormentillae rhizoma – Review for an Underestimated European Herbal Drug<sup>#</sup>

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## ABSTRACT

*Potentilla erecta* is a medicinal plant described under its traditional name Tormentil in medieval herbal books and used until today in many European countries. Today monographs for Tormentillae rhizoma in the European pharmacopeia, as well as a monograph of the Herbal Medicinal Product Commission as a drug for traditional use, exist. The present review summarizes published investigations in phytochemistry and pharmacology, together with new findings reflecting the mechanisms of action of ellagitannins as one of the main ingredients of this herbal drug. Taken together all *in vitro* and *in vivo* investigations' data support the traditional use for treatment of diarrhea and mucosal inflammation despite a lack of sufficient clinical studies.

## Introduction

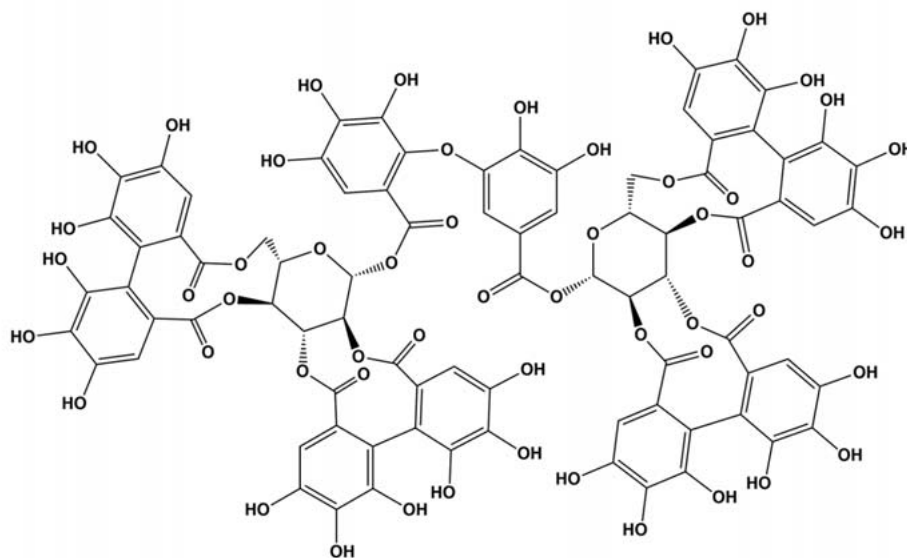
Plant-based therapeutics and botanical supplements are increasingly offered and used all over the world. At present, there is a need for scientific evaluation and standardization of all these products. This development also concerns the use of herbal drugs with a long therapeutic tradition. With the elaboration of monographs by the Herbal Medicinal Product Commission (HMPC), a decision has been made that supports further therapeutic administration based on scientific evidence. One of these herbal drugs with long tradition is Tormentil derived from *Potentilla erecta* L., Rosaceae [1]. Although there is no approved herbal drug available in European community, the drug is traditionally used and attracts attention in complementary medicine [2].

The following review focuses mainly on the biological and pharmacological effects of drug preparations with respect to their therapeutic use.

## Botanical Description

*Potentilla erecta* is widely distributed throughout Eurasia in a variety of environments including bogs, heaths, moors, grasslands, open woods, and alpine slopes. It is an herbaceous perennial with a stout, hard rootstock. Procumbent and erect stems (10–25 cm) are non-rooting, and the height is greater where the land is damp and not grazed by sheep. The alternate leaves are unstalked, toothed at the apex, and hairy underneath. The leaves occur in groups of 3 with 2 stipules that resemble small leaflets, so it appears to have 5 leaflets. The yellow flowers occur in summer in cymes and have 4 petals and many yellow stamens. There are 4 sepals and a 4-sectioned epicalyx. All other *Potentilla* species have 5 petals. The seed is an achene [3]. The accepted botanical name of this plant is *Potentilla erecta* L., but in many European countries, the traditional name is Tormentil (Engl.), Tormentille (Fr.) or Tormentilla (Ital.) coming

<sup>#</sup> Dedicated to Professor Dr. Wolfgang Kubelka on the occasion of his 85th birthday.



► Fig. 1 Structure of agrimoniin.

from the synonyms *Potentilla tormentilla* Neck. or *Tormentilla erecta* L. The name of genus “*Potentilla*” refers to the Latin word “potential” meaning power and is related to the powerful pharmacological activity of the plant, which has been used for several indications in the past. In the medieval age, the traditional name “Tormentil” also referred to the Latin word “*tormentina*”, which means intestinal colic and also points to the specific use of the herbal drug to cure enteritis and spasmodic colics. In the German-speaking regions in Europe, the name is “Blutwurz” and refers to the red color of the broken roots, which is the result of the formation of red-colored tannins and also indicates the therapeutic use for stopping bleedings in former times [4].

## Phytochemistry of the Underground Parts

About 55 compounds have been described for the underground parts of *P. erecta*. With a total of 15–20%, condensed tannins (syn. proanthocyanidins, nonhydrolyzable tannins) are the most abundant group of compounds. Monomeric, dimeric, and trimeric proanthocyanidins of type B were isolated and their structures elucidated. They are usually transconfigured and connected via 4,8-, 4,6-, 6,6- or 6,8-bonds, like the [4,6]-all-trans-bi-(+)-catechin (Procyanidin B6) and the [4,8]-all-trans-bi-(+)-catechin (Procyanidin B3). The [4,8]-2,3-trans-3,4-cis-bi-(+)-catechin is a rare example of a cis-configured dimeric proanthocyanidin. The Procyanidins B1, B2, and B5 were only detected in traces. Tetra-, penta-, and hexamers have been also detected, but their structures were not completely elucidated [5–10]. The fraction of the condensed tannins consists of 49–62% monomers, dimers, and trimers, 24–37% of tetramers, and 10–15% of pentamers and hexamers, depending on the author [9–11]. Several precursors for condensed tannins were identified like (+)-catechin, (–)-epicatechin, (+)-gallocatechin, (–)-epigallocatechin, and (–)-epigallocatechingallate [8, 9, 12].

Up to 3.5% hydrolyzable tannins form another important group of compounds [13]. Apart from pentagalloylglucose, 1 monomeric and 3 dimeric ellagitannins were isolated [8, 9, 14]. Within the ellagitannins group, agrimoniin (► Fig. 1) is one of the most representative and most complex compounds, and it is found in many plant materials belonging to the Rosaceae family. Agrimoniin ( $C_{82}H_{54}O_{52}$ ) is a dimeric ellagitannin with a molecular weight of 1871.282, having 2D-glucopyranose cores with  $\alpha$ -glucosidic linkages in both units. The absolute configuration of all 4 atropoisomeric biaryl hexahydroxydiphenyl (HHDP) groups is S-configuration [15]. Yields of about 2% (w/w) can be found in the underground parts of *P. erecta* [16]. Laevitagin B and Laevitagin F (Tormentillin) are also dimeric ellagitannins and quite rare derivatives of Agrimoniin [17]. Pedunculagin, a monomeric ellagitannin, can yield about 0.4% (w/w) in the underground parts of *P. erecta* [16]. The biaryl HHDP groups can also be seen as dimers of hexahydroxydiphenic acid and precursors of ellagic acid. Ellagic acid is the dilactone of hexahydroxydiphenic acid, and yields of about 0.4% can be found [16, 18]. As a structural element, it is related to the ellagitannins.

Nine triterpenoid compounds were isolated and elucidated, generally based on an Ursan- or an Olean skeleton, and present as aglycones and/or C-28-O- $\beta$ -D-glucosyl esters. None of the triterpens bared a sugar moiety at a C-3-OH-Group, if present [5]. Best investigated are Tormentoside (Rosamultin), a glucopyranosylester, and its aglycon, Tormentenic acid. Overall, the fraction of triterpens yields between 0.6–1.7% [19, 20].

Further ingredients include a series of organic acids and phenol carboxylic acids like caffeic acid, gallic acid, or salicylic acid. Some of these compounds are only present after hydrolysis of more complex structures [21, 22]. Some flavonoids like a cyanidinglucoside, kaempferol, and leucoanthocyanidin are also present but are more abundant in the aerial parts of *P. erecta* [8, 12, 23]. ► Table 1 summarizes the phytochemical findings for the tannins and triterpens.

## Traditional Use

Presumably, the plant was not used in the ancient world, but therapeutic reports from medieval herbal books are known [4]. In the *Contrafayt Kreüterbuch* by Otto Brunfels (1532). Tormentilla was used for the treatment of hemorrhaging, excessive menstruation, diarrhea, or cholera [29]. Some of these indications have importance until today. The use of an infusion or alcoholic extract of the drug (tincture) for the treatment of diarrhea with and without vomiting, enteritis, intestinal bleedings, and dysentery were reported as standard medicinal therapy until the middle of the 20th century. The use as gargle in case of oropharyngeal inflammations or as a compress/ointment for wound healing in exudative eczema, as well as for contusions and hematomas, has also been reported and is still used today for self-medication. The dosage ranged from 2–4 g of the powdered drug or 15–20 g of a decoction of the dried rhizome. The drug has long been monographed as “Rhizoma tormentillae” in many pharmacopeias in Europe [4]. Today, we have monographs for “Tormentillae rhizoma” (Ph. Eur. 9.0/1478) and “Tormentillae tinctura” (Ph. Eur. 9.0/1895) in the European Pharmacopoeia, standardized on the concentration of tannins. In addition, there is a monograph elaborated by the HMPC as a drug for traditional use with 2 indications: 1. oral application of a tea or an extract preparation for symptomatic treatment of mild diarrhea; and 2. application of an extract preparation for symptomatic treatment of mild oropharyngeal inflammations [30]. Both indications reflect the traditional use of the drug for more than 500 y. There is a monograph with a broad spectrum of phytochemical, pharmacological, and toxicological data published by the European Scientific Cooperative on Phytotherapy with nearly identical indications as those given by the HMPC monograph.

In this regard, it is rather surprising that, on the European market, no approved phytotherapeutic product containing a preparation of *P. erecta* is available, only homeopathic medicines. The reason for that seems to be due to the lack of a sufficient number of convincing clinical studies.

## Pharmacology

The review regarding pharmacological investigations is based on an evaluation of literature collected by PubMed until December 2019. Using the keywords “*Potentilla erecta*”, “*Potentilla tormentilla*”, and “Tormentil”, in total only 44 references were shown. The most recent article was published in July 2019. The topics describe, besides phytochemical findings, mainly biological and pharmacological effects. The first articles with clear reference to human application were published in the early 1950s and describe the use of Tormentil root preparations as astringents by dentists, according to the HMPC monograph for the symptomatic treatment of mild oropharyngeal inflammation [31–33].

## In vitro Investigations

In addition to the reports on the use of Tormentil root preparations by dentists as mentioned before, *in vitro* inhibitory effects of an aqueous extract against cariogenic *Streptococcus* spp. strains

► **Table 1** Compounds of the underground parts of *Potentilla erecta* L. (modified from [8]).

Compound class	Compound	References	
<b>Hydrolysable tannins</b>			
▪ Monomers	Pedunculagin	[24]	
	Pentadagalloylglucose	[14]	
▪ Dimers	Agrimoniin	[25]	
	Laevigatin B	[26]	
	Laevigatin F (= Tormentillin)	[17]	
<b>Condensed tannins (proanthocyanidins)</b>			
▪ Dimers	[4, 6]-all-trans-bi-(+)-Catechin (= Procyanidin B6)	[7]	
	[4, 8]-2,3-trans-3,4-cis-bi-(+)-Catechin	[7]	
	[4, 8]-all-trans-bi-(+)-Catechin (= Procyanidin B3)	[7]	
	[6',6]-all-trans-bi-(+)-Catechin	[6]	
	Procyanidin B1	[9]	
	Procyanidin B2	[9]	
	Procyanidin B5	[9]	
	▪ Trimers	(+)-Catechin-[4, 8]-(+)-catechin-[4, 8]-(+)-catechin	[6]
		(+)-Catechin-[6', 8]-(+)-catechin-[4, 8]-(+)-catechin	[6]
	<b>Triterpenoids</b>		
	2 $\alpha$ ,3 $\beta$ -Dihydroxyurs-12-en-28-oic acid $\beta$ -D-glucopyranosyl ester	[27]	
	3-epi-Pomolic acid 28-O- $\beta$ -D-glucoside	[28]	
	3 $\beta$ ,19 $\alpha$ -Dihydroxyolean-12-en-28-oic acid $\beta$ -D-glucopyranosyl ester	[27]	
	3 $\beta$ ,19 $\alpha$ -Dihydroxyurs-12-en-28-oic acid $\beta$ -D-glucopyranosyl ester	[27]	
	Arjunetin	[20]	
	Chinovic acid	[25]	
	Euscaphic acid 28-O- $\beta$ -D-glucoside (= Kaji-ichogoside F1)	[20]	
	Tormentic acid	[19]	
	Tormentoside (= Rosamultin)	[20]	

were also investigated. It was demonstrated that the extract moderately inhibited the growth of oral *Streptococci*. The preparation exhibited inhibitory effects on water-insoluble alpha-(1,3)-, alpha-(1,6)-linked glucan (mutan) and artificial dental plaque formation. The results indicate that the extract could become a useful supplement for pharmaceutical products as new anticariogenic agent in a wide range of oral care products [34]. A possible explanation for this activity could be provided by studies that focused on the mechanisms of the innate immune defense against bacteria. The (pseudo)halogenating activity of lactoperoxidase (LPO) is known to be an essential part of the maintenance of oral microbiological homeostasis. Any disturbance of this system is associated with oral diseases like caries or gingivitis. The LPO is re-

leased from secretory epithelial cells into saliva and contributes to innate immune responses by catalyzing the oxidation of thiocyanate to antimicrobial hypothiocyanite. An ethanolic extract of Tormentil and some other compounds such as ellagic acid or methyl gallate were found as potent LPO-enzyme-regenerating compounds. These results may provide a further reason for the application of Tormentil extract, which is known for its antibacterial and anti-inflammatory, as well as plaque inhibiting, effects in the mouth [35]. In addition, the Tormentil extract processed in mucoadhesive dosage forms was able to significantly reduce artificial biofilm formation by cariogenic *Streptococcus mutans* in a porcine buccal mucosa model *in vitro*. For all *Streptococci*, complete inhibition was revealed at a final concentration of the extract of 2 mg/ml [36]. All results taken together, there is clear evidence for the beneficial effect of Tormentil extracts used to treat bacteriosis in the oral cavity. Interestingly, the extract is also active against some problematic gram-positive and gram-negative bacteria of the genera *Azotobacter*, *Bacillus*, and *Pseudomonas* as well as against opportunistic pathogens like *B. cereus*, *E. coli*, *P. aeruginosa*, and *S. aureus* strains [37]. A review article from 2009 summarizes the antibacterial activity of different preparations of *P. erecta* against a broad spectrum of bacteria, including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Helicobacter pylori*. Additionally, also the methanolic extract from the aerial parts of *P. erecta* showed moderate antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Candida krusei* [8].

In accordance with the traditional use of Tormentil extract for treatment of inflammatory bowel disease (IBD), its antioxidative effects were studied because reactive oxygen metabolites produced by inflamed colonic mucosa may be pathogenic. Chemiluminescence was used after mucosal biopsies from 23 patients with active ulcerative colitis (UC) to detect the extract's effect on the generation of oxygen radicals. The Tormentil extract showed a potent antioxidative potential and superoxide-scavenging effect. The reported results indicate that a number of widely used herbal preparations including Tormentil have antioxidant effects in both cell-free and mucosal biopsy assay systems. Consideration should be given to formal evaluation of the therapeutic potential of Tormentil in patients with IBD and other chronic inflammatory conditions *in vivo* [38].

Phytochemical studies have shown that procyanidins (dimers and trimers) extracted from the rhizomes of *P. erecta* displayed the highest antioxidative activity towards lipid-peroxidation. Regarding the inhibition of the pro-inflammatory enzyme elastase, pentamers and hexamers possessed the most significant properties [11]. The extracts showed also inhibitory activity on prostaglandin biosynthesis and platelet activating factor-induced exocytosis *in vitro* [39]. Summarizing all these effects with respect to inflammatory damage on skin and mucosa, the use of extracts of *P. erecta* for treatment according to the HMPC monograph is supported by the *in vitro* investigations.

## Animal Studies

Due to the diverse pharmacological activities of polyphenols, the polyphenol-rich Tormentil extract was shown to affect the metabolism of arachidonic acid, and by that, it exerts both anti-inflammatory and antioxidant activities, which also suggests a possible effect in thrombotic processes. In a rat model of thrombosis, a water-methanol extract from *P. erecta* rhizome was orally administered for 14 days in doses of 100, 200, and 400 mg/kg. The Tormentil extract (400 mg/kg) significantly decreased thrombus weight and prolonged the time to carotid artery occlusion and bleeding time without changes in the blood pressure. In *ex vivo* experiments, the extract (400 mg/kg) reduced thromboxane production and decreased t-PA activity without changes in total t-PA concentration. The authors concluded that Tormentil extract inhibits arterial thrombosis in platelet- and endothelial-dependent mechanisms without hemodynamic changes [40]. Whether these effects are mediated by polyphenols itself or by metabolites of microbiota was not explained but should be investigated in future. The Tormentil extract showed also an increase of insulin secretion in a diabetic mice model after oral administration, possibly induced by tormentoside. The authors speculated that in an initial diabetic stage, extracts from the drug might be used as supplementary treatment, helpful in prevention of diabetic complications such as neuropathy and retinopathy [8]. Recently it was demonstrated that Tormentil rhizome extract, applied to diabetic rats in high dosage of 400 mg, showed an antithrombotic effect and inhibited primary hemostasis despite its antifibrinolytic activity. The authors concluded that the extracts at that high dosage had a beneficial effect on hemostasis, which may be the result of a more pronounced action of urolithins–metabolites of ellagitannins with a proven protective effect towards endothelial cells [41].

## Studies in Humans

Only 4 clinical studies were published but were cited in 6 reviews on the treatment of IBD. Complementary therapies are widely used by a majority of patients with IBD, particularly those with long-term disorders and prior hospitalization, and the overall use has generally increased in the population in recent y [42]. Based on the traditional use of Tormentil to cure enteritis, intestinal bleedings, and dysentery and on the positive reports of individual patients with UC who have used this drug as a complementary therapy for chronic IBD, a Tormentil extract was investigated in patients with active UC. The aim of this open-label, dose-escalating study was to assess the safety, pharmacology, and clinical effects of different doses of the used extract. Sixteen patients with active UC received an ethanolic dry extract from the rhizome of *P. erecta*, which contained 200 mg per capsule (15–22% tannins besides triterpenes and flavonoids) and was licensed in Germany for the treatment of unspecific diarrhea until 2015. The extract was applied in escalating doses of 1200, 1800, 2400, and 3000 mg/d for 3 weeks each. Each treatment phase was followed by a 4-week washout phase. The outcome parameters were side effects, clinical activity index, C-reactive protein-, and tannin levels in patients' sera. The study showed that the extract appeared safe up to a dosage of 3000 mg/day. During therapy with

2400 mg extract per day, the median CAI and C-reactive protein levels improved significantly. The CAI especially decreased in all patients, whereas it increased again during the washout phase. Tannins from the extract were not systemically absorbed. The authors concluded that the results were promising, but randomized placebo-controlled studies with endoscopic control are needed to confirm the results [43]. This pilot-study was highlighted by the editors of the publishing journal because of its importance for patients and for clinicians examining whether complementary therapies are safe and beneficial. Despite a number of limitations in this study (e.g. small sample size, lack of documented endoscopic activity, nonspecific symptom score, and lack of meaningful statistical analysis), the study provides evidence of some efficacy for Tormentil extract in the treatment of symptoms of UC in patients receiving the conventional therapy. Although the results were promising, they were inconclusive. Until a randomized controlled trial has been conducted and the safety and efficacy are clearly demonstrated, caution must be applied in the use of this herbal drug in active UC [44]. Since 2007, the situation has not changed; no further clinical study has been published about Tormentil extract for treatment of active UC. A review on drug-herb-interactions in the elderly patient with IBD refers only to the study published in 2007, stating that the exact mechanism of action is unknown. The plant is generally well tolerated, apart from a few cases of mild stomachache only. There are no known interactions with IBD drugs [45]. In comparison to a variety of other herbal products, Tormentil extract was assessed as the most promising herbal product for treatment of IBD [46]. Despite the lack of clinical facts, Tormentil extract has been mentioned in review articles concerning complementary and alternative medicine for the treatment of IBD [47–49]. Possibly, the pharmacological effects of such tannin-rich herbal drugs, such as *P. erecta*, could not be convincingly explained, since the tannins are not bioavailable and thus are not absorbed in the gastrointestinal tract.

The situation changed in 2014 with a publication that showed the role of human intestinal microbiota in the metabolism of ellagitannin-rich plant material in connection with such drugs that are traditionally used to treat inflammation in the intestine. The authors showed that tannins of the ellagitannin-type like agrimoniin, as present in *P. erecta*, were metabolized by the microbiota after oral application and form urolithins, which show anti-inflammatory effects in human cells [50]. These data were the “missing link” between pharmacological efficacy and scientific explanation of the observed effects after oral ingestion. Now agrimoniin has received wide interest as a result of some interesting biological effects and therapeutic activities. Local effects seem to be directly connected with its tannin-character. Much evidence is provided that the systemic effects are based on the microbiotic metabolites, the urolithins, as they are found in micromolar concentrations in body fluids and tissues after ingestion of products containing ellagitannin [15]. Urolithin A significantly enhances the gut barrier function and inhibits unwarranted inflammation via the activation of aryl hydrocarbon receptor-nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent pathways that upregulate epithelial tight junction proteins. The treatment with such compounds mitigated colitis in pre-clinical models by improving barrier dysfunction in addition to anti-inflammatory activities

and showed that, by enhancing barrier functions and reducing inflammation, they had a protective property from colonic diseases [51]. *In vitro* experiments with normal human colon cells showed that *Potentilla* extracts, especially at lower concentration, decreased IL-6 production in myofibroblasts but in epithelial cells the level of the cytokine was stable. IL-10 analysis revealed that a Tormentil extract decreased cytokine level in myofibroblasts, and only in higher concentration in epithelial cells. The extract significantly influenced cellular cytoskeleton organization and the lining of the human colon wall by modulating the viability or cytokine production of the cells. The authors concluded that the Tormentil extract, with the additional property of a free radical scavenger, could be successfully used in the prevention of inflammatory colon disorders [52].

According to a second traditional use for Tormentil preparations, that of curing diarrhea, a randomized, double-blind, controlled trial was conducted in 2003 with an oral administration of a Tormentil root extract in children with rotavirus-induced diarrhea. The extract was prepared at the hospital pharmacy from 1 part of dried root with 10 parts 40% ethanol. The concentration of polyphenols in the extract was approximately between 30 and 40% as determined by HPLC. As a placebo, an alcoholic extract of Indian teas was prepared, which was identical in appearance and taste to Tormentil root extract. Forty children aged 3 mo to 7 y were divided into 2 groups: a treatment group of 20 children treated with Tormentil root extract and a control group of 20 children who received a placebo. All patients received 3 drops per y of age of either the Tormentil extract (approx. 1–1.5 mg tannins/kg BW/day) or the placebo extract, 3 times daily until the end of diarrhea but for a maximum of 5 days. The measurement of stool and vomit output was used to evaluate diarrhea, and physical examination was used to assess degree of dehydration in children. The duration of diarrhea in the Tormentil treatment group was 3 days, compared with 5 days in the control group. In the treatment group, 40% of the children were diarrhea-free 48 h after admission to the hospital, compared with 5% in the placebo group. Patients in the treatment group received smaller volumes of parenterally administered fluids compared to patients in the placebo group. The authors concluded that the treatment with Tormentil extract appears to be an effective therapy [53]. Unfortunately, apart from a few review articles referring to this particular clinical trial, no other studies have been published. In some European countries, the tincture of Tormentil is traditionally used to treat diarrhea, as indicated in the HMPC monograph [30]. A review article on herbal medicinal products for gastrointestinal disorders in children evaluated the use of herbal preparations of *P. erecta* as a safe adjunct remedy for diarrhea [2]. Only 1 study described that the local application of codfish oil and gargling with a tincture from *P. erecta* in patients with the erosive ulcerative form of lichen planus of the buccal mucosa is beneficial to a quicker control of the process. The authors examined 53 patients but focused on a therapy using of codfish oil enriched with polyunsaturated fatty acids [54]. Although the use of the tincture of *P. erecta* was rather adjuvant in this case, it supports the HMPC indication as described above.

Tormentil root has traditionally been used to treat inflammatory diseases of the skin and mucous membranes. In some Euro-



pean countries (e.g. Poland, Switzerland and Germany), ointments containing the fluid extract of Tormentil rhizomes are on the market for the treatment of skin diseases such as eczema. In a combination of experimental *in vitro* and *in vivo* pharmacology, the anti-inflammatory effect of agrimoniin-enriched fractions of a *P. erecta* extract was investigated in both human skin cell models and in test persons. In this study, an extract from the rhizome of *P. erecta* was used, which was prepared with 40% ethanol and then fractionated on a Sephadex LH20 column. Fractions with an increased agrimoniin content were examined on HaCaT keratinocytes. The expression of cyclooxygenase-2 (COX-2) induced by ultraviolet-B (UVB) radiation and the PGE<sub>2</sub> concentration in the cell culture supernatant were analyzed. The extracts inhibited the UVB-induced COX-2 expression in HaCaT cells and reduced dose dependently the PGE<sub>2</sub>-concentration in the supernatant. In a subsequent human placebo-controlled UV-erythema study, it was demonstrated, that agrimoniin in increased concentrations could dose dependently inhibit UVB-induced inflammation *in vivo* in a dose-dependent manner. Similarly, increased concentrations of agrimoniin significantly reduced UVB-induced PGE<sub>2</sub> production in fluids gained with the suction blister technique *in vivo*. The authors concluded that fractions of *P. erecta* with a high agrimoniin content display anti-inflammatory effects in *in vitro* and *in vivo* in models of UVB-induced inflammation in connection with skin damage [55]. With a similar experimental set-up, the anti-inflammatory and vasoconstrictive properties of a *P. erecta* extract were investigated. In irradiated or TNF- $\alpha$  stimulated HaCaT cells, the herbal extract strongly reduced the formation of IL-6 and PGE<sub>2</sub> or the activation of NF- $\kappa$ B. Furthermore, the extract showed a blanching effect in human skin comparable to hydrocortisone. However, in contrast to glucocorticoids, the extract did not cause nuclear translocation of the glucocorticoid receptor in HaCaT cells. The blanching effect was at least partially attributable to a scavenger effect of nitric oxide (NO) and the inhibition of endothelial NO synthase. The authors concluded that the investigated extract showed anti-inflammatory and vasoconstrictive effects, supporting the traditional use of topical treatment of inflammatory skin disorders [56]. Taken together, the human studies support preparations of *P. erecta* for the traditional use of this tannin-rich herbal drug and its broad therapeutic spectrum to treat diseases and damages related to the mucosa or the skin. Furthermore, antineoplastic, antiviral, antidiabetic, anti-inflammatory, spasmolytic, and hepatoprotective activities of extracts of *P. erecta* have been reported. However, most of the results shown originate from *in vitro* experiments [8]. The presumed antineoplastic activity tested in cell models corresponds to cytotoxic effects rather than a true antitumor activity.

Already more than 40 y ago, moderate antiviral effects against *Herpesviridae* have been demonstrated for extracts of *P. erecta* rhizomes and of hydrolyzable and condensed tannins isolated from them. In particular, the antiviral activity against *Herpes virus* types I and II was reported, as well as the cytotoxic activity against *Influenza virus* type A2 and *Cowpox* [57]. An animal test system with mice supported the demonstrated antiviral effects of a *P. erecta* rhizome extract against the *Vaccine virus* together with an induction of interferon synthesis [25].

## Toxicology

Due to the limited nature of studies in humans, animal models are used as alternatives to evaluate the safety of herbs. Acute toxicity of an aqueous extract of Tormentil rhizomes was assessed in rats and mice using a single dose of 2.5 and 6.8 g/kg BW administered with a gavage probe. No apparent toxic effect was observed 2 weeks after administration. The authors concluded that extracts should be considered safe for acute toxicity when applied to humans [58].

## Conclusion

Despite interesting individual results, comprehensive investigations are missing. The nonspecific interaction of different polyphenols with proteins leads to inhibition of more or less all biological activities in pharmacological model systems. The main problem seems to be the differentiation between unspecific and specific pharmacological effects of the drug preparation. This fact might be 1 explanation for the rather small importance of *P. erecta* and its preparations in current phytotherapy, which is based on the principles of evidence-based medicine. The situation could change with the recent findings on the interaction between microbiome and ellagitannins, which are associated with specific anti-inflammatory effects induced by defined metabolites of the tannins.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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