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A review on the ethnobotany, phytochemistry, pharmacology and toxicology of butterbur species (*Petasites* L.)

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ABSTRACT

Ethnopharmacological relevance: Petasites (butterbur, Asteraceae) species have been used since Ancient times in the traditional medicine of Asian and European countries to treat central nervous system (migraine), respiratory (asthma, allergic rhinitis, bronchitis, spastic cough), cardiovascular (hypertension), gastrointestinal (ulcers) and genitourinary (dysmenorrhea) disorders.
Aim of the review: This study summarized and discussed the traditional uses, phytochemical, pharmacological and toxicological aspects of *Petasites* genus.
Materials and methods: A systematic search of *Petasites* in online databases (Scopus, PubMed, ScienceDirect, Google Scholar) was performed, with the aim to find the phytochemical, toxicological and bioactivity studies. The Global Biodiversity Information Facility, Plants of the World Online, World Flora Online and The Plant List databases were used to describe the taxonomy and geographical distribution.
Results: The detailed phytochemistry of the potentially active compounds of *Petasites* genus (e.g. sesquiterpenes, pyrrolizidine alkaloids, polyphenols and essential oils components) was presented. The bioactivity studies (cell-free, cell-based, animal, and clinical) including the traditional uses of *Petasites* (e.g. anti-spasmolytic, hypotensive, anti-asthmatic activities) were addressed and followed by discussion of the main pharmacokinetical and toxicological issues related to the administration of butterbur-based formulations.
Conclusions: This review provides a complete overview of the *Petasites* geographical distribution, traditional use, phytochemistry, bioactivity, and toxicity. More than 200 different sesquiterpenes (eremophilanes, furanoeremophilanes, bakkenolides), 50 phenolic compounds (phenolic acids, flavonoids, lignans) and volatile compounds (monoterpenes, sesquiterpenes) have been reported within the genus. Considering the phytochemical complexity and the polypharmacological potential, there is a growing research interest to extend the current therapeutical applications of *Petasites* preparations (anti-migraine, anti-allergic) to other human ailments, such as central nervous system, cardiovascular, malignant or microbial diseases. This research pathway is extremely important, especially in the recent context of the pandemic situation, when there is an imperious need for novel drug candidates.

1. Introduction

Genus *Petasites* L. (Asteraceae, butterbur or coltsfoot) comprises herbaceous perennial plants with thick, creeping, underground rhizomes and large hat-like leaves (Toman, 1972). The genus consists of 19 widely accepted species, excluding subspecies and varieties (Table 1) (Hai et al., 2018). The most common butterbur species (*P. hybridus* L. "G. Gaertn., B.Mey. & Scherb") is distributed all over Europe, Asia and North America and it can grow up to 1 m tall, being usually found in wet, marshy ground, damp forests or adjacent to rivers or streams (Johnston, 2001). A detailed geographical distribution of various *Petasites* species is presented in Table 1. Figures of the plants growing in their natural habitat are presented in Supplementary material (Figs. S1-S6).

Over the years, two main drugs were clinically approved, namely Tesalin® – Ze 339 (Max Zeller Söhne AG), containing a butterbur leaf extract obtained through a patented sub-critical CO_2 extraction and recommended for treating the intermittent (seasonal) allergic rhinitis and related symptoms of the eyes, nose and throat (https://zellerag.co

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Table 1
Taxonomy and geographical distribution of Petasites species.

Species name	Synonyms	Geographical distribution
P. albus (L.) Gaertn.	*P. sabaudus* Gand., *Tussilago alba* L.	Central Europe, Caucasus
P. fominii Bordz.	*Nardosmia fominii* (Bordz.) Kuprian.	Caucasus
P. formosanus Kitam.	–	Taiwan
P. fragrans (Vill.) C. Presl	*Cacalia alliariifolia* Poir.	Western Europe, Northern Africa, New Zealand, Tasmania
P. frigidus (L.) Fr.	*Nardosmia angulosa* Kuprian., *Nardosmia frigida* (L.) Hook., *Nardosmia nivalis* (B.D. Greene) Jurtzev, *P. alaskanus* Rydb., *P. corymbosus* (R.Br.) Rydb., *P. gracilis* Britton, *P. hyperboreus* Rydb., *P. nivalis* Greene, *P. palmatus* (Aiton) A.Gray, *Tussilago frigida* L.	Arctic, Northern Europe, Northern Asia, Northern North America
P. hybridus (L.) G. Gaertn., B.Mey. & Scherb.	*Cineraria hybrida* Bernh., *P. georgicus* Manden., *P. officinalis* Moench, *P. ovatus* Hill, *P. pratensis* Jord., *P. vulgaris* Desf., *Tussilago hybrida* L., *Tussilago petasites* L.	Europe, Northern Asia, North America
P. japonicus (Siebold & Zucc.) Maxim.	*Nardosmia japonica* Siebold & Zucc., *P. albus* A.Gray, *P. liukiuensis* Kitam., *P. spurius* Miq., *Tussilago petasites* Thunb.	China, Japan, Korea, Sakhalin, Europe, North America
P. kablikianus Tausch ex Bercht.	*P. glabratus* (Maly) Borbás	Balkans, Sudetes, Carpathians
P. kamengicus Deb	–	Himalaya, China
P. paradoxus (Retz.) Baumg.	*P. niveus* (Vill.) Baumg., *Tussilago nivea* Vill., *Tussilago paradoxa* Retz.	Alps
P. pyrenaicus (L.) G. López	*Nardosmia fragrans* (Vill.) Rchb., *Tussilago fragrans* Vill., *Tussilago pyrenaica* L.	Western Europe, North Africa
P. radiatus (J.F.Gmel.) J.Toman	*Nardosmia laevigata* (Willd.) DC., *Nardosmia radiata* (J.F. Gmel.) Holub, *Nardosmia straminea* Cass., *P. laevigatus* (Willd.) Rchb., *Tussilago laevigata* Willd., *Tussilago radiata* J.F.Gmel.	Eastern Russia, Kazakhstan, Mongolia, Western Siberia
P. rubellus (J.F.Gmel.) Toman	*Nardosmia laevigata* var. *subfaeminea* DC., *Nardosmia saxatilis* Turcz., *Tussilago rubella* J.F.Gmel., *Tussilago saxatilis* Turcz. ex DC.	Central Asia, Eastern Russia, Korea
P. saxatilis (Turcz.) Kom.	–	Central Asia, Eastern Russia
P. sibiricus (J.F.Gmel.) Dingwall	*Endocellion boreale* Turcz. ex Herder, *Endocellion gmelinii* (Turcz. ex DC.) Panigrahi, *Nardosmia gmelinii* Turcz. ex DC., *P. gmelinii* (Turcz. ex DC.) Polunin, *Tussilago sibirica* J.F.Gmel.	Eastern Russia, Mongolia
P. spurius (Retz.) Rchb.	*Tussilago spuria* Retz.	Eastern Europe, Western Siberia
P. tatewakianus Kitam.	–	Manchuria, Primorye, Sakhalin
P. tricholobus Franch.	*P. himalaicus* Kitam., *P. mairei* H.Lév., *P. petelotii* (Merr.) Kitam., *P. vaniotii* H.Lév.	Himalaya, China, Pakistan, Vietnam
P. versipilus Hand.-Mazz.	–	China

Data in the table are listed according to the Global Biodiversity Information Facility (GBIF, https://www.gbif.org/), Plants of the World Online (http://www.plantsoftheworldonline.org/), World Flora Online (http://www.worldfloraonline.org/) and The Plant List (TPL, http://www.theplantlist.org/).

m/en/products/tesalin-ze-339/), and Petadolex® (Weber & Weber GmbH & Co.), formulating a butterbur root extract indicated in the treatment of migraine (https://weber-weber.de/presse/presse-petadolex-kapseln/). Nevertheless, the commercialization of the latter was discontinued in 2009, as the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) refused its reauthorization after the adaptation of the extraction method from the classical dichloromethane extraction to supercritical CO_2 extraction (SFE-CO_2). Both extracts are standardized in petasins, a group of eremophilane-type sesquiterpenes considered the main active ingredients of *P. hybridus* (Danesch and Rittinghausen, 2003). In addition, a special emphasis is given to the presence of pyrrolizidine alkaloids (PAs), a class of naturally occurring constituents from Boraginaceae, Fabaceae and Asteraceae families, including *Petasites* species, and incriminated for serious hepato-, pneumo- geno- and cyto-toxicity. Nonetheless, Petadolex® and Tesalin® – Ze 339 contain PAs-free materials, obtained through an efficient removal during the patented extraction steps.

Aside from the petasins and PAs, other sesquiterpenes (such as bakkenolides), flavonoids, phenolic acids and volatile constituents are also documented in various *Petasites* species, including *P. japonicus* (Siebold & Zucc.) Maxim., *P. formosanus* Kitam. and *P. tatewakianus* Kitam (Aydin and Letzel, 2013; Mihajilov-Krstev et al., 2020; Park et al., 2018b; Sun et al., 2011; Toropkina and Minina, 1976; Zhang et al., 2011). Furthermore, various biological activities of these species are currently investigated in different cell-free, cell-based or animal studies, with respect to their putative anti-inflammatory, anti-oxidant, anti-obesity and neuroprotective properties (Ahn et al., 2020; K.-P. Lee et al., 2015; Park et al., 2020; Sun et al., 2011; Wang et al., 2014).

Up to date, the previous reviews focused around different aspects of the *Petasites* genus; for instance, Aydın et al. (2013) summarized the analytical and physiological effects of PAs in butterbur, whereas Tys et al. (2015) shortly presented the botanical and pharmacological description of the genus. Ożarowski et al. (2013) briefly addressed the phytochemical, pharmacological and clinical studies of *P. hybridus*, whilst its clinical effectiveness in the prophylaxis of migraine was reviewed by Agosti et al. (2006). Lastly, Hiemori-Kondo (2020) compiled the studies presenting the chemical composition and biological activities of *P. japonicus*. Nevertheless, a comprehensive review to cover up also the recent aspects related to the chemical profile and the (ethno)pharmacological relevance was missing. A quick search in the SCOPUS database (with "*Petasites*" as the key word) retrieved around 270 published papers within the period 2012–2021. Therefore, the current review addresses not only the well-established chemico-biological facets of the genus, but also the latest advances in *Petasites* research. A systematic search of *Petasites* in online databases (Scopus, PubMed, ScienceDirect, Google Scholar) was performed. Databases were searched from inception to January 2022, with the aim to find the phytochemical, toxicological and bioactivity studies on *Petasites* genus. The study includes all known *Petasites* species. The Global Biodiversity Information Facility, Plants of the World Online, World Flora Online and The Plant List databases were used to describe the taxonomy and geographical distribution.

2. Traditional uses

Petasites species have an outstanding recognition since Ancient times; in the first century AD, the Greek physician Dioscorides referred to butterbur as "a shoot, taller than a cubit and thick as a thumb, bearing large, hat-shaped leaves, as if they were mushrooms, and […] good for malignant and cancerous ulcers" (Beck, 2017). The Greek name of the genus *petasos* which translates as the 'rain hat', comes from the fact that the giant leaves were sometimes used for protection against the rain. The German name Hutpflanze translates as the 'hat plant', whereas the other German names, such as Pestwurz ('plague root') or Pestilenzkraut ('pestilence herb'), originate from the Middle Ages, when the odour and smoke obtained by burning the butterbur roots was thought to fight the bubonic plague. Nevertheless, the most common name of the genus (butterbur) comes from the times when its big leaves were used to be wrapped around butter to protect it against the hot weather (Johnston, 2001; Sutherland and Sweet, 2010); on the other hand, the 'plague--flower' name was mentioned by the English botanist Nicholas Culpeper in his book "*The English Physician*" from 1652 (Culpeper and Flannery, 2014).

The rhizomes with roots (rootstocks, *Petasiti rhizoma cum radicibus*) and leaves (*Petasiti folium*) have been used empirically in the traditional medicine of numerous countries (Table 2) to treat migraine, hypertension, respiratory (asthma, allergic rhinitis, bronchitis, spastic cough), gastrointestinal (ulcers) and genitourinary (dysmenorrhea) disorders (Sadler et al., 2007). The edible parts of *P. japonicus* (fukinoto) together with its rootstocks and leaves are used in the traditional Korean, Japanese and Chinese medicine (Choi et al., 2016). Nowadays, the most researched therapeutic effects of butterbur concern its anti-migraine and anti-allergic properties (Lipton et al., 2004; Oelkers-Ax et al., 2008; Pothmann and Danesch, 2005).

Table 2
Traditional medicinal uses of Petasites species.

Species	Common names	Parts	Traditional uses	References
P. hybridus	Butterbur Bog rhubarb Bogshorn Devil's hat Blatterdock Butter-dock Pestwurz Lagwort Pestilence wort Plague flower	Leaves Rootstocks	Bubonic plague, pestilential fever Cough, mucus cough, asthma, bronchitis Skin wounds (topical application) Gastrointestinal disorders (colic, cramps, obstruction of bile flow) Urogenital disorders (urogenital tracts spasms) Dysmenorrhea Migraine, aches and pains	Johnston (2001) Tys et al. (2015) Sutherland and Sweet (2010) Brune et al. (1993)
P. japonicus	Fuki Fukinoto Great butterbur Giant butterbur Sweet coltsfoot	Vegetables (bulb-like shoots) Leaves Rootstocks	Asthma, allergic diseases Tonsilitis Contusion Poisonous snake bite	Choi et al. (2016) Yaoita and Kikuchi (1994)
P. tricholobus	–	Flower buds	Cough, bronchitis, asthma	Hai et al. (2018)
P. formosanus	–	Leaves Rootstocks	Mucus cough Aches and pains Poisonous snake bite Hypertension	Lin et al. (2003)

3. Phytochemistry

3.1. Sesquiterpenes

Over 200 different sesquiterpene structures have been reported in *Petasites* genus (Table 3; Fig. 1); they can be formally grouped into three main classes: eremophilane-type, furanoeremophilane-type and bakkenolide-type. Most eremophilane-type sesquiterpenes from *Petasites* (collectively referred to as 'petasins') are esters of petasol, isopetasol or neopetasol with 2-methylbut-2-enoic acid (angelic acid) or 3-methylsulfanylprop-2-enoic acid. Furanoeremophilane-type sesquiterpenes are formally obtained by oxidation and cyclization from the previous type of sesquiterpenes, whereas bakkenolides have *cis*-hydrindane skeleton with a β-methylene-γ-butyrolactone moiety.

P. hybridus is reported to contain both eremophilanes (e.g. petasin, isopetasin, neopetasin, *S*-petasin, iso-*S*-petasin, neo-*S*-petasin, 8β-H-eremophilanolide) and furanoeremophilanes (e.g. furanoeremophilane, 9-hydroxyfuranoeremophilane, furanopetasin, 2-senecioylfuranopetasol, 2-tigloylfuranopetasol and 2-methylthioacryloylfuranopetasol) (Debrunner et al., 1995; Debrunner and Neuenschwander, 1995; Siegenthaler and Neuenschwander, 1997). Actually, Novotný et al. (1966) proposed the existence of two chemovares of *P. hybridus*, namely petasin and furanopetasin chemotypes. It is assumed that the petasin chemovar lacks the enzymes necessary for the oxidation of eremophilane derivatives to furanoeremophilanes that are characteristic for the furanopetasin chemovar. Nevertheless, the two chemotypes cannot be distinguished morphologically; furthermore, it was noticed that not only populations housing plants of the petasin chemotype or of the furanopetasin chemotype can be encountered in the spontaneous flora, but also populations displaying plants of both chemotypes. Chizzola et al. (2006) performed experimental crossings within and between plants of both chemotypes to study the genetic basis of the sesquiterpene occurrence. The differentiation between the two chemotypes was proposed to be governed by the combined action of two dominant genes; for the formation of petasin, at least two dominant alleles must be present, whereas the furanopetasin chemotype is under recessive genetic control.

Nonetheless, furanoeremophilanes are more often reported in *P. albus*, with albopetasin, petasalbin, 6-angeloyl-albopetasol, 6-senecioyl-albopetasol, petalbusin, petalbin and petalbone as a few examples (Bagirova et al., 2011; Bagirova and Serkerov, 2012; Siegenthaler and Neuenschwander, 1996). On the other hand, bakkenolides (e.g. bakkenolides A-V) are the predominant group from *P. japonicus* (Abe et al., 1968; Shirahata et al., 1968; Wang et al., 2013). Nevertheless, three chemotypes of *P. japonicus*, namely isopetasin-type, fukinone-type (both eremophilanes) or bakkenolide A-type have been proposed (Shibata and Shimizu, 1978). Furthermore, sesquiterpene lactones possessing unusual seco-eremophilane norsesquiterpenoid skeleton have been also reported in the Japanese butterbur (Yaoita et al., 2012).

The occurrence of sesquiterpenes was often used in different chemotaxonomic studies; for instance, *P. hybridus*, *P. japonicus* and *P. albus* were proposed as three independent sections of the *Petasites* genus, whereas other species, such as *P. kablikianus* and *P. paradoxus*, represent the same section of the genus as *P. albus* (Novotný et al., 1972). However, other studies (Novotný et al., 1966) showed that *P. kablikianus* should be considered as an independent species of hybrid origin. In addition, the same group noticed the resemblance between *P. albus* and *P. japonicus*, suggesting that the European species *P. albus* is substituted in East Asia by the vicarious species *P. japonicus*. Both taxa possess a striking morphological similarity of their vegetative organs, contain eremophilane-type sesquiterpenes in rootstocks (rhizomes, roots and runners) and show an identical occurrence of bakkenolide A in their stems (Novotný et al., 1972).

The distribution of sesquiterpenes between different organs as well between different seasons and collection sites was also investigated in numerous phytochemical studies. For instance, Novotný et al. (1972) observed no differences in the components isolated from *P. hybridus*

Table 3
Sesquiterpenes reported in *Petasites* genus.

No.	Compound name	Formula	Species	References
1	[1S-[1α(R*), 3aβ, 7α, 7aα]]-octahydro-1- (1-hydroxyethyl)-4-methylene-7-(1-methylethyl)-2H-inden-2-one	$C_{15}H_{24}O_2$	*P. tatewakianus*	M. Wang et al. (2014)
2	(15R)-6β-Angeloyloxy-3β, 15-epoxy-9β,15-dihydroxyeremophil-7(11)-en-12,8α-olide	$C_{24}H_{26}O_7$	*P. japonicus*	Yaoita and Kikuchi (1996a)
3	(8R)-2-[(2-Methylpropanoyl)oxy]eremophil-7(11)-en-12,8-olid	$C_{19}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
4	(8R)-2-[(Angeloyl)oxy]eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
5	(8R)-2-[(Methacroyl)oxy]ere-mophil-7(11)-en-12,8-olid	$C_{19}H_{26}O_4$	*P. hybridus*	Bodensieck et al. (2007)
6	(8R)-2-[(Senecioyl)oxy]eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
7	(8R)-2-[(Tigloyl)oxy]-eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
8	(8R,9β)-2-[(Angeloyl)oxy]-8,9-dihydroxyeremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_6$	*P. hybridus*	Bodensieck et al. (2007)
9	(8R,9 β)-2-[(Angeloyl)oxy]-9-hydroxyeremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_5$	*P. hybridus*	Bodensieck et al. (2007)
10	(8S)-2-[(Angeloyl)oxy]eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
11	(8S)-2-[(Senecioyl)oxy]eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
12	(8S)-2-[(Methacroyl)oxy]ere-mophil-7(11)-en-12,8-olide	$C_{19}H_{26}O_4$	*P. hybridus*	Bodensieck et al. (2007)
13	(8S)-2-[(Tigloyl)oxy]eremophil-7(11)-en-12,8-olide	$C_{20}H_{28}O_4$	*P. hybridus*	Bodensieck et al. (2007)
14	(8S)-2-{[(Z)-3-(Methylsulfanyl)prop-2-enoyl]oxy}eremophil-7(11)-en-12,8-olide	$C_{19}H_{26}O_4S$	*P. hybridus* *P. japonicus*	Bodensieck et al. (2007) Matsumoto et al. (2020)
15	1-Oxobakkenolide S	$C_{15}H_{20}O_4$	*P. tricholobus*	Hai et al. (2018)
16	2-Angelylfuroeremophilane	$C_{15}H_{22}O_3$	*P. kablikianus*	Novotný et al. (1966)
17	2-Methylthioacryloyl-furanopetasol	$C_{19}H_{26}O_4S$	*P. hybridus*	Siegenthaler and Neuenschwander (1997)
18	2-Senecioyl-furanopetasol	$C_{19}H_{28}O_4$	*P. hybridus*	Siegenthaler and Neuenschwander (1997)
19	2-Tigloyl-furanopetasol	$C_{19}H_{28}O_4$	*P. hybridus*	Siegenthaler and Neuenschwander (1997)
20	2α-Hydroxy-9-oxo-10α-H-furoeremophilane	$C_{15}H_{20}O_3$	*P. hybridus*	Novotný et al. (1972)
21	3β,6β-Diangeloyloxyeremophil-7(11)-en-12,8β-olide	$C_{25}H_{34}O_6$	*P. japonicus*	Yaoita et al. (1992)
22	3β,6β-Dihydroxy-3-oxoeremophil-7(11)-en-12,8α-olide	$C_{15}H_{18}O_5$	*P. japonicus*	Yaoita et al. (2012)
23	3β,6β-Dihydroxyeremophil-7(11)-en-12,8α-olide	$C_{15}H_{20}O_4$	*P. japonicus*	Yaoita and Kikuchi (1996a)
24	3β,8α-Dihydroxy-6β-tigloyloxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{26}O_6$	*P. japonicus*	Yaoita and Kikuchi (1994a)
25	3β,8β-Dihydroxy-6β-tigloyloxyeremophil-7(11)-en-12,8α-olide	$C_{20}H_{26}O_6$	*P. japonicus*	Yaoita and Kikuchi (1994a)
26	3β-Hydroxy-6α-methoxyeremophil-7(11)-en-12,8β-olide	$C_{16}H_{22}O_4$	*P. japonicus*	Yaoita and Kikuchi (1995)
27	3β-Hydroxy-6β-methoxyeremophil-7(11)-en-12,8α-olide	$C_{16}H_{22}O_4$	*P. japonicus*	Yaoita and Kikuchi (1995)
28	3β-Hydroxy-6β,8α-dimethoxyeremophil-7(11)-en-12,8β-olide	$C_{17}H_{24}O_5$	*P. japonicus*	Yaoita and Kikuchi (1994a)
29	3β-Hydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide	$C_{16}H_{22}O_4$	*P. japonicus*	Yaoita and Kikuchi (1994a)
30	3β-Hydroxy-6β-tigloyloxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_5$	*P. japonicus*	Yaoita et al. (1992)
31	3β-Hydroxy-8-oxoeremophil-6-en-12-oic acid methyl ester	$C_{20}H_{26}O_5$	*P. japonicus*	Yaoita and Kikuchi (1995)
32	3β-Hydroxyeremophil-7(11)-en-12,8β-olide	$C_{15}H_{20}O_3$	*P. japonicus*	Yaoita and Kikuchi (1994a)
33	3-O-β-D-6′-sulfonated-glucopyranosyl-6-(3-oxo-2-butenylidenyl)-l, 1, 5-trimethylcyclohexan-5-ol	$C_{19}H_{30}O_{11}S$	*P. tricholobus*	Zhang et al. (2014)
34	6-Acetylfuranofukinol	$C_{17}H_{24}O_4$	*P. japonicus*	Naya et al. (1971a)
35	6-Angelylfuranofukinol	$C_{20}H_{28}O_4$	*P. japonicus*	Naya et al. (1971a)
36	6-Hydroxyeremophilenolide	$C_{15}H_{22}O_3$	*P. japonicus* *P. albus*	Naya et al. (1971a) Novotný et al. (1962, 1964)
37	6β-(3′-Chloro-2′-hydroxy-2′-methylbutyroyloxy)-3β, 8β-dihydroxyeremophil-7-(11)-en-12,8α-olide	$C_{20}H_{29}ClO_7$	*P. japonicus*	Yaoita and Kikuchi (1996a)
38	6β-(3′Chloro-2′-hydroxy-2′-methylbutyloyloxy)-3β-hydroxyeremophil-7 (11)-en-12,8β-olide	$C_{20}H_{29}ClO_6$	*P. japonicus*	Yaoita and Kikuchi (1995)
39	6β,8β-Dihydroxy-3-oxoeremphil-7(11)-en-12,8α-olide	$C_{15}H_{20}O_5$	*P. japonicus*	Yaoita and Kikuchi (1996a)
40	6β-Angeloyloxy-8β-hydroxy-3-oxoeremophil-7(11)-en-12,8α-olide	$C_{20}H_{26}O_6$	*P. japonicus*	Yaoita and Kikuchi (1994a)
41	6β-Angeloyloxy-3β,8α-dihydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_6$	*P. japonicus*	Sugama et al. (1985)
42	6β-Angeloyloxy-3β,8β,9β-trihydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_7$	*P. japonicus*	Yaoita and Kikuchi (1995)
43	6β-Angeloyloxy-3β,8β-dihydroxyeremophil-7(11)-en-12,8α olide	$C_{20}H_{28}O_6$	*P. japonicus*	Sugama et al. (1985)
44	6β-Angeloyloxy-3β,9α dihydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_6$	*P. japonicus*	Yaoita and Kikuchi (1995)
45	6β-Angeloyloxy-3β,9β- dihydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_6$	*P. japonicus*	Yaoita and Kikuchi (1995)
46	6β-Angeloyloxy-3β-hydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_5$	*P. japonicus*	Yaoita et al. (1992)
47	6β-Epoxyangeloyloxy-3β-hydroxyeremophil-7(11)-en-12,8β-olide	$C_{20}H_{28}O_6$	*P. japonicus*	Yaoita and Kikuchi (1995)
48	8,12-Epoxy-2-[(senecioyl)oxy]eremophil-7,11-dien-9-one	$C_{20}H_{26}O_4$	*P. hybridus*	Bodensieck et al. (2007)
49	8β-H-Eremophilanolide	$C_{15}H_{22}O_2$	*P. hybridus*	Bodensieck et al. (2007)
50	8-Hydroxyeremophil-7(11)-en-12,8-olide	$C_{15}H_{20}O_3$	*P. hybridus* *P. tatewakianus* *P. japonicus*	Bodensieck et al. (2007) Xie et al. (2011) Matsumoto et al. (2020)
51	8β-Hydroxy-3-oxoeremophil-7(11)-en-12,8α-olide	$C_{15}H_{18}O_4$	*P. japonicus*	Yaoita and Kikuchi (1995)
52	9-Acetoxyfukinanolide	$C_{17}H_{24}O_4$	*P. japonicus*	Naya et al. (1972)
53	9-Hydroxyfuranoeremophilane	$C_{15}H_{22}O_2$	*P. hybridus*	Hochmannová et al. (1962a); Vokáč et al. (1972); Siegenthaler and Neuenschwander (1997)
54	9-Hydroxyisobakkenolide	$C_{20}H_{28}O_5$	*P. hybridus*	Bodensieck et al. (2007)
55	9-Oxofuranopetasin	$C_{20}H_{24}O_4$	*P. hybridus*	Bodensieck et al. (2007)
56	14-acetoxy-7β-senecioyloxy-notonipetranone	$C_{22}H_{32}O_5$	*P. tatewakianus*	M. Wang et al. (2014)
57	Albopetasol	$C_{15}H_{22}O_3$	*P. albus*	Novotný et al. (1962, 1964)
58	Angelyljaponicin	$C_{20}H_{28}O_4$	*P. albus* *P. kablikianus*	Novotný et al. (1966)
59	Bakkenolide A (Fukinanolid)	$C_{15}H_{22}O_2$	*P. japonicus*	Abe et al. (1968); Kitaharan et al. (1969)
60	Bakkenolide B	$C_{22}H_{30}O_6$	*P. japonicus* *P. tricholobus* *P. tatewakianus* *P. formosanus*	Abe et al. (1968); Kitaharan et al. (1969) Cheng (1999) Dong et al. (2010) Wu et al. (1999a)

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Table 3 (*continued*)

No.	Compound name	Formula	Species	References
61	Bakkenolide C	$C_{20}H_{28}O_5$	*P. japonicus*	Abe et al. (1968); Kitaharan et al. (1969)
62	Bakkenolide D (*S*-Fukinolide)	$C_{21}H_{28}O_6S$	*P. japonicus*	Abe et al. (1968); Kitaharan et al. (1969)
			P. tricholobus	Cheng (1999)
			P. tatewakianus	M. Wang et al. (2014)
			P. tricholobus	Hai et al. (2018)
			P. formosanus	Wu et al. (1999a)
63	Bakkenolide Db	$C_{21}H_{28}O_7S$	*P. tricholobus*	Hai et al. (2018)
			P. formosanus	Wu et al. (1999a)
64	Bakkenolide Dc	$C_{21}H_{28}O_7S$	*P. formosanus*	Wu et al. (1999a)
65	Bakkenolide Dd	$C_{21}H_{28}O_6S$	*P. formosanus*	Wu et al. (1999a)
66	Bakkenolide De	$C_{21}H_{28}O_7S$	*P. formosanus*	Wu et al. (1999a)
67	Bakkenolide Df	$C_{21}H_{28}O_7S$	*P. formosanus*	Wu et al. (1999a)
68	Bakkenolide Dg	$C_{21}H_{28}O_7S$	*P. formosanus*	Wu et al. (1999a)
69	Bakkenolide Dh	$C_{21}H_{28}O_7S$	*P. formosanus*	Wu et al. (1999a)
70	Bakkenolide E	$C_{22}H_{30}O_6$	*P. japonicus*	Shirahata et al. (1968); Kitaharan et al. (1969)
			P. formosanus	Wu et al. (1999a)
71	Bakkenolide Fa	$C_{25}H_{36}O_6$	*P. formosanus*	Wu et al. (1999a)
72	Bakkenolide Fb	$C_{25}H_{36}O_6$	*P. formosanus*	Wu et al. (1999a)
73	Bakkenolide G	$C_{15}H_{22}O_2$	*P. tricholobus*	Cheng (1999)
			P. formosanus	Wu et al. (1999a)
74	Bakkenolide H	$C_{23}H_{34}O_6$	*P. formosanus*	Wu et al. (1999a)
75	Bakkenolide I	$C_{19}H_{28}O_4$	*P. formosanus*	Wu et al. (1999a)
76	Bakkenolide III	$C_{15}H_{22}O_4$	*P. tatewakianus*	M. Wang et al. (2014)
			P. japonicus	Xu et al. (2016)
			P. formosanus	Wu et al. (1999a)
77	Bakkenolide J	$C_{20}H_{30}O_4$	*P. formosanus*	Wu et al. (1999a)
78	Bakkenolide K	$C_{24}H_{34}O_6$	*P. formosanus*	Wu et al. (1999a)
79	Bakkenolide L	$C_{19}H_{26}O_6$	*P. tatewakianus*	Xie et al. (2011)
			P. formosanus	Wu et al. (1999a)
80	Bakkenolide M	$C_{24}H_{36}O_6$	*P. formosanus*	Wu et al. (1999a)
81	Bakkenolide Na	$C_{24}H_{36}O_6$	*P. formosanus*	Wu et al. (1999a)
82	Bakkenolide Nb	$C_{24}H_{36}O_6$	*P. formosanus*	Wu et al. (1999a)
83	Bakkenolide O	$C_{25}H_{38}O_6$	*P. formosanus*	Wu et al. (1999a)
84	Bakkenolide P	$C_{25}H_{38}O_6$	*P. formosanus*	Wu et al. (1999a)
85	Bakkenolide Q	$C_{25}H_{38}O_6$	*P. formosanus*	Wu et al. (1999a)
86	Bakkenolide R	$C_{20}H_{28}O_5$	*P. formosanus*	Wu et al. (1999a)
87	Bakkenolide S	$C_{15}H_{228}O_3$	*P. formosanus*	Wu et al. (1999a)
88	Bakkenolide T	$C_{24}H_{34}O_7S$	*P. formosanus*	Wu et al. (1999a)
89	Bakkenolide Ua	$C_{19}H_{28}O_5$	*P. formosanus*	Wu et al. (1999a)
90	Bakkenolide Ub	$C_{19}H_{28}O_5$	*P. formosanus*	Wu et al. (1999a)
91	Bakkenolide Uc	$C_{19}H_{28}O_5$	*P. formosanus*	Wu et al. (1999a)
92	Bakkenolide V	$C_{20}H_{30}O_5$	*P. formosanus*	Wu et al. (1999a)
93	Bakkenolide VI	$C_{25}H_{36}O_6S$	*P. tatewakianus*	Sun et al. (2011)
94	Bakkenolide VIa	$C_{24}H_{32}O_7$	*P. japonicus*	Xie et al. (2016)
95	Bakkenolide W	$C_{22}H_{30}O_7$	*P. formosanus*	Wu et al. (1999a)
96	Bakkenolide X	$C_{17}H_{24}O_5$	*P. japonicus*	Xu et al. (2016)
			P. formosanus	Wu et al. (1999a)
97	Bakkenolide Ya	$C_{19}H_{26}O_6S$	*P. formosanus*	Wu et al. (1999a)
98	Bakkenolide Yb	$C_{19}H_{26}O_6S$	*P. formosanus*	Wu et al. (1999a)
99	Bakkenolide Za	$C_{24}H_{34}O_6$	*P. formosanus*	Wu et al. (1999a)
100	Bakkenolide Zb	$C_{24}H_{34}O_6$	*P. formosanus*	Wu et al. (1999a)
101	Bakkenolide Ia	$C_{25}H_{34}O_6$	*P. tricholobus*	Wang et al. (2009)
102	Bakkenolide Ib		*P. japonicus*	Hai et al. (2018)
103	Bakkenolide IIa	$C_{25}H_{34}O_6$	*P. tricholobus*	Wang et al. (2009)
104	Bakkenolide IIb	$C_{24}H_{32}O_6S$	*P. japonicus*	Hai et al. (2018)
105	Bakkenolide IIIa	$C_{24}H_{32}O_6S$	*P. tricholobus*	Wang et al. (2009)
106	Bakkenolide IIIb	$C_{24}H_{32}O_6S$	*P. japonicus*	Hai et al. (2018)
107	Bakkenolide IVa	$C_{24}H_{32}O_6S$	*P. tricholobus*	Wang et al. (2009)
108	Bakkenolide IVb	$C_{24}H_{32}O_6S$	*P. japonicus*	Hai et al. (2018)
109	Bakkenolide Va	$C_{23}H_{32}O_6S$	*P. tricholobus*	Zhang et al. (2008)
110	Bakkenolide Vb	$C_{24}H_{32}O_6S$	*P. tricholobus*	Hai et al. (2018)
111	Caryolane-1,9β-diol	$C_{15}H_{26}O_2$	*P. japonicus*	Xu et al. (2016)
112	Clovane-2β,9α-diol	$C_{15}H_{26}O_2$	*P. japonicus*	Xu et al. (2016)
113	Diangelyljaponicin	$C_{25}H_{34}O_5$	*P. albus*	Novotný et al. (1966)
			P. kablikianus	
114	Dimethoxydihydrofuroeremophilane	$C_{18}H_{30}O_2$	*P. hybridus*	Hochmannová et al. (1962a); Vokáč et al. (1972)
115	Epieremophilenolide	$C_{15}H_{22}O_2$	*P. japonicus*	Matsumoto et al. (2020)
116	Epoxyeremopetasinorol	$C_{13}H_{20}O_3$	*P. japonicus*	Yaoita et al. (2012)
117	Eremofukinone	$C_{15}H_{24}O$	*P. japonicus*	Naya et al. (1972)
118	Eremopetasidione	$C_{14}H_{20}O_3$	*P. japonicus*	Yaoita and Kikuchi (1994b)
119	Eremopetasinorol	$C_{13}H_{20}O_2$	*P. japonicus*	Yaoita and Kikuchi (1996b)
120	Eremopetasinorone B	$C_{13}H_{18}O_2$	*P. japonicus*	Yaoita et al. (2012)
121	Eremopetasinorone A	$C_{13}H_{18}O_2$	*P. japonicus*	Yaoita and Kikuchi (1996b)
122	Eremopetasinsulphoxide	$C_{19}H_{26}O_4S$	*P. japonicus*	Tori et al. (1998)
123	Eremopetasitenin A1	$C_{20}H_{28}O_6$	*P. japonicus*	Tori et al. (1998)
124	Eremopetasitenin A2	$C_{20}H_{28}O_6S$	*P. japonicus*	Tori et al. (1998)

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Table 3 (*continued*)

No.	Compound name	Formula	Species	References
125	Eremopetasitenin B1	$C_{20}H_{28}O_6$	*P. japonicus*	Tori et al. (1998)
126	Eremopetasitenin B2	$C_{24}H_{32}O_7S$	*P. japonicus*	Tori et al. (1998)
127	Eremopetasitenin C1	$C_{21}H_{30}O_6$	*P. japonicus*	Tori et al. (1998)
128	Eremopetasitenin C2	$C_{25}H_{34}O_7S$	*P. japonicus*	Tori et al. (1998)
129	Eremopetasitenin C3	$C_{21}H_{30}O_6S$	*P. japonicus*	Tori et al. (1998)
130	Eremopetasitenin D1	$C_{21}H_{30}O_6$	*P. japonicus*	Tori et al. (1998)
131	Eremopetasitenin D2	$C_{25}H_{34}O_7S$	*P. japonicus*	Tori et al. (1998)
132	Eremopetasitenin D3	$C_{17}H_{26}O_5$	*P. japonicus*	Tori et al. (1998)
133	Eremophilene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a, b); Křepinský et al. (1968);
			P. albus	Vokáč et al. (1972)
			P. kablikianus	Naya et al. (1971a)
			P. japonicus	
134	Eremophilene lactam	$C_{15}H_{23}NO$	*P. hybridus*	Jizba et al. (1977)
135	Eremophilenolide	$C_{15}H_{22}O_2$	*P. hybridus*	Novotný et al. (1961)
			P. japonicus	Matsumoto et al. (2020)
136	Eremosulphoxinolide A	$C_{24}H_{32}O_7S$	*P. japonicus*	Yaoita and Kikuchi (1996b)
137	Eremosulphoxinolide B	$C_{24}H_{32}O_7S$	*P. japonicus*	Yaoita and Kikuchi (1996b)
138	Fukinone	$C_{15}H_{24}O$	*P. japonicus*	Naya et al. (1968)
139	Fukinoside A	$C_{21}H_{34}O_{10}S$	*P. japonicus*	Yoshikawa et al. (2006)
140	Furanoeremophilane	$C_{15}H_{22}O$	*P. hybridus*	Hochmannová et al. (1962a); Vokáč et al. (1972)
			P. japonicus	Naya et al. (1971a)
141	Furanoeremophilone	$C_{15}H_{20}O_2$	*P. hybridus*	Novotný et al. (1961)
142	Furanofukinol	$C_{15}H_{22}O_3$	*P. japonicus*	Naya et al. (1971a)
143	Furanojaponin	$C_{20}H_{28}O_3$	*P. japonicus*	Naya et al. (1971a)
144	Furanopetasin	$C_{20}H_{28}O_4$	*P. hybridus*	Novotný et al. (1961)
145	Homofukinolide	$C_{25}H_{34}O_6$	*P. japonicus*	Xu et al. (2016)
146	Icariside B1	$C_{19}H_{30}O_8$	*P. tricholobus*	Zhang et al. (2014)
147	Isopetasin	$C_{20}H_{28}O_3$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. formosanus	Lin et al. (1998b)
			P. fragrans	Sugama et al. (1983)
			P. kablikianus	Novotný et al. (1972)
148	Isopetasol	$C_{15}H_{22}O_2$	*P. formosanus*	Lin et al. (1998b)
			P. fragrans	Sugama et al. (1983)
149	Isopetasoside	$C_{21}H_{32}O_7$	*P. japonicus*	Yamada et al. (1978a)
150	Iso-*S*-petasin	$C_{19}H_{26}O_3S$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. formosanus	Lin et al. (1998b)
151	Japonipene A	$C_{21}H_{30}O_6$	*P. japonicus*	Wang et al. (2013)
			P. tatewakianus	M. Wang et al. (2014)
152	Japonipene B	$C_{24}H_{32}O_6S$	*P. japonicus*	Novotný et al. (1968a, b); Wang et al. (2013)
153	Japonipene C	$C_{24}H_{34}O_6S$	*P. japonicus*	Wang et al. (2013)
154	Japonipene D	$C_{24}H_{32}O_7S$	*P. japonicus*	Wang et al. (2013)
155	Japonipene E	$C_{24}H_{32}O_7S$	*P. japonicus*	Wang et al. (2013)
156	Japonipene F	$C_{23}H_{32}O_7S$	*P. japonicus*	Wang et al. (2013)
157	Japonipene G	$C_{25}H_{35}ClO_6$	*P. japonicus*	Wang et al. (2013)
158	Japonipene H	$C_{25}H_{37}ClO_6$	*P. japonicus*	Wang et al. (2013)
159	Kablicin	$C_{25}H_{34}O_6$	*P. kablikianus*	Novotný et al. (1968a, b)
160	Ligularone	$C_{15}H_{20}O_2$	*P. japonicus*	Naya et al. (1971a)
161	Ligularenolide	$C_{15}H_{18}O_2$	*P. hybridus*	Bodensieck et al. (2007)
162	Megastigman-7-ene-3, 5, 6, 9-tetrol-3-O-β-D-6′-sulfonated-glucopyranoside	$C_{19}H_{34}O_{12}S$	*P. tricholobus*	Zhang et al. (2014)
163	Neopetasin	$C_{20}H_{28}O_3$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. fragrans	Sugama et al. (1983)
164	Neo-*S*-petasin	$C_{19}H_{26}O_3S$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. fragrans	Sugama et al. (1983)
165	Oplodiol	$C_{15}H_{26}O_2$	*P. tatewakianus*	Xie et al. (2011)
166	Oplopanone	$C_{15}H_{26}O_2$	*P. tatewakianus*	Xie et al. (2011)
167	Petasalbin (Ligularol)	$C_{15}H_{22}O_2$	*P. japonicus*	Naya et al. (1971a)
			P. albus	Novotný et al. (1962, 1964)
168	Petasalbin angelate (albopetasin)	$C_{20}H_{28}O_3$	*P. japonicus*	Naya et al. (1971a)
			P. albus	Novotný et al. (1962, 1964)
169	Petasalbin methyl ether (Furanofukinin)	$C_{16}H_{24}O_2$	*P. japonicus*	Naya et al. (1971a)
170	Petasin	$C_{20}H_{28}O_3$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. formosanus	Lin et al. (1998b)
			P. fragrans	Sugama et al. (1983)
171	Petasindiol	$C_{14}H_{18}O_4$	*P. tricholobus*	Hai et al. (2018)
172	Petasinol	$C_{19}H_{28}O_4S$	*P. formosanus*	Lin et al. (1998b)
173	Petasinone A	$C_{19}H_{26}O_4$	*P. formosanus*	Lin et al. (1998b)
174	Petasinone B	$C_{19}H_{26}O_4$	*P. formosanus*	Lin et al. (1998b)
175	Petasinone C	$C_{19}H_{26}O_4$	*P. formosanus*	Lin et al. (1998b)
176	Petasinone D	$C_{19}H_{26}O_3S$	*P. formosanus*	Lin et al. (1998b)
177	Petasipaline A		*P. palmatus*	Hayashi (1989)
178	Petasipaline B	$C_{19}H_{28}O_5$	*P. palmatus*	Hayashi (1989)
			P. tatewakianus	Xie et al. (2011)
179	Petasipene A	$C_{22}H_{31}ClO_7$	*P. japonicus*	Xu et al. (2016)
180	Petasipene B	$C_{19}H_{28}O_4S$	*P. japonicus*	Xu et al. (2016)
181	Petasitesterpene I	$C_{19}H_{28}O_4S$	*P. japonicus*	Matsumoto et al. (2020)
182	Petasitesterpene II	$C_{19}H_{28}O_4S$	*P. japonicus*	Matsumoto et al. (2020)

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Table 3 (*continued*)

No.	Compound name	Formula	Species	References
183	Petasitesterpene III	$C_{21}H_{32}O_8$	*P. japonicus*	Matsumoto et al. (2020)
184	Petasitesterpene IV	$C_{15}H_{24}O_3$	*P. japonicus*	Matsumoto et al. (2020)
185	Petasitesterpene V	$C_{21}H_{34}O_7$	*P. japonicus*	Matsumoto et al. (2020)
186	Petasitesterpene VI	$C_{19}H_{28}O_5S$	*P. japonicus*	Matsumoto et al. (2020)
187	Petasitin	$C_{20}H_{28}O_4$	*P. japonicus*	Naya and Takagi (1968)
188	Petasitolide A	$C_{20}H_{28}O_4$	*P. hybridus*	Novotný et al. (1961)
189	Petasitolide B	$C_{20}H_{28}O_4$	*P. hybridus*	Novotný et al. (1961)
190	Petasitolone	$C_{15}H_{24}O_2$	*P. japonicus*	Naya et al. (1971b)
191	Petasol	$C_{15}H_{22}O_2$	*P. formosanus*	Lin et al. (1998b)
			P. fragrans	Sugama et al. (1983)
192	Petasone A	$C_{19}H_{26}O_4S$	*P. formosanus*	Lin et al. (1998a)
193	Petasone B	$C_{19}H_{26}O_4S$	*P. formosanus*	Lin et al. (1998a)
194	Petatewalide A	$C_{22}H_{30}O_6$	*P. tatewakianus*	Dong et al. (2010)
195	Petatewalide B	$C_{22}H_{31}ClO_7$	*P. japonicus*	Choi et al. (2016)
196	*S*-Japonin	$C_{19}H_{28}O_3S$	*P. japonicus*	Naya et al. (1972)
197	*S*-petasitin	$C_{19}H_{26}O_4S$	*P. formosanus*	Lin et al. (1998a)
198	Secoeremopetasitolide A	$C_{19}H_{26}O_7$	*P. japonicus*	Yaoita and Kikuchi (1996c)
199	Secoeremopetasitolide B	$C_{21}H_{30}O_7$	*P. japonicus*	Yaoita and Kikuchi (1996c)
200	*S*-Furanopetasitin	$C_{24}H_{32}O_5S$	*P. japonicus*	Naya et al. (1971a)
201	*S*-Petasin	$C_{19}H_{26}O_3S$	*P. hybridus*	Aebi et al. (1955, 1958); Stoll et al. (1956)
			P. formosanus	Lin et al. (1998a)
			P. fragrans	Sugama et al. (1983)
202	*S*-Petasitolide A	$C_{19}H_{26}O_4S$	*P. hybridus*	Novotný et al. (1961)
203	S-Petasitolide B	$C_{19}H_{26}O_4S$	*P. hybridus*	Novotný et al. (1961)
204	Pulioplopanone B	$C_{15}H_{26}O_3$	*P. tatewakianus*	Xie et al. (2011)
205	Tatewakipene A	$C_{21}H_{30}O_6$	*P. tatewakianus*	M. Wang et al. (2014)
206	Tatewakipene B	$C_{23}H_{32}O_6$	*P. tatewakianus*	M. Wang et al. (2014)
207	Tatewakipene C	$C_{20}H_{30}O_4$	*P. tatewakianus*	M. Wang et al. (2014)
208	Tsoongianolide B	$C_{15}H_{20}O_3$	*P. hybridus*	Bodensieck et al. (2007)
209	Tussilagone	$C_{23}H_{34}O_5$	*P. tatewakianus*	M. Wang et al. (2014)

materials collected in the autumn *vs*. spring or originated from andro-*vs*. gyno-morphous specimens. Debrunner et al. (1995) studied the profile of isopetasin, neopetasin, petasin, iso-*S*-petasin, neo-*S*-petasin and *S*-petasin in the different plant organs (rootstocks, leaves, stems) of *P. hybridus*, showing that the content of petasins was significantly higher in rootstocks *vs*. leaves and stems (Table 4). Similarly, the rootstocks of *P. hybridus* specimens collected in four different habitats in Bulgaria were found to be richer in sesquiterpenes (petasin, isopetasin, neopetasin, *S*-petasin) than the leaves (Uzunova et al., 2020).

Siegenthaler and Neuenschwander (1997) showed that only the rootstocks are suited for investigating the presence of furanoeremophilanes in the furanopetasin chemotype of *P. hybridus*, whereas the aerial organs exposed to air (leaves, flowers) contain mostly 9-oxo-furanoeremophilanes, oxidation products of furanoeremophilanes.

Further studies focused on the influence of season and location of plant harvesting on the content of petasins. In six populations from Switzerland and Germany, the concentration of petasin was generally high and varied only moderately, depending on location, whereas a population very rich in neopetasin was found in Niedereichsel (Germany). When investigated over a complete vegetation period, plants of the habitat Gurnigel (Switzerland) showed the highest amounts of sesquiterpenes in the spring time and the lowest concentrations in summer, indicating that spring is the suitable season for their harvest (Debrunner and Neuenschwander, 1995). A similar seasonal trend was noticed in the rootstocks of *P. hybridus* and *P. albus*, with the levels of albopetasin, petasalbin and 6-angeloyl-albopetasol surprisingly small from July until October, relatively high in winter and peaking in May (Siegenthaler and Neuenschwander, 1997).

A special attention should be paid to the stability of petasins; it was found that, over a period of 72 days (40 °C, in the dark), sesquiterpenes with petasol and neopetasol skeletons slowly isomerize to the corresponding derivatives with isopetasol skeletons. For instance, neopetasin and petasin are both converted in a time-dependent manner to isopetasin, the more thermodynamically stable isomer (Debrunner and Neuenschwander, 1995).

3.2. Pyrrolizidine alkaloids

PAs are common metabolites of Asteraceae, Boraginaceae and Fabaceae families and serve as chemical defence compounds mainly against herbivores. Structurally, they consist of 1,2-unsaturated necine rings (heliotridine-, retronecine-, platynecine- and otonecine-type) usually esterified at C-7 and/or C-9 as monoesters or open-chain and cyclic diesters (Kitajima et al., 2019). In plant materials, they can occur either as free bases or as a mixture of free bases and their N-oxides (PANOs). Since the first reports from the 1970s on their negative health effects, especially hepatotoxicity and carcinogenicity (Bull et al., 1970), an enormous amount of data on their structure, content in medicinal plants and harmful health effects has been provided.

More than 20 diverse PAs have been identified in different species of *Petasites* genus (Table 5, Fig. 2). For instance, senecionine, seneciophylline, 7-angeloylretronecine, 9-angeloylretronecine, intergerrimine and senkirkine have been documented in *P. hybridus* (Avula et al., 2012, 2015; Luthy et al., 1983; Mroczek et al., 2002; Schenk et al., 2015). Senkirkine was found in *P. albus* (Mroczek et al., 2002), whereas petasitenine, neopetasitenine, senkirkine and fukinotoxin were reported in *P. japonicus* (Furuya and Hikichi, 1976; Hirono et al., 1973, 1975, 1977; Niwa et al., 1983). In addition, petasitenine, neopetasitenine, senkirkine, neosenkirkine and seneciophylline were retrieved in *P. paradoxus*: (Roeder and Abdel Ghani, 1990), whilst senkirkine, farfugine, tussilagine were isolated from *P. spurius* (Roeder et al., 1993).

Different quantitative studies revealed that the PAs content depends on the plant organ, age and developmental stage of the plant, season, location, etc (Chizzola, 1992). For instance, the PAs content of 77 populations of butterbur from Austria were analyzed by Chizzola et al. (2000), revealing that: the leaves usually contained lower concentration of PAs than the rhizomes; the highest alkaloid content was observed in the young thickenings just below the emerging leaves, while the young runners were much richer in PAs than the old runners; seasonal variation of PAs content in the rhizomes were low, although the alkaloid levels were higher in the spring than in the summer and autumn; PAs-free cultivars of *P. hybridus* have not been found, but considering their low levels in the leaves (<10 mg/kg), the latter can be regarded as a safer

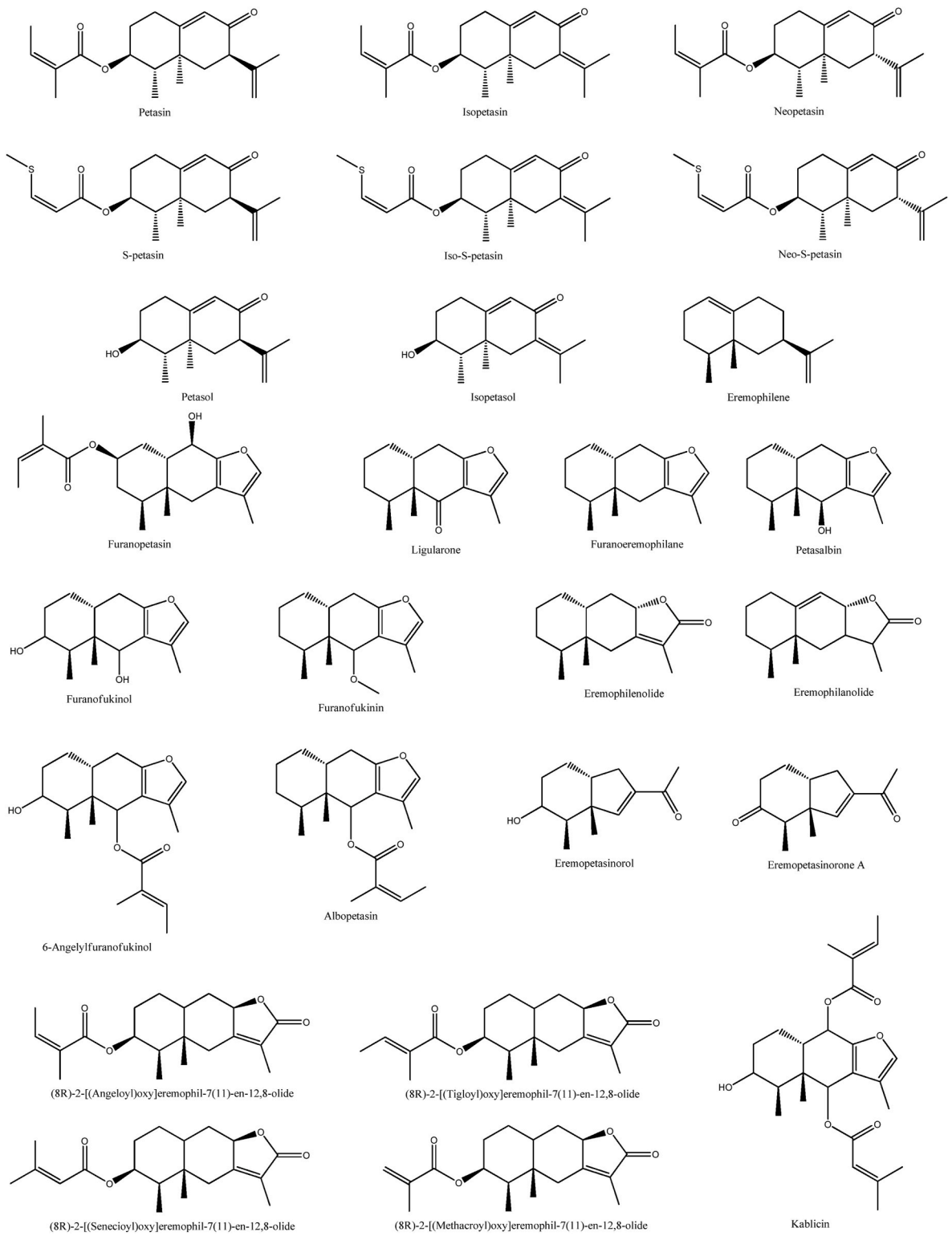

Fig. 1. Chemical structures of main sesquiterpenes from *Petasites* genus.

source of bioactive petasins (Chizzola et al., 2000). Therefore, even though the leaves have slightly lower amounts of bioactive petasins (7.4–15.3 mg/g petasin in rhizomes *vs*. 3.3–11.4 mg/g petasin in leaves, as reported by Wildi et al. (1998)), they are generally recommended as a more suitable source of petasins than the rootstocks, due to a lower PAs content (5–90 ppm PA in rhizomes *vs*. 0.02–1.50 mg/g petasin in leaves). A similar trend was also presented by Langer et al. (1996), when the alkaloid content in *P. hybridus* leaves was determined to be only 3.86 ppm, while the content in the rhizomes was 104.8 ppm.

Due to their incriminating toxicity, considerable efforts have been made to, either find and select PAs-free chemotypes (as mentioned above) or eliminate the PAs from plant extracts. For the scope of depletion, *Petasites* extracts can be processed with the help of cation exchange resins (Mauz et al., 1985). However, genetic crossing

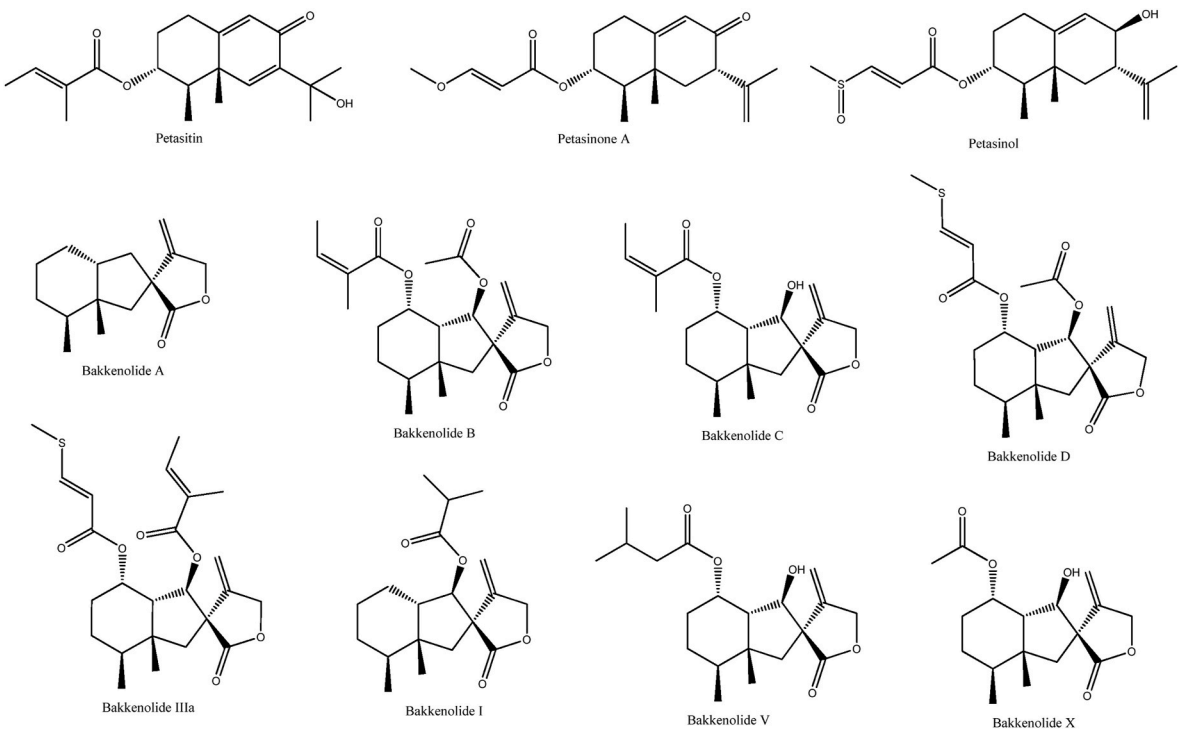

Fig. 1. (*continued*).

Table 4
The content of petasins in different plant organs of *P. hybridus*.

Organ	Isopetasin	Neopetasin	Petasin	Iso-*S*-petasin	Neo-*S*-petasin	*S*-petasin	References
	μg/g d.w. plant material						
Leaves	337	1885	2771	45	382	305	Debrunner et al. (1995)
Leaves	–	–	3300–11400	–	–	–	Wildi et al. (1998)
Rhizomes	–	–	7400–15300	–	–	–	Wildi et al. (1998)
Rhizomes	113	2341	9376	79	1399	980	Debrunner et al. (1995)
Roots	114	2463	7002	59	1043	643	Debrunner et al. (1995)
Rootstocks	1200–2450	1150–2580	5970–12200	400–540	710–1350	1660–2970	Uzunova et al. (2020)
Rootstocks	300	–	600	–	–	100	Avula et al. (2012)
Rootstocks	129	2197	9495	114	1324	678	Debrunner et al. (1995)
Runners	156	1940	7018	71	1225	1174	Debrunner et al. (1995)
Stalks	0.1	0.4	79	1.3	1.6	6.7	Debrunner et al. (1995)

experiments to obtain progenies with lower contain of PAs did not achieve PA-free cultivars (Pank et al., 2002).

3.3. Phenolic compounds

Over 50 phenolic compounds have been identified in *Petasites* genus. They can be classified as phenolic acids (e.g. fukiic acid, caffeic acid and other hydroxycinnamic acid derivatives), flavonoids and their glycosides (e.g. kaempferol, quercetin, rutin), and lignans (e.g. petasitesins A and B). Fukiic and fukinolic acids (derivative of fukiic and caffeic acids) are two distinctive compounds found in the leaves and stems of *P. japonicus* (Sakamura et al., 1969, 1973). Petasiphenol is another caffeic acid derivative that can be found in the flower stalks of *P. japonicus* (Iriye et al., 1992). The phenolic compounds reported in *Petasites* genus are presented in Table 6, and exemplary structures of phenolic compounds are presented in Fig. 3.

3.4. Volatile compounds

The most important volatile compounds reported in *Petasites* genus are presented in Table 7. Miyazawa et al. (2003) characterized 69 volatile compounds in the essential oils of *P. japonicus*. This analysis showed that the major components of the essential oils from the leaves, rootstocks and flower stems are β-caryophyllene (22% of leaves essential oil), angelic acid (18% of rootstocks essential oil) and valencene (12% of flower stems essential oil). Saritas et al. (2002) identified 26 volatile compounds (e.g. albene, petasitene, pethybrene) in the essential oil obtained by hydro-distillation from *P. hybridus* rhizomes. The analysis of the essential oil obtained from *P. albus* aerial parts collected in Iran showed the occurrence of euparin (73%), α-eudesmol (13.2%), and β-selinene (4.5%) as the major volatile components (Mohammadi et al., 2012). In another study, the major compounds of the essential oils of *P. albus* and *P. hybridus* (leaves, flower stems and rhizomes from Croatia) were identified as oxygenated sesquiterpenes, such as bisabola-2, 10-diene-1-one and fukinanolid (bakkenolide A) (Friščić et al., 2019). The analysis of essential oils from leaves and rhizomes of *P. hybridus* ssp. *ochroleucus* from the Balkans allowed the identification of 42 volatile components in the leaves oil, with a fukinanolide as the major compound (33.42%) and 60 constituents in the rhizomes oil, with nonenal as the major compound (11.23%). The analysis showed the low concentration of potentially biologically active isopetasin (3,9%) in the essential oil of rhizomes. However, the toxic pyrrolizidine alkaloids

Table 5
Pyrrolizidine alkaloids reported in *Petasites* genus.

No.	Compound name	Formula	Species	References
210	7-Acetyl-9-(2,3-dimethylbutyryl) retronecine	$C_{16}H_{25}NO_4$	*P. hybridus*	Aydin and Letzel (2013)
211	7-Angeloylretronecine	$C_{13}H_{19}NO_3$	*P. fragrans* *P. hybridus*	Wiedenfeld et al. (2002) Avula et al. (2015)
212	7-Angeloylretronecine-*N*-oxide	$C_{13}H_{19}NO_4$	*P. hybridus*	Avula et al. (2012)
213	9-Angeloylretronecine	$C_{13}H_{19}NO_3$	*P. hybridus*	Avula et al. (2012)
214	9-Angeloylretronecine-*N*-oxide	$C_{13}H_{19}NO_4$	*P. hybridus*	Avula et al. (2012)
215	Acetylpetasitenine	$C_{21}H_{29}NO_8$	*P. hybridus*	Aydin and Letzel (2013)
216	Farfugine	$C_{13}H_{21}NO_3$	*P. spurius*	Roeder et al. (1993)
217	Intergerrimine	$C_{18}H_{25}NO_5$	*P. hybridus* *P. frigidus*	Luthy et al. (1983) Avula et al. (2012)
218	Integerrimine-*N*-oxide	$C_{18}H_{25}NO_6$	*P. hybridus* *P. frigidus*	Avula et al. (2012)
219	Isotussilagine	$C_{10}H_{17}NO_3$	*P. spurius*	Roeder et al. (1993)
220	Isotussilaginine	$C_{10}H_{17}NO_3$	*P. spurius*	Roeder et al. (1993)
221	Neopetasitenine	$C_{21}H_{29}NO_8$	*P. japonicus* *P. paradoxus*	Hirono et al. (1977) Roeder and Abdel Ghani (1990)
222	Petasinine	$C_{13}H_{21}NO_3$	*P. japonicus* *P. fragrans*	Yamada et al. (1978b) Wiedenfeld et al. (2002)
223	Petasinoside	$C_{28}H_{37}NO_9$	*P. japonicus*	Yamada et al. (1978b)
224	Petasitenine (Fukinotoxin)	$C_{19}H_{27}NO_7$	*P. japonicus* *P. paradoxus*	Furuya and Hikichi (1976) Hirono et al. (1977) Roeder and Abdel Ghani (1990)
225	Secopetasitenine	$C_{20}H_{31}NO_8$	*P. japonicus*	Kitajima et al. (2019)
226	Senecionine	$C_{18}H_{25}NO_5$	*P. hybridus* *P. frigidus*	Luthy et al. (1983) Avula et al. (2012)
227	Senecionine-*N*-oxide	$C_{18}H_{25}NO_6$	*P. hybridus* *P. frigidus*	Avula et al. (2012)
228	Seneciphylline	$C_{18}H_{23}NO_5$	*P. paradoxus* *P. hybridus*	Roeder and Abdel Ghani (1990) Sener and Ergun (1996)
229	Senkirkine	$C_{19}H_{27}NO_6$	*P. hybridus* *P. japonicus* *P. paradoxus* *P. spurius* *P. fragrans* *P. frigidus*	Luthy et al. (1983) Yamada et al. (1978a) Roeder and Abdel Ghani (1990) Roeder et al. (1993) Wiedenfeld et al. (2002) Avula et al. (2012)
230	Symphytine	$C_{20}H_{31}NO_6$	*P. hybridus*	Aydin and Letzel (2013)
231	Tussilagine	$C_{10}H_{17}NO_3$		

Table 5 (*continued*)

No.	Compound name	Formula	Species	References
			P. spurius *P. hybridus*	Roeder et al. (1993) Sener and Ergun (1996)

were below the detection limit in leaves and rhizomes essential oils (Mihajilov-Krstev et al., 2020).

4. Biological activities

Santini can be considered one of the pioneers in unveiling the pharmacological activities of *Petasites* genus, as his studies showed for the first time the beneficial effects of *P. hybridus* in treating hypertension, anxiety and asthma (Santini, 1953). The subsequently documented biological effects of *Petasites* extracts as well as of isolated constituents, such as anti-migraine, anti-inflammatory, anti-allergic, anti-asthmatic, neuroprotective, spasmolytic, anti-hypertensive or anti-cancer, are discussed in the following subsections and reviewed in Table S1 (Biological activity reported in *Petasites* genus).

4.1. Anti-migraine activity

The most comprehensive preclinical and clinical research of the pharmacological activity of *Petasites* extracts concerns their anti-migraine effects. Degenring and Bommer (1995) carried out a randomized, placebo controlled, double-blind trial in 60 patients with migraine; the subjects received either SFE-CO_2 butterbur rootstock extract (Petaforce®, 2 capsules, 25 mg of extract, twice daily) or placebo over a 16-week period. The authors reported a 50% reduction in the frequency of migraine attacks among 70% of the butterbur-treated patients. In addition, the headache durations were reduced by 55% and the pain intensity was diminished in 57% of butterbur recipients (Degenring and Bommer, 1995). The re-analysis of the original data of this study, performed by a third-party biometrical institute, confirmed the efficacy of used extracts in the prophylaxis of migraine (Diener et al., 2004). A subsequent placebo-controlled trial on 60 human subjects investigated the efficacy and tolerance of SFE-CO_2 extract of *P. hybridus* rootstocks (Petadolex®, capsules, 25 mg extract, with a minimum content of 15% petasins) in the prophylaxis of migraine. The patients received a dosage of two capsules, twice daily, over 12 weeks. The reduction of the migraine attacks was found significant compared to placebo and no side-effects were observed (Grossmann and Schmidramsl, 2000). In a later study, 202 patients with migraine were randomized into three groups: two receiving Petadolex® (50 mg and 75 mg butterbur extracts, respectively) and one placebo group. The trial showed that only the dose of 75 mg was significantly more effective than placebo and decreased the migraine attack frequency over 4 months of treatment (Lipton et al., 2004). A multicenter, prospective, open-label clinical study proved the potential of *P. hybridus* in the migraine prophylaxis for children and teenagers; 108 patients with ages between 6 and 17 were treated with Petadolex® (50–150 mg extract daily, depending on age) over 4 months; the results showed a reduction in the frequency of migraine attacks (Pothmann and Danesch, 2005).

In view of the little evidence of the pharmacological and non-pharmacological options in the prophylaxis of migraine in children, the clinical studies of butterbur were continued for this age group. One of the studies compared the administration of Petadolex®, music therapy and placebo for a period of 28 weeks. The dosing of Petadolex® depended on age: 50 mg daily for 8–9 years old children and 100 mg daily for 10–12 years old children. If no headache relief was observed, the dose was raised to 75 or 150 mg daily, respectively. It was noticed that, 8 weeks after the treatment, only music therapy was superior to placebo, whereas 6 months after the start of treatment, both music

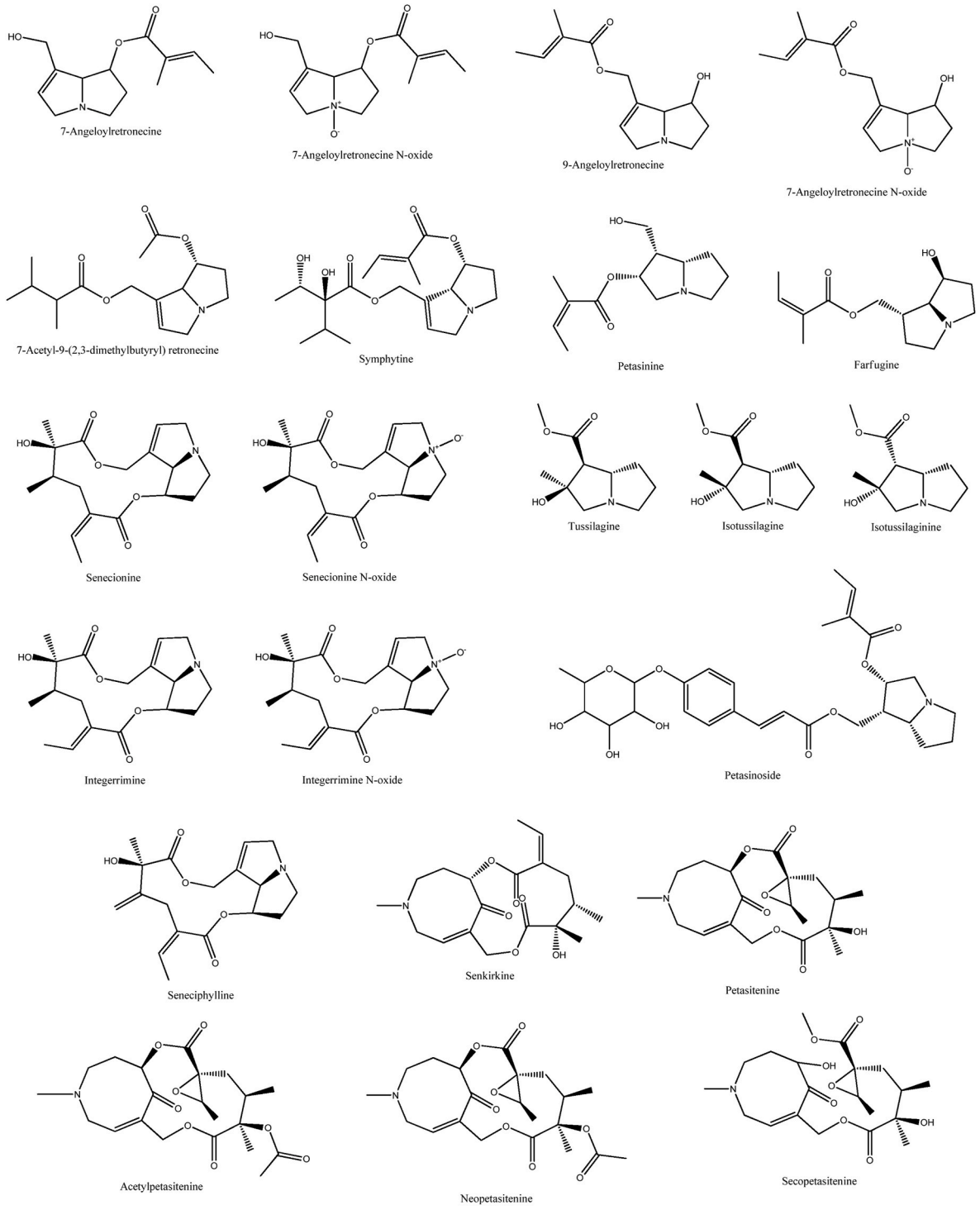

Fig. 2. Chemical structures of the main pyrrolizidine alkaloids from *Petasites* genus.

therapy and butterbur were superior to placebo in preventing the migraine attacks (Oelkers-Ax et al., 2008).

Due to the strong scientific evidence in migraine prophylaxis, butterbur was included in numerous recommendations for practitioners. For instance, in 2008, *Petasites* extract (Petadolex®, 75 mg twice daily) was considered as a second-choice drug in the prophylaxis of migraine by the German Migraine and Headache Society and the German Neurological Society. However, the users and practitioners were alerted for the potential side effects, e.g. eructation, stomach pain or liver dysfunction, whereas the pregnancy and breastfeeding were contraindicated, due to the lack of relevant studies (Evers et al., 2008). In 2012, the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society classified butterbur (the recommendation refers to the research on Petadolex®) as level A medication with established efficacy in evidence-based recommendations for migraine prophylaxis (Holland et al., 2012). Likewise, the Canadian Headache Society guidelines strongly recommend butterbur for the same indication (Pringsheim et al., 2012). However, the potential toxicity of *P. hybridus* extracts containing PAs remains controversial and raises serious health issues. In all recommendations, consumers are

Table 6
Phenolic compounds reported in *Petasites* genus.

No.	Compound name	Formula	Species	References
232	1,3-di-*O*-caffeoylquinic acid hexoside	$C_{31}H_{34}O_{17}$	*P. japonicus*	Choi et al. (2017)
233	1,5-di-*O*-Caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. japonicus*	Choi et al. (2017)
234	1-Caffeoyl-3-feruloylquinic acid	$C_{26}H_{26}O_{12}$	*P. hybridus*	Jaiswal et al. (2011)
235	1-Caffeoyl-4-feruloylquinic acid	$C_{26}H_{26}O_{12}$	*P. hybridus*	Jaiswal et al. (2011)
236	2-Hydroxy-5-acetylbenzoic acid	$C_9H_8O_4$	*P. tricholobus*	Zhang et al. (2012)
237	5-Hydroxy-3,7,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	*P. tatewakianus*	M. Wang et al. (2014)
238	3-(4β-D-Glucopyranosyloxy-3,5-dimethoxy)-phenyl-2E-propenol	$C_{17}H_{24}O_9$	*P. tricholobus*	Zhang et al. (2012)
239	3,4,5-Tri-*O*-caffeoylquinic acid	$C_{34}H_{30}O_{15}$	*P. japonicus*	Watanabe et al. (2007)
240	3,4-Di-*O*-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. japonicus*	Choi et al. (2017)
241	3,5-dihydroxy-7,3′,4′,5′-tetramethoxy flavanonol hydroxy feruloyl glucoside	$C_{35}H_{38}O_{17}$	*P. japonicus*	Choi et al. (2017)
242	3,5-Di-*O*-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. hybridus* *P. japonicus*	Jaiswal et al. (2011) Watanabe et al. (2007)
243	4,5-Di-*O*-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. hybridus* *P. japonicus*	Jaiswal et al. (2011) Kim et al. (2012)
244	4-Hydroxy-2, 6-dimethoxyphenol-1-*O*-β-D-glucopyranoside	$C_{14}H_{20}O_9$	*P. tricholobus*	Zhang et al. (2012)
245	4-Hydroxymethyl-2,6-dimethoxyphenyl-1-*O*-β-D-glucopyranoside	$C_{15}H_{22}O_9$	*P. tricholobus*	Zhang et al. (2012)
246	5-Caffeoylquinic acid	$C_{16}H_{18}O_9$	*P. hybridus* *P. japonicus*	Jaiswal et al. (2011) Kim et al. (2012)
247	5-Feruloylquinic acid	$C_{17}H_{20}O_9$	*P. hybridus*	Jaiswal et al. (2011)
248	*cis*-3,5-Di-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. hybridus*	Jaiswal et al. (2011)
249	*cis*-4,5-Di-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	*P. hybridus*	Jaiswal et al. (2011)
250	Afzelin	$C_{21}H_{20}O_{10}$	*P. tricholobus*	Zhang et al. (2012)
251	Arbutin	$C_{12}H_{16}O_7$	*P. tricholobus*	Zhang et al. (2012)
252	Caffeic acid	$C_9H_8O_4$	*P. japonicus* *P. tricholobus* *P. formosanus*	Matsuura et al. (2002) Zhang et al. (2012) Wu et al. (1999a)
253	Chlorogenic acid	$C_{16}H_{18}O_9$	*P. japonicus* *P. tricholobus* *P. formosanus*	Watanabe et al. (2007) Zhang et al. (2012)
254	Chrysoeriol-methyl ether	$C_{17}H_{14}O_6$	*P. japonicus*	Choi et al. (2017)
255	Cimicifugic acid D	$C_{20}H_{18}O_{10}$	*P. japonicus*	Lee et al. (2019)
256	Dihydrosyringin	$C_{17}H_{26}O_9$	*P. tricholobus*	Zhang et al. (2012)
257	Ferulic acid	$C_{10}H_{10}O_4$	*P. formosanus*	Wu et al. (1999a)
258	Fukiic acid	$C_{11}H_{12}O_8$	*P. japonicus*	Sakamura et al. (1969)
259	Fukinolic acid	$C_{20}H_{18}O_{11}$	*P. japonicus*	Sakamura et al. (1969)
260	Kaempferol	$C_{15}H_{10}O_6$	*P. japonicus*	Kim et al. (2008)
261	Kaempferol-3-*O*-(6″-acetyl)-β- glucopyranoside	$C_{23}H_{22}O_{12}$	*P. japonicus*	Kim et al. (2012)
262	Kaempferol-3-*O*-(6″-acetyl)-β-D-glucoside	$C_{16}H_{18}O_9$	*P. japonicus*	D. G. Lee et al. (2015)
263	Kaempferol-3-*O*-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside	$C_{33}H_{40}O_{20}$	*P. tricholobus*	Zhang et al. (2012)
264	Kaempferol-3-*O*-β-D-glucopyranoside	$C_{21}H_{20}O_{11}$	*P. tricholobus* *P. japonicus*	Zhang et al. (2012) D. G. Lee et al. (2015)
265	Liquiritin	$C_{21}H_{22}O_9$	*P. japonicus*	Choi et al. (2017)
266	Luteolin-7-*O*-[6′-dihydrogalloyl]-glucosyl-8-*C*-pentosyl-(1 → 2)-glucoside	$C_{39}H_{44}O_{24}$	*P. japonicus*	Choi et al. (2017)
267	Methyl caffeate	$C_{10}H_{10}O_4$	*P. fragrans* *P. formosanus*	Sugama et al. (1983) Wu et al. (1999a)
268	Methyl paraben	$C_8H_8O_3$	*P. formosanus*	Wu et al. (1999a)
269	Methyl protocatechuate	$C_8H_8O_4$	*P. formosanus*	Wu et al. (1999a)
270	Morin	$C_{15}H_{10}O_7$	*P. formosanus*	Wu et al. (1999a)
271	Naringenin hexoside	$C_{21}H_{22}O_{10}$	*P. japonicus*	Choi et al. (2017)
272	*N*-*p*-Coumaroyltyramine	$C_{17}H_{17}NO_3$	*P. formosanus*	Wu et al. (1999a)
273	Petasiphenol	$C_{18}H_{16}O_7$	*P. japonicus* *P. tricholobus*	Iriye et al. (1992) Zhang et al. (2012)
274	Petasitesin A	$C_{18}H_{14}O_6$	*P. japonicus*	Lee et al. (2019)
275	Petasitesin B	$C_{18}H_{16}O_7$	*P. japonicus*	Lee et al. (2019)
276	Petaslignolide A	$C_{26}H_{32}O_{12}$	*P. japonicus*	Min et al. (2005)
277	*p*-Hydroxybenzoic acid	$C_7H_6O_3$	*P. tricholobus*	Zhang et al. (2012)
278	*p*-Hydroxyphenylpropionic acid	$C_9H_{10}O_3$	*P. tricholobus*	Zhang et al. (2012)
279	Protocatechuic acid	$C_7H_6O_4$	*P. formosanus*	Wu et al. (1999a)
280	Protocatechuic aldehyde	$C_7H_6O_3$	*P. tricholobus*	Zhang et al. (2012)
281	Quercetin	$C_{15}H_{10}O_7$	*P. hybridus*	Toropkina and Minina (1976)
282	Quercetin 3-*O*-β-D-glucoside	$C_{21}H_{19}O_{12}$	*P. japonicus* *P. tricholobus*	Matsuura et al. (2002)

(*continued on next page*)

Table 6 (*continued*)

No.	Compound name	Formula	Species	References
				Zhang et al. (2012)
283	Quercetin-3-*O*-(6″-acetyl)-β-glucopyranoside	$C_{23}H_{22}O_{13}$	*P. japonicus*	Kim et al. (2012)
284	Quercitrin	$C_{21}H_{20}O_{11}$	*P. hybridus*	Toropkina and Minina (1976)
285	Rutin	$C_{21}H_{20}O_{11}$	*P. hybridus* *P. japonicus* *P. tricholobus*	Toropkina and Minina (1976) Matsuura et al. (2002) Zhang et al. (2012)
286	Sulfonated benzyl glucoside	$C_{12}H_{16}O_7S$	*P. tricholobus*	Zhang et al. (2012)
287	Tangshenoside II	$C_{29}H_{42}O_{18}$	*P. tricholobus*	Zhang et al. (2012)
288	Vanillic acid	$C_8H_8O_4$	*P. formosanus*	Wu et al. (1999a)
289	Vanillin	$C_8H_8O_3$	*P. formosanus*	Wu et al. (1999a)
290	Quercetin-3-*O*-β-D-6″-*O*-acetylglucoside	$C_{23}H_{22}O_{13}$	*P. japonicus*	Matsuura et al. (2002)

cautioned to only use products in which the PAs have been removed and the content of petasins have been standardized (Mauskop et al., 2013; Rajapakse and Pringsheim, 2016).

To complement the clinical evidences, several research efforts were put also into investigating the *in vitro* mechanisms of action of butterbur in migraine. A few sesquiterpenes, such as *S*-petasin and iso-*S*-petasin were shown to block the voltage-dependent calcium $Ca_v2.1$ channels, thus contributing to the migraine-prophylactic properties of *P. hybridus* (Horak et al., 2009). Additionally, *S*-petasin was proven to prevent the secretion of calcitonin gene-related peptide (CGRP), a pivotal messenger in the inflammatory processes linked to migraine (Slavin et al., 2016). On the other hand, isopetasin was shown to specifically activate the transient receptor potential cation channel, subfamily A, member 1 (TRPA1) channels; this can lead to an initial neuronal excitation followed by a marked desensitization of the afferent and efferent function of the peptidergic nociceptors (Benemei et al., 2017). In another study, petasin and isopetasin reduced CGRP release from the trigeminal afferents by activating TRPA1 and transient receptor potential cation channel, subfamily V, member 1 (TRPV1) channels; a cooperative action on these two channels may contribute to the migraine prophylactic effect of petasins (Kleeberg-Hartmann et al., 2021). These mechanistic studies indicate that butterbur extracts (containing pharmacologically active petasin and isopetasin) could be included in a new group of anti-migraine drugs – TRPA1 channel inhibitors.

4.2. Anti-inflammatory, anti-allergic ant anti-asthmatic activity

The studies assessing the anti-inflammatory effects of *P. hybridus*

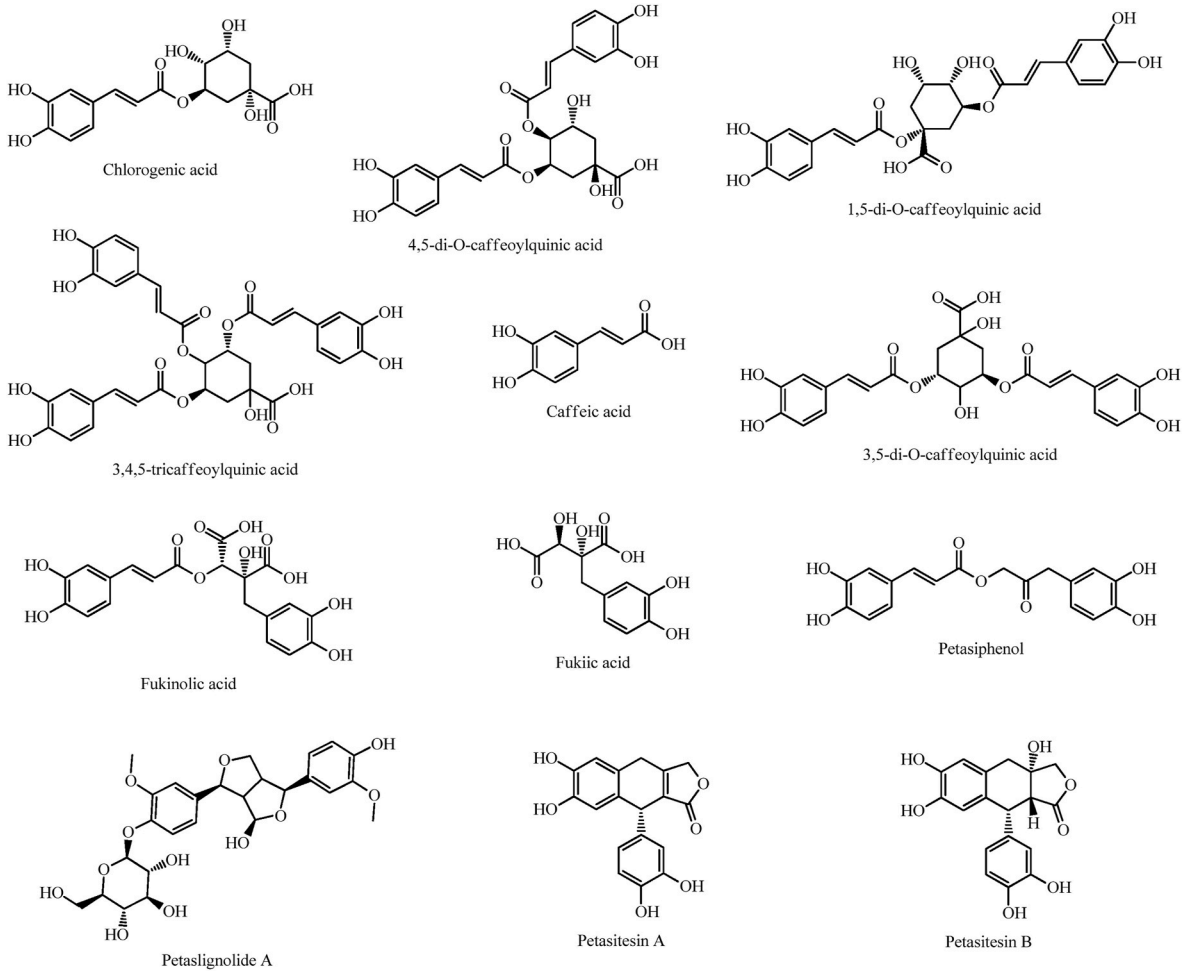

Fig. 3. Chemical structures of the main phenolic compounds from *Petasites* genus.

Table 7
Compounds reported in *Petasites* essential oils.

No.	Compound name	Formula	Species	References
291	(2*E*)-Nonenal	$C_9H_{16}O$	*P. hybridus*	Mihajilov-Krstev et al. (2020)
292	1-Nonene	C_9H_{18}	*P. hybridus*	Mihajilov-Krstev et al. (2020)
293	3-Carene	$C_{10}H_{16}$	*P. japonicus*	Naya et al. (1971a)
294	7-epi-α-Eudesmol	$C_{15}H_{26}O$	*P. hybridus* *P. hybridus*	Mihajilov-Krstev et al. (2020)
295	α-Euparin	$C_{13}H_{12}O_3$	*P. albus* ae	Mohammadi et al. (2012)
296	α-Humulene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a)
297	α-Phellandrene	$C_{10}H_{16}$	*P. japonicus*	Miyazawa et al. (2003)
298	α-Santalene	$C_{15}H_{24}$	*P. japonicus*	Naya et al. (1971a)
299	β-Bisabolene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a)
300	β-Caryophyllene	$C_{15}H_{24}$	*P. japonicus*	Miyazawa et al. (2003)
301	β-Elemene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a)
302	β-Humulene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a)
303	β-Selinene	$C_{15}H_{24}$	*P. albus*	Mohammadi et al. (2012)
304	γ-Bisabolene	$C_{15}H_{24}$	*P. hybridus*	Hochmannová et al. (1962a)
305	Eudesmol	$C_{15}H_{26}O$	*P. albus*	Mohammadi et al. (2012)
306	Geramacrene D	$C_{15}H_{24}$	*P. hybridus* *P. hybridus*	Mihajilov-Krstev et al. (2020)
307	Linalool	$C_{10}H_{18}O$	*P. hybridus*	Mihajilov-Krstev et al. (2020)
308	Pethybrene	$C_{15}H_{24}$	*P. hybridus*	Saritas et al. (2002)
309	Phellandrene	$C_{10}H_{16}$	*P. japonicus*	Miyazawa et al. (2003)
310	Thymol methyl ether	$C_{11}H_{16}O$	*P. japonicus*	Naya et al. (1971a)
311	*t*-Muurolol	$C_{15}H_{26}O$	*P. albus*	Friščić et al. (2019)
312	Tricosane	$C_{23}H_{48}$	*P. hybridus*	Friščić et al. (2019)
313	Valencene	$C_{15}H_{24}$	*P. japonicus* *P. japonicus*	Miyazawa et al. (2003)

extracts are closely linked to their clinical use in allergic rhinitis and asthma. In a randomized, double-blind, parallel group study, the anti-allergic effects of *P. hybridus* were comparable to those of cetirizine in patients with hay fever; 125 patients were randomized and received Ze 339 SFE-CO_2 *P. hybridus* leaves extract (1 tablet, four times a day) or cetirizine (one 10 mg tablet a day) for 2 weeks. The effects of butterbur were similar to those of cetirizine (Schapowal, 2002). Butterbur extract was proven to attenuate adenosine monophosphate (AMP)-induced nasal responsiveness in patients with grass-pollen-sensitized seasonal allergic rhinitis (SAR), as observed in a small randomized, double-blind, cross-over clinical study with 20 patients who received Petaforce ® 50 mg, twice daily or placebo for 2 weeks (Lee et al., 2003). Furthermore, both *P. hybridus* extract (Petaforce® 50 mg, twice daily) and fexofenadine (180 mg, once daily) were equally effective in improving nasal symptoms in comparison to placebo in 16 patients with perennial allergic rhinitis (randomized, double-blind, cross-over study) (Lee et al., 2004a).

On the other hand, a double-blind, placebo-controlled, cross-over study on 35 patients with intermittent allergic rhinitis (IAR) showed that there was no significant clinical efficacy of *P. hybridus* extract (Petaforce ®, 50 mg, twice daily) *vs.* placebo (Gray et al., 2004). Notwithstanding, a prospective, randomized, double-blind, placebo--controlled, parallel-group study with patients with IAR randomized into 3 groups (high dose group - 1 tablet 3 times daily, low dose group - 1 tablet twice daily and placebo group) showed a significant dose-dependent improvement of the IAR symptoms in the groups receiving butterbur extract, relative to placebo (Schapowal, 2004). These results were confirmed in another prospective, randomized, double-blind, parallel group trial with 330 patients. Ze 339 extract (1 tablet, 3 times daily, 2 weeks) and fexofenadine (180 mg, once daily) were revealed to be comparably efficacious relative to placebo in patients with IAR (Schapowal, 2005). An open post-marketing surveillance study proved the efficacy and safety of Tesalin® (Ze 339) in SAR; 580 patients received 2 tablets of Ze 339 daily for 2 weeks. The symptoms of SAR (e.g. rhinorrhea, sneezing, nasal congestion) were improved in 90% of patients (Käufeler et al., 2006). However, a randomized, double-blind crossover study comparing Ze 339 with acrivastine in skin test reactivity (in 8 patients with respiratory allergy and in 10 healthy volunteers) showed no anti-allergic, particularly anti-histaminic, effects of this extract in skin tests reactivity (assessed 90 min after a double dose of Ze 339, acrivastine or placebo) (Gex-Collet et al., 2006). In a double-blind randomized cross-over study, Ze 339 (20 mg twice daily) showed better efficacy in relieving nasal obstruction symptoms and inhibiting inflammatory mediators (e.g. interleukin 8, leukotriene B_4) than desloratadine (5 mg once daily) in 18 patients with allergic rhinitis symptoms (patients received Ze 339, desloratadine or placebo 5 days before the challenge with grass pollen extract) (Dumitru et al., 2011). The effectiveness and safety profile of Ze 339 extract in allergic rhinitis was further confirmed in a larger clinical study on 927 patients with SAR. The evolution of the clinical symptoms was evaluated within 28 days (1 tablet, 2–3 times/-day); the patients were allowed to take any concomitant medication except antibiotics. After 28 days, approximately 95% of patients were free of symptoms (as assessed by physicians and patients) (Rodríguez de Marquis and González, 2012). A sub-analysis of this study was carried out to investigate the effects of Ze 339 in children and adolescents. From the group of 927 patients, the analysis included 53 patients under 18 years old. The study showed that significant improvement of allergic rhinitis symptoms was observed in 86.8% of patients (under 18 years old) after 28 days of treatment (Moll et al., 2015). Furthermore, a non-interventional, observational clinical study was performed to investigate the efficacy of Ze 339 extract in 226 patients with seasonal or perennial allergic rhinitis. Patients received 1, 2, or 3 tablets of Ze 339 daily, with 58.5% taking Ze 339 as a monotherapy. The period of the treatment ranged from 3 to 217 days (the average time of the study was 63 days, 75% of patients were treated for at least 4 weeks). The impact on the quality of life, effectiveness on symptoms and tolerability were assessed. The study showed significant improvement in allergic and inflammatory symptoms, with few cases of side effects, i.e., nausea, malaise and abdominal pain (Blosa et al., 2021).

A Polish clinical study investigated the activity of pulverized and encapsulated *P. hybridus* in asthma and chronic obstructive bronchitis. The study included 70 patients divided into 5 groups (3 test groups and 2 control groups). Two tested groups included patients with moderate/severe asthma who were receiving corticosteroids, whereas a third group included patients who were not receiving corticosteroids. In the first group, one-time administration of 600 mg of butterbur improved the lung function after 3 h. In the second group, the same dose reduced bronchial reactivity to methacholine challenge after 2 h. In the third group, butterbur in dose of 600 mg three times daily for 14 days caused a substantial reduction in bronchial hyper-responsiveness (Ziolo and Samochowiec, 1998). A prospective non-randomized open clinical study of 80 patients suggested that butterbur extract is an effective therapy for the treatment of asthma. In this clinical trial, the patients received butterbur rootstocks extract (Petadolex®) in a dose of 50 mg three times daily (children received 50–150 mg, depending on age) for 2 months (followed by 2 months with “optional” intake of preparation). The numbers of asthma attacks were decreased, as well as their severity and duration. The asthma symptoms (e.g. coughing), peak flow and forced expiratory volume were improved. Furthermore, the intake of asthma medications was reduced by the end of investigation in over 40% of the treated patients (Danesch, 2004). *P. hybridus* may be effective as add-on therapy with corticosteroids, as revealed by a double-blind placebo--controlled cross-over randomized study with 16 asthmatic patients that received inhaled corticosteroids; it was noticed that the chronic co-administration conferred complementary anti-inflammatory activity.

The patients received 25 mg of butterbur extract Petaforce® or placebo twice daily in 1-week period (Lee et al., 2004b).

Beside *P. hybridus*, other *Petasites* species were shown to possess strong anti-inflammatory/anti-allergic properties. Hydroethanolic (70%) extracts of *P. japonicus* (flowers and stems) inhibited the degranulation of mast cells, suggesting anti-type I allergic properties (Choi, 2002; Shimoda et al., 2006). Fukinoside A, bakkenolide B and petatewalide B can be considered as the active anti-allergic compounds of *P. japonicus* (Choi et al., 2016; Lee et al., 2013; Yoshikawa et al., 2006), whereas several eremophilenolides (e.g. 6β-hydroxyeremophilenolide) isolated from the rhizomes of *P. japonicus* showed anti-allergic and anti-histaminic properties in guinea pig models (Tobinaga et al., 1983). The anti-inflammatory activity of hot water extracts of *P. japonicus* leaves was shown in lipopolysaccharide (LPS)-induced RAW264.7 cells line (monocyte/macrophage-like murine cells) model. The results suggested that *P. japonicus* exerts inhibitory activity on LPS-mediated inflammatory response (Kim et al., 2020). The same model was used to investigate petasitesins A (lactone lignan) and cimicifugic acid D (isolated from the hot water extract of *P. japonicus* leaves) anti-inflammatory activity through the inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) (Lee et al., 2019). *S*-petasin (the major sesquiterpene of *P. formosanus*) showed anti-allergic and anti-inflammatory activities *via* inhibition of mast cells degranulation (in RBL-2H3 mast cells line model), suppression of iNOS and nitric oxide (NO) production (in mouse peritoneal macrophages) and suppression of inflammatory cell accumulation (in ovalbumin-induced mouse asthma model) (K.-P. Lee et al., 2015).

The evaluation of the anti-inflammatory activity of compounds isolated from *P. tricholobus* Franch. rootstocks (bakkenolide-B, -D) in guinea pig trachea model showed significant inhibitory effects on the tracheal contraction induced by histamine (Wang et al., 2006). Several sesquiterpenes (e.g. 14-acetoxy-7β-senecioyloxy-notonipetranone) isolated from *P. tatewakianus* leaves extracts showed inhibitory activity on LPS-induced NO production in murine microglial BV-2 cell line, with the strongest effect exerted by 14-acetoxy-7β-senecioyloxy-notonipetranone (Wang et al., 2014).

Regarding the proposed mechanisms of the anti-allergic/anti-inflammatory/anti-asthmatic activity of *Petasites*, various *in vitro* and *in vivo* experiments revealed:

- inhibition of prostaglandins (e.g. prostaglandin E_2) and leukotrienes (e.g. leukotriene C_4) synthesis in skin fibroblasts (Scheidegger et al., 1998);
- inhibition of leukotrienes (e.g. leukotriene B_4) in leucocytes, eosinophils and neutrophils *via* 5-lipooxygenase and phospholipase A_2 blockage (and probably other calcium-related pathways) (Thomet et al., 2001a, 2001b, 2002, 2001a);
- inhibition of cytokines and other pro-inflammatory mediators production and release (e.g. tumor necrosis factor α (TNF α), inteleukin-2, -4, -5, -6 -13) (Brattström et al., 2010; Fu et al., 2017; Lee et al., 2011; Qian et al., 2016);
- inhibition of mast cells degranulation (Choi, 2002; Shimoda et al., 2006);
- inhibition of iNOS, COX-2, phospholipase A_2 and phosphodiesterases (PDE) 1–5 (Choi et al., 2016; Fiebich et al., 2005; Ko et al., 2011; K.-P. Lee et al., 2015; Lee et al., 2013); .
- inhibition of Janus kinase (JAK) and signal transducer and activators of transcription (STAT)-signaling pathways (which are the key regulators of various inflammatory processes) in nasal epithelial cells (Steiert et al., 2017).

4.3. Neuroprotective activity

Various extracts of *P. japonicus* were evaluated in regard with their neuroprotective properties. For instance, the butanol fraction of the methanolic extract of *P. japonicus* leaves, showed neuroprotective effects (glutathione-sparing activity and prevention against lipid peroxidation in brain) in a kainic acid-induced neurotoxicity model in mice, when administered orally for 5 days (Sok et al., 2006). Similar results were obtained in mice challenged with kainic acid by using the combination of *Aster scaber* Moench. butanol extract and *P. japonicus* butanol extract (administered intraperitoneally for 4 days). This combination decreased the lethality and neurotoxicity behavioral signs and increased the glutathione level in mouse brain (Oh et al., 2005). The neuroprotective activity of japonipene-A, -B. –C, bakkenolide-X and -IIIa isolated from the ethyl acetate fraction of the methanolic extract of *P. japonicus* (whole plant) was shown in a cobalt chloride-induced neuronal cell death model in SH-SY5Y human dopaminergic cells (Wang et al., 2013). On the other hand, the ethyl acetate fraction of the ethanolic extract of *P. japonicus* aerial parts displayed a significant inhibitory activity on β-secretase and suppression of neurotoxicity induced by β-amyloid protein in B103 neuroblastoma cells line (Hong et al., 2011; Song et al., 2008). A further study suggested that kaempferol-3-*O*-(6″-acetyl)-β-glucopyranoside may be the active neuroprotective compound of the ethyl acetate fraction of *P. japonicus* extract (Song et al., 2012). These results suggest the potential applications of *P. japonicus* extract in neurological disorders like Alzheimer's disease.

Furthermore, different other compounds isolated from *P. japonicus*, *P. tricholobus*, *P. trichinous* or *P. tatewakianus* also displayed significant neuroprotective effects. For instance, kaempferol (isolated from the *P. japonicus* stems) was proven to attenuate the glutamate-induced oxidative stress in mouse hippocampal neuronal cells (HT22) (Yang et al., 2014). Bakkenolide B and petatewalide B isolated from the leaves of *P. japonicus* showed anti-neuro-inflammatory properties (e.g. alleviated production of interleukin-1β, −6, −12, and TNF α) in mouse BV2 microglial cells. The proposed mechanism of action of these sesquiterpenes involves the up-regulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/activated protein kinase (AMPK) signaling pathway which plays a significant role in neuroprotection (Park et al., 2018a, 2018b, 2020, 2018a). Additionally, petatewalide B showed neuroprotective activity against oxygen-glucose deprivation/reoxygenation-induced injury in human neuroblastoma SH-SY5Y cell line by upregulation of the AMPK/Nrf2 signaling pathway (Park et al., 2020). Bakkenolides-Ia, -IIa. -IIIa, -Iva, -Va isolated from *P. tricholobus* rhizomes were proven to possess neuroprotective activity in cultured rat cortical cells exposed to oxygen-glucose deprivation and oxidative insults (Wang et al., 2009; Zhang et al., 2008). Similar results were obtained for bakkenolide-VI isolated from the rhizomes of *P. tatewakianus* (Sun et al., 2011). The total bakkenolides fraction and bakkenolide-IIIa isolated from *P. tricholobus* increased the neuron viability and decreased the amount of apoptotic cells in cultured hippocampal neurons in an oxygen-glucose deprivation model. Furthermore, bakkenolide-IIIa increased the survival rate of the cerebral damage rats model (Jiang et al., 2014, 2015).

Petaslignolide A, a furofuran lignan isolated from a *P. japonicus* leaves extract, showed antiseizure activity in kainic acid-treated mice. The oral administration of petaslignolide A to mice for 4 days before the kainic acid injection delayed the onset time of seizures (from 12.5 to 29 min); however, a single administration of petaslignolide A did not prevent the seizure (Min et al., 2005).

4.4. Spasmolytic activity

With respect to the spasmolytic activity of *Petasites*, it was noticed that the existing studies are outdated, despite the fact that some promising effects were reported in different experimental *in vitro* and *in vivo* models. For instance, several studies from the 1950s showed comparable spasmolytic properties of a methanolic extract of *P. hybridus* rootstocks as papaverine in a guinea-pig ileum model (Bucher, 1951; Valesini, 1955). Petasin and *S*-petasin were already suspected as the main spasmolytic agents (Aebi et al., 1958). Later, the petroleum ether extracts of *P. hybridus* rootstocks were found to inhibit the vasoconstrictive

peptido-leukotriene (e.g. leukotriene-E_4) biosynthesis in isolated peritoneal macrophages, which may contribute to the spasmolytic activity. A direct correlation between the spasmolytic activity and the content of isopetasin in the extract was also noticed (Bickel et al., 1994; Brune et al., 1993). Furthermore, *S*-petasin and iso-*S*-petasin (found in the aerial parts of *P. formosanus*) showed relaxant effects in isolated guinea pig trachea, primarily due to a non-specific antispasmodic effect of *S*-petasin and antimuscarinic effect of iso-*S*-petasin (Ko et al., 2001).

4.5. Cardio-vasculo-protective activity

The vasorelaxant effects of *P. hybridus* extracts were initially documented in studies from 1950s to 1960s, with their activity linked to the inhibition of voltage-dependent Ca^{2+} channels (Crema et al., 1957; Efimova and Petrov, 1965). Furthermore, individual sesquiterpenes, such as *S*-petasin and iso-*S*-petasin, were shown to exert anti-hypertensive-related effects. For instance, *S*-petasin (isolated from *P. formosanus*) showed vasorelaxant effects in vascular smooth muscle cells through inhibition of voltage-dependent Ca^{2+} channels (Wang et al., 2001) and negative chronotropic and inotropic effects in the rat heart muscle *via* a calcium-antagonizing activity (Wang et al., 2004). The vasodilatory effects of *S*-petasin were also evidenced in rat isolated aortas and mesenteric arteries. The study also described the Ca^{2+} channel blocking effect of eremophilanolactones (e.g. the angelic ester of 2β-hydroxy-8αH-7(11)-eremophilene-12,8-olid). Furthermore, the eremophilanolactones and *S*-petasin inhibited the DNA synthesis in cardiomyocytes and smooth muscle cells (Sheykhzade et al., 2008). The L-type voltage-dependent Ca^{2+} channels were identified as the site of action of petasins (Wang et al., 2010). Moreover, iso-*S*-petasin was shown to depresses the ventricular contraction possibly through inhibition of voltage-dependent Ca^{2+} channels in rat ventricular myocytes (Esberg et al., 2003).

Several *in vitro* and *in vivo* studies proved the beneficial effects of *P. japonicus* in metabolic diseases, with indirect beneficial effects on the cardiovascular function. For instance, the ethanolic extract of *P. japonicus* flower buds showed anti-obesity properties through suppression of murine preadipocyte differentiation and reduction of visceral fat accumulation in mice fed a high-fat diet supplemented with 1% *P. japonicus* extract (compared with mice fed a normal diet and a no-supplemented high-fat diet) (Watanabe et al., 2010). The Japanese butterbur extract (80% ethanol) was found to improve the obesity-related inflammatory and adipogenic responses in raw 264.7 macrophages (e.g. inhibition of LPS-stimulated NO production) and 3T3-L1 adipocytes (e.g. monocyte chemoattractant protein 1 inhibition) (Ahn et al., 2020). The ethyl acetate fraction of a *P. japonicus* methanolic extract and quercetin-3-*O*-β-D-glucoside isolated from this fraction manifested a potent aldose reductase inhibitory activity (Adachi et al., 2014; D. G. Lee et al., 2015). Moreover, petasin displayed anti-obesity and anti-diabetic properties exerted through the modulation of glucose metabolism and activation of AMP-activated protein kinase *via* inhibition of mitochondrial respiration. Furthermore, *S*-petasin exerted anti-adipogenic activity against 3T3-L1 cell differentiation by inhibiting the signaling of peroxisome proliferator-activated receptor γ (PPAR-γ) pathway (Guo et al., 2019).

P. japonicus ethanolic extract was proven to exert antiplatelet activity through the impairment of platelet aggregation and reduction of thrombus formation in rats (Ji et al., 2014), whereas an enzyme (chymotrypsin like serine protease) extracted from the leaves of *P. japonicus* was shown to exhibit fibrinolytic properties (Kim et al., 2015). In addition, several *in vitro* studies indicated the antiplatelet and fibrinolytic properties (e.g. inhibition of the platelet-activating factor/-PAF)-induced platelet aggregation in washed rabbit platelets) of bakkenolides G and H (Liao et al., 1997; Wu et al., 1999b).

4.6. Anticancer activity

Various studies of *Petasites* extracts and isolated active compounds showed a promising cytotoxic activity in different cell-based assays: e.g. *P. hybridus* rootstocks extract in two breast cancer cell lines, MDA-MB-231 and MCF-7 (Tzoneva et al., 2021); *P. japonicus* leaves methanolic extracts in human cancer cell lines and rat liver epithelial cells WB-F344 (Kang et al., 2010; Shinmoto et al., 2001); bakkenolide A in various cell lines, including HeLa (human cervical carcinoma cells) (Jamieson et al., 1976); bakkenolide-D, -G, –H, -Uc in Hep G2, HepG2.2.15 and P-338 cell lines (Wu et al., 1999a); bakkenolide B and petatewalide A isolated from the rhizomes of *P. tatewakianus* in HeLa, human breast cancer (MCF-7), murine Lewis lung carcinoma (LLC) cell lines (Dong et al., 2010); benzofuran derivatives (e.g. 1-(6-hydroxy-2-isopropenyl-1-benzofuran-5-yl)-1-ethanone) in human breast cancer MCF-7 cells (Khaleghi et al., 2011; Soleimani et al., 2015); petasitesterpenes I, II, VI and *S*-japonin isolated from the methanolic extract of the aerial parts of *P. japonicus* in human astrocytoma U-251MG cancer cells and in breast cancer cells MDA-MB-231 (Matsumoto et al., 2020).

Regarding the potential mechanisms of action, it was noticed that bakkenolide A inhibited leukemia cells (K562 cell line) by down-regulation of histone deacetylase (HDAC) 3 and phosphoinositide 3-kinase (PI3K)-regulated signaling pathway (Zhang et al., 2016), whereas petasin exhibited cytotoxic effects in colon cancer SW-620 cells *via* inactivation of protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway (Lyu et al., 2019). In addition, *S*-petasin showed potential anti-melanoma activity in B16F10 cells and A375 cells through apoptosis induction and inhibition of cell migration by activation of p53 signaling pathway (Guo et al., 2020). Furthermore, a recent study suggested that isopetasin and iso-*S*-petasin can be novel reactive oxygen species (ROS)-generating and apoptosis-inducing P-glycoprotein inhibitors against multidrug-resistant cancer cells, i.e. leukemia cells CCRF-CEM, P-gp-overexpressing CEM/ADR5000 cells and breast cancer BCRP-transfected-MDA-MB-231-BCRP cells (Abdelfatah et al., 2021). Petasiphenol from *P. japonicus* was proven to possess anti-mutagenic properties and inhibit DNA polymerase λ (Matsubara et al., 2004; Mizushina et al., 2002).

4.7. Antioxidant activity

A number of *in vitro* and *in vivo* studies indicated promising antioxidant activities of extracts obtained from various *Petasites* species. The isolated compounds from *P. formosanus* leaves (e.g. sodium dupracine) showed antioxidant activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay (Lin et al., 2003). Furthermore, a furofuran lignan isolated from the butanol fraction of a methanolic extract of *P. japonicus* leaves showed antioxidant activity in the same antioxidant assay (Min et al., 2005). The determination of DPPH radical scavenging of the methanolic extracts of *P. japonicus* showed a half maximal inhibitory concentration (IC_{50}) of 42.9 mg/100 g (Heo et al., 2007). The ethanolic extract of *P. hybridus* flowers and leaves showed significant antioxidant activity in DPPH assay (IC_{50} values of 0.059 mg/mL and 0.050 mg/mL, respectively) (Koleckar et al., 2008). The aqueous extract of the edible parts of *P. japonicus* showed a 24% DPPH radical scavenging activity and 108 mmol/L antioxidant activity in ferric-reducing antioxidant power (FRAP) assay. The total polyphenol content of the aqueous *P. japonicus* extract was 86 mg gallic acid equivalent (GAE)/g (Kyung-A et al., 2011). Moreover, the 70% methanol extract of the *P. japonicus* leaves decreased the value of the thiobarbituric acid reactive substance (TBARS) and showed better color stability in the ground beef patties (which indicate their possible use as preservatives in meat-based products) (Kim et al., 2013). The ethyl acetate fraction of the ethanolic extract of *P. japonicus* stems showed significant antioxidant effect in DPPH radical scavenging, TBARS and lipoxygenase inhibition assay. Further investigation identified kaempferol as the main antioxidant component of the ethyl acetate fraction of *P. japonicus* (Kim et al., 2008).

Another polyphenol compound, fukinolic acid (isolated from the leaves of *P. japonicus*), showed antioxidant effects against superoxide anion, NO and DPPH (Watanabe et al., 2007). The dependence of the *P. japonicus* antioxidant activity with polyphenolic content was proved in DPPH, 2–2′-azino-*bis*(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{+}$) and FRAP assays. The study showed that the antioxidant capacity depends on the polyphenol concentration and it was the highest in the leaves (with higher concentration of polyphenols) and the lowest in the stem (with lower concentration of polyphenols) (Choi et al., 2017). The on-line HPLC-ABTS screening system coupled to DAD, MS/MS and NMR of methanolic extracts of *P. japonicus* rootstocks and leaves allowed the identification of the major antioxidant compounds, such as 5-*O*-caffeoylquinic acid, fukinolic acid, 3,5-di-*O*-caffeoylquinic acid and 4,5-di-*O*-caffeoylquinic acid (Kim et al., 2012). The online HPLC-DPPH analysis coupled to LC-MS also allowed the identification of caffeic acid, 3-O-caffeoylquinic acid, fukinolic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 4,5-di-O-caffeoylquinic acid antioxidant compounds as the main antioxidants in *P. japonicus* (80 % ethanol extract of flower buds) (Hiemori-Kondo and Nii, 2020). The investigation of the antioxidant activity of the butanol fraction obtained from the methanolic extract of *P. japonicus* leaves in mice challenged with monosodium L-glutamate showed the improvement of the plasma lipid profiles and oxidative damage of the liver (e.g. increase of the glutathione reductase and peroxidase) (Park et al., 2010). The antioxidant activity of *P. hybridus* extract was considered as the pivotal effect responsible for decreasing the ovalbumin-induced liver hypersensitivity in mice (Alhusayan et al., 2020). Ji et al. investigated the effect of the extraction methods on the polyphenolic composition, antioxidant activity and anti-melanogenic activity of *P. japonicus* and indicated the potential use of this plant extract as a source of natural antioxidants for skincare products (Ji et al., 2020). Kim et al. indicated that the high antioxidant activity of the *P. japonicus* (ethyl acetate fraction of the methanolic extract) may be a result of up-regulation of Nrf2 signaling pathway (Kim et al., 2016). The antioxidant activity of the essential oils isolated from *P. hybridus* subsp. *ochroleucus* (tested in DPPH and ABTS assays) showed higher activity of the leaves' essential oils than that of the rootstocks (in DPPH assay, the IC_{50} values of rhizomes' and leaves' essential oils were 154 mg/mL and 80 mg/mL, respectively) (Mihajilov-Krstev et al., 2020).

4.8. Miscellaneous biological activities

Several studies indicate other properties and potential applications of plants from the genus *Petasites*. For instance, the insect deterrent properties of sesquiterpenes isolated from *P. hybridus* and *P. albus* were shown in a few experiments; the repellent effects may be the purpose for the biosynthesis of sesquiterpenes (e.g. petasins) by the genus *Petasites* (Hägele et al., 1996, 1998; Harmatha and Nawrot, 1984). In another study, *S*-petasin was shown to have modulatory effects on the endocrine system; *S*-petasin decreased the production of testosterone in rat testicular interstitial cells (Lin et al., 2000) and corticosterone release from rat zona fasiculata-reticularis cells *via* inhibition of cAMP formation, reduction of the activities of key enzymes P450scc and 11β-hydroxylase and down-regulation of the expression of steroidogenic acute regulatory protein (Chang et al., 2002, 2004). The numerous bioactivities of the genus *Petasites* and their mechanisms of actions are summarized in Fig. 4.

5. Pharmacokinetics and toxicological issues

To justify the human use of herbal products, other issues beside the pharmacological activity and efficacy should be addressed, such as the pharmacokinetics and toxicological (safety) aspects. A pharmacokinetic study evaluated the release of petasins from Ze 339 tablets and their dissolution, absorption and metabolism. It was shown that petasins exhibited a pH-independent low solubility. However, a high permeability through human colorectal adenocarcinoma Caco-2 cells (used as an intestinal epithelium model) was demonstrated. A high absorption capacity was found in duodenum, jejunum and ileum of *in situ* rat models. The same models indicated a high metabolism of petasins in Caco-2 cells and in the rat intestine. Additionally, the *in vitro* enzyme assays of rat and human liver and intestinal S9 fractions (containing cytosol and microsomes obtained as supernatant after organ homogenization) showed higher metabolic rates in the liver cells than in the intestinal cells. However, an important metabolism of petasins was postulated also for the intestine (Disch et al., 2018).

The toxicity of plants of the genus *Petasites* is mainly related to the presence of PAs. PAs can exhibit acute toxicity when are consumed in high amounts. However, a long-term consumption can lead to chronic toxicity (e.g. hepatocellular necrosis, liver carcinoma, hemangioendothelial sarcoma and tumors in lung, pancreas and intestine). PAs can also cause hepatic veno-occlusive disease. The mechanism of the toxic activity of PAs include oxidative activation (catalyzed by cytochrome P450) of PAs into dehydro-pyrrolizidine esters, which form adducts with proteins and DNA (Schrenk et al., 2020).

The first reports of carcinogenicity related to the presence of PAs in *Petasites* appeared in Japan. A high incidence of liver hemangioendothelial sarcoma in rats fed with a diet containing young flower stalks of *P. japonicus* was noticed (Hirono et al., 1973, 1975). Further studies on the toxicity of fukinotoxin (petasitenine) isolated from the flower stalks of *P. japonicus* proved its carcinogenic activity in rats. However, Katsumasa et al. (1978) found no significant difference in tumor incidence between thr experimental groups of mice and hamsters fed with a diet containing flower stalks of *P. japonicus* and the corresponding control group. This fact was attributed to the different PA-susceptibility of the animal strains. A study focused on the metabolism of neopetasitenine and petasitenine, PAs isolated from *P. japonicus*, showed a rapid absorption of neopetasitenine and conversion to petasitenine after oral administration in rats. The metabolic profiles in humans extrapolated from rat data suggested that dangerous amount of petasitenine could be present in human plasma if *P. japonicus* were daily consumed as a food (Yanagi et al., 2021). However, no signs of toxicity were observed in the single oral dose toxicity and the two-week repeated oral dose toxicity study of the aqueous *P. japonicus* leaves extract in Sprague-Dawley rats. The no observable adverse effect level (NOAEL) was considered to be 5000 mg/kg/day. Moreover, no mutagenicity was observed, as evaluated by bacterial reverse mutations assay, chromosomal aberrations assay in Chinese hamster lung cells and micronucleus assay in mice (Park et al., 2021).

The acute oral toxicity study of the methanolic extract of *P. hybridus* rootstocks showed no toxic symptoms in skin, fur, eyes or behavioral pattern in rats and mice (Şeremet et al., 2016). However, the toxicity study of *P. hybridus* rootstocks extract (50% acidified methanol) in crustaceans (*Artemia salina* and *Daphnia magna*) showed lethal concentrations 50% (LC_{50}) of 296 μg/mL and 340 μg/mL in *A. salina* and *D. magna*, respectively; substances with $LC_{50} < 1000$ μg/mL are considered toxic (Şeremet et al., 2018).

To avoid the toxicological issues related to the presence of PAs, only alkaloid-free *P. hybridus* extracts were approved clinically. The acute and chronic toxicity studies of butterbur rootstock SFE-CO_2 extract in Wistar rats showed no adverse effects for the doses generally recommended in humans. However, the post-marketing surveillance of the safety profile of Petadolex® indicated a potential risk for hepatotoxicity (Danesch and Rittinghausen, 2003). Moreover, independent reports indicated several induced liver injuries after the use of Petadolex®; notwithstanding, those cases were rare and confounded by co-medications (Anderson and Borlak, 2019). A series of *in vivo* (rats) and *in vitro* (hepatocytes isolated from human livers) evidenced a possible hepatotoxicity of petasins (Petadolex®). However, the induction of hepatotoxicity (e.g. cytotoxicity, increase of transaminases) was observed only in the extracts rich in petasins and at 200-fold therapeutic doses in a 28-day toxicity study (in rats) and at >170-fold of therapeutic

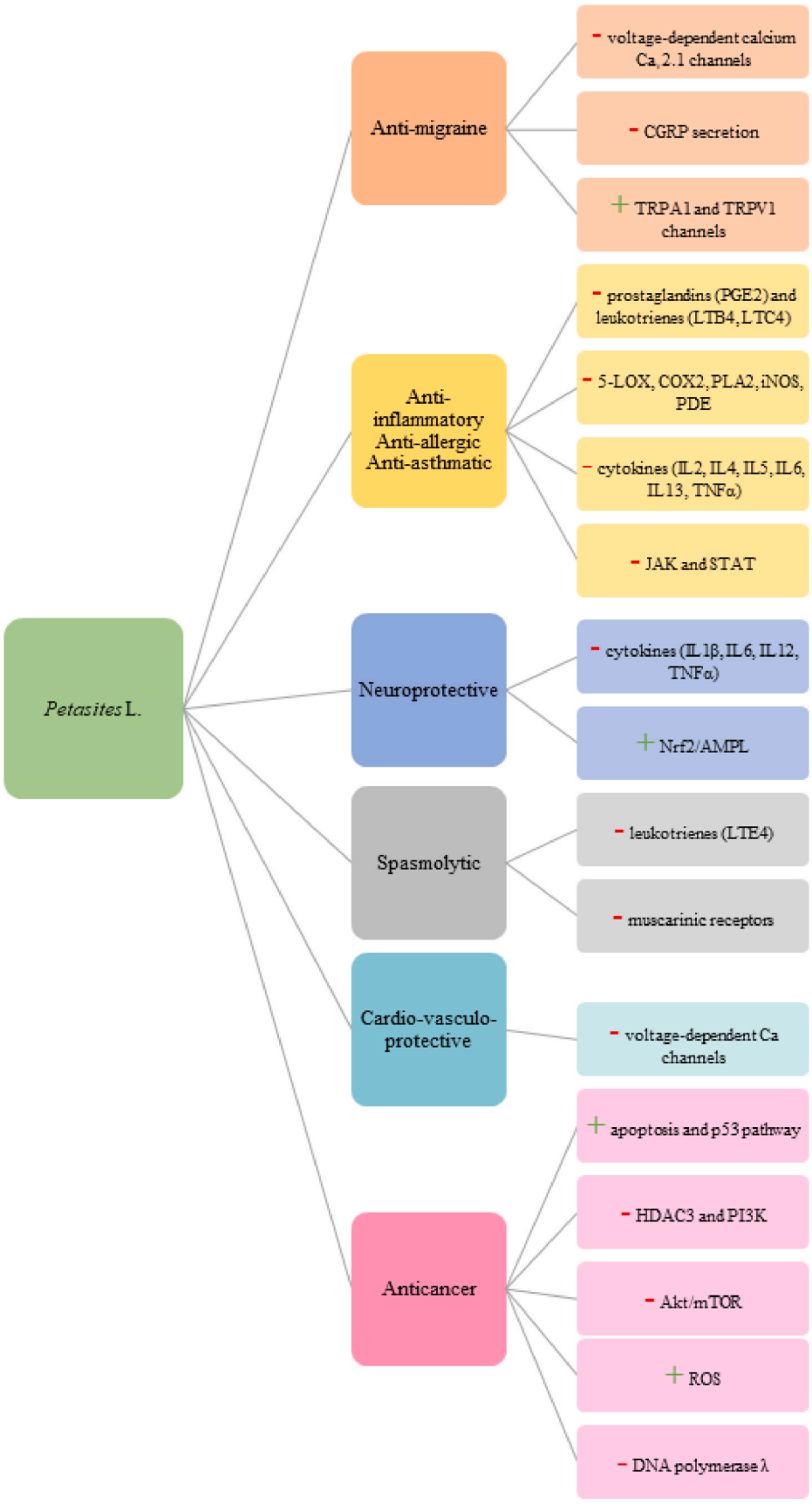

Fig. 4. Biological activites of the genus *Petasites* and their mechanisms of actions.

C_{max} levels in the *in vitro* study (Anderson et al., 2009). The clinical studies of the Ze 339 indicated rare side effects, e.g. eructation, liver dysfunction, nausea, abdominal pain and malaise (Blosa et al., 2021; Käufeler et al., 2006). Further investigations of the cytotoxicity of Ze 339 and its main constituents (e.g. petasin and isopetasin) showed higher toxicity in cell lines having a higher cytochrome activity (e.g. H-4-II-E rat cells). Furthermore, when using different S9 fractions (from rats, dogs and humans), it was noticed that cells from the rats were more sensitive to the toxic activity of Ze 339 than those from the dogs and humans (*in vitro*). Therefore, it can be concluded that the use of Ze 339 in the recommended doses (two or three tablets per day) is safe (Forsch et al., 2020).

6. Conclusions and future perspectives

This paper provides a complete overview of the *Petasites* (butterbur, Asteraceae) genus, covering up aspects related to their geographical distribution, ehtnobotanical uses, chemical composition and pharmacotoxicological relevance. Distributed all over Europe, Asia and North America, the butterbur rhizomes with roots and leaves have been used since Ancient times to treat central nervous system (migraine), respiratory (asthma, allergic rhinitis, bronchitis, spastic cough), cardiovascular (hypertension), gastrointestinal (ulcers) and genitourinary (dysmenorrhea) disorders. These ethnobothanical uses represented the starting point for the first pharmacological studies, with the anti-migraine and anti-allergic properties as the most researched therapeutic effects. On the quest to find out the key molecules responsible for the observed bioactivities, more than 200 different sesquiterpenes (eremophilanes, furanoeremophilanes, bakkenolides), 50 phenolic compounds (phenolic acids, flavonoids, lignans) and volatile compounds (monoterpenes, sesquiterpenes) have been reported within the genus. Nonetheless, the phytochemical studies also revealed a downside – the presence of PAs, a class of specialized metabolites incriminated over the years for a multi-level toxicity. To overcome this issue, PAs-free chemotypes or PAs-depleted plant materials have been developed, creating the propice background for the first two ever market-approved drugs, Tesalin® – Ze 339 and Petadolex®, to be formulated with PAs-free extracts with superior efficacy and safety profile.

Despite the great body of knowledge on the chemical complexity of the butterbur, relevant chemotaxonomical investigations that make use of state-of-the-art spectro-chromatographic techniques (such as liquid chromatography hyphenated with high-resolution high-accurate tandem mass spectrometry) or isolation studies based on modern separation technologies (e.g. liquid-liquid chromatography) that can yield high recoveries of biologically active compounds with advanced purities and under high-throughput conditions are missing. Considering the phytochemical complexity and the polypharmacological potential, there is a growing research interest to extend the current therapeutical applications of *Petasites* preparations (anti-migraine, anti-allergic) to other human ailments, such as cardiovascular, malignant or microbial diseases. This research pathway is extremely important, especially in the recent context of the pandemic situation, when there is an imperious need for novel drug candidates. For instance, a preliminary study from 2022 has shown the antiviral effects of Ze 339 extract against the original SARS-CoV-2 virus (Wuhan) and its Delta variant, with IC_{50} values in SARS-CoV-2-infected Vero E6 cells comparable to remdesivir (Urda et al., 2022). These interesting properties were actually linked to already proven pharmacological effects of *P. hybridus* preparation, such as the modulation of the leukotriene synthesis or inhibition of the cytokine and chemokine response in nasal epithelial cells after viral mimetics stimulation, but more relevant research to evaluate the virus-host interactions is required.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Łukasz Kulinowski: Conceptualization, Data curation, Investigation, Software, Writing – original draft, Writing – review & editing. **Simon Vlad Luca:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. **Mirjana Minceva:** Formal analysis, Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing. **Krystyna Skalicka-Woźniak:** Formal analysis, Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jep.2022.115263.

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