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Ethnopharmacology, phytochemistry, and bioactivities of *Hieracium* L. and *Pilosella* Hill (Cichorieae, Asteraceae) species

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ABSTRACT

Ethnopharmacological relevance: Species of the genera *Hieracium* and *Pilosella* have been used in folk medicine for centuries in many parts of the world. The most wiedly used species is *P. officinarum* Vaill., included in the British and French Pharmacopoeias and sold as part of different commercial products.
Aim of the study: This review critically appraises the state-of-art of ethnopharmacology, specialised metabolites, bioactivities, and toxicity of members of *Hieracium* and *Pilosella*. Thus, gaps in scientific knowledge can be identified, also focusing on the development of products with pharmacological applications.
Materials and methods: Literature data of *Hieracium* and *Pilosella* species were mainly retrieved using different electronic databases such as Web of Science, Google Scholar, SciFinder, and PubMed. Other electronic resources included worldwide databases on ethnobotany, ethnopharmacology, and phytochemistry as well as government reports. Additionally, ancient texts and local information such as PhD and MSc theses, and books were consulted.
Results: A comprehensive analysis of the above mentioned sources revealed that only 34 out of the about 850 described species within the genera *Hieracium* and *Pilosella* have been reported in the context of traditional medicinal and ethnobotanical knowledge. The most often mentioned species is *P. officinarum* which has been widely used due to its diuretic effects. Other popular uses of *Hieracium* and *Pilosella* species include the treatment of skin, gastric, and intestinal diseases as well as respiratory and vascular ailments. Moreover, taxa of the two genera have been used as antiobiotics, antiseptics, antidiabetics, tonics, antiepileptics, antiphlogistics, emetics, wound healing drugs, astringents, haemostatics, and detoxificants. Finally, uses as a wild vegetable, fodder, plant for hunting and for charming rituals have also been mentioned. Phytochemical research revealed a richness in phenolic compounds and flavonoids. Moreover, coumarins, sesquiterpene lactones, terpenoids, and phytosterols were found in *Hieracium* and *Pilosella*. Experimental research conducted to support traditional uses mainly include *in vitro* tests, while assays based on *in vivo* models (including humans) are rather limited. Also, the vast majority of the studies did not identify the compounds responsible for the detected bioactivities. These established bioactivities include antidiabetic, anti-inflammatory, antibacterial, antimycotic, antiviral, cytotoxic and antiproliferative, diuretic, gastroprotective, antiepileptic, hypotensive, anti-obesity, arthropodicidal, and skin rejuvenating activities. Finally, limited toxicity studies have been conducted on members of *Hieracium* and *Pilosella*.
Conclusion: Taxa belonging to *Hieracium* and *Pilosella* have been confirmed to exert diuretic, anti-inflammatory, and antimicrobial effects, which is in line with their long traditional use. Moreover, the above mentioned fields of application hint to the most promising routes for the development of new marketable products. Nonetheless, additional data from an in-depth research on bio-active specialised metabolites such as sesquiterpenoids, sesquiterpene lactones, and coumarines, their bioactivities and toxicity, and their biosynthesis are still warranted.

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1. Introduction

The genera *Hieracium* L. and *Pilosella* Hill, in English both commonly called hawkweeds, include a complex of shrubs having mostly yellow flowerheads of strap-shaped florets (ligules) that normally grow in pastures distributed in the temperate areas of the world, excluding Australasia (Garland, 1990; Heywood, 1993; Gottschlich, 1996). A limited number of taxa have been introduced into North America and New Zealand; some of those are very invasive weeds (Travers, 1884; Wilson, 2006). Both genera were usually treated as two subgenera of the *Hieracium* genus. However, the main differences to separate *Pilosella* from *Hieracium* are based on morphological characters (presence/absence of stolons; pappus hairs in one row/pappus hairs in two rows) and differing mechanisms of apomixis: apospory/diplospory (Zidorn et al., 2002)). *Hieracium* and *Pilosella* are members of the tribe Cichorieae (Asteraceae) and comprise more than 850 wild species and subspecies, and over 10,000 micro-species, constituting two of the most diverse genera in the entire plant kingdom (Nägeli and Peter, 1885; Nägeli and Peter, 1886–1889; Zahn, 1921–1923; Gottschlich, 1996). For this reason, it is not surprising that species belonging to these genera had traditional uses in ethnopharmacology, as well as certain popularity as medicinal plant-derived products. For instance, *P. officinarum* Vaill. was introduced in the European Union market of medicinal herbs in 1986 due to its diuretic properties (EMA/HMPC/680374/2013). Along with the diuretic activity of this species, it has gained popularity as antioxidant due to its content in phenolic acids (Becker et al., 2017; Borisova-Jan et al., 2017). The current medicinal importance of *P. officinarum* is evidenced by the recent increasing number of scientific publications dealing with its therapeutical value, potential applications, and quality control of its commercial products. In this regard, Bilia et al. (2007) studied the stability and content of bioactive metabolites in herbal drug preparations (tinctures and mother tinctures) made from this species. Also, Borisova-Jan et al. (2017) developed an HPLC method for the quantitative determination of caffeoylquinic acid derivatives as characteristic constituents used as analytical markers in the quality control of the herbal material of *P. officinarum*. Fritz (2011) performed anatomical analyses of *P. officinarum* and *H. murorum* L. rhizomes as comparative studies on underground parts of medicinally used drugs and possible adulterations of these taxa. Also, Becker et al. (2017) demonstrated that grinding and sieving increased the bioactive compounds content and improved the antioxidant activity of *P. officinarum* powders when processing for commercial products supply. In addition, some patents are based on products containing *P. officinarum* in their formulas. For instance, a dermocosmetic mixture was patented for depigmentation in conditions of hyperchromia

(https://patents.google.com/patent/US5869031?oq = Pilosella + officinarum + patent). Bae et al. (2013) also patented a nine-plants mixture containing *H. albiflorum* Hook. aimed to treat allergic skin inflammations. Most of the works reported to date have been focused on *P. officinarum*. However, given the wide diversity within *Hieracium* and *Pilosella* genera, it is certainly interesting to investigate whether other species also present medicinal properties. In this regard, we address the following questions: What other species of *Hieracium* and *Pilosella* are traditionally used in folk medicine? What of these applications are supported by experimental proofs of biological activity? What do we know about specialised metabolites present in these species? Are these compounds responsible to exert the tested biological activities? In order to answer these questions, this work tries to undertake a comprehensive review on the ethnopharmacology, phytochemistry, biological, and pharmacological activities, as well as toxicology of members of the genera *Hieracium* and *Pilosella*. The traditional uses and how this information is linked to the known chemical constituents and proven bioactivities is critically discussed. Specific gaps in our knowledge, methodological considerations on the previously published studies, as well as future research lines and applications are also highlighted in order to gain new insights into the possible revalorisation of *Hieracium* and *Pilosella* as medicinal plants.

2. Methodology

Literature data were mainly retrieved using the electronic databases Web of Science, Google Scholar, SciFinder, and PubMed. The search strategy included the following keywords: *Hieracium*, *Pilosella*, ethnopharmacology, ethnomedicine, phytochemistry, bioactivities. For Web of Science the search strategy was based on the equation: ("ethnobotany" OR "phytochemistry" OR "ethnopharmacology" OR "bioactivities" OR "traditional uses" OR "secondary metabolism" OR "activity" OR "chemical composition" OR "natural products") AND ("*Hieracium*" OR "*Pilosella*"). Other electronic resources were checked and those where information on *Hieracium* and *Pilosella* species was found included: China National Knowledge Infrastructure (CNKI), Duke's Phytochemical and Ethnobotanical Databases, Ethnobotanical Database of Bangladesh (EDB), European Medicines Agency (EMA), International Ethnobotany Database (ebDB), Indian Medicinal Plants Database (FRLHT), Native American Ethnobotany Database (BRIT), Tesauro de Plantas Medicinales (Base Jerarquizada). Also, ancient texts (Lonitzer, 1551; Fuchs, 1557; Laguna, 1563; Matthiole, 1572; Lemery,

Fig. 1. Iconographies of pre-Linnean mentions of *Hieracium* and *Pilosella* species: (**a**) *H. parvum* (Fuchs, 1557), (**b**) *P. maior* (Lonitzer, 1551), (**c**) *P. minor* (Lonitzer, 1551), (**d**) *H. majus* (Matthiole, 1572), (**e**) *H. minus* (Matthiole, 1572).

1714; Scopoli, 1760) were consulted (Fig. 1). Local information such as PhD and MSc theses, books, etc. were also checked. All entries until December 2020 were considered. In the particular case of local traditional uses, only primary data revealed in ethnobotanical works were taken into account. Sources referring to traditional uses from other texts (e.g. reviews) were cited if the authors could not find the original reference. On the other hand, literature not providing additional information to articles previously found (e.g. same authors for the same research area and species) have not been cited. Exact spelling of scientific botanical names (including the abbreviations for botanical authors) was brought in line with standard usage recommended by "World Flora Online" (http://www.worldfloraonline.org/) or "Global Composite Checklist" (https://compositae.landcareresearch.co.nz/Default.aspx) and "Cichorieae Portal" (http://cichorieae.e-taxonomy.net/portal/node/8). The authors named the analysed taxa as they were found in the original reference and checked using the above-mentioned databases. Specialised metabolites reported for the genera *Hieracium* and *Pilosella* are displayed in Figs. 2–17. Substituents including sugar moieties used in abbreviated forms in Figs. 2–17 are depicted and explained in Fig. 18. Primary metabolites such as fatty acids, as well as monoterpenes detected by GC-MS analyses are not included (Feulner et al., 2009, 2011; Ugur et al., 2010). Clifford and Abrankó (2017) pointed out the ambiguous nature of the trivial name isochlorogenic acid refering to different (di-)caffeoylquinic acids in literature. Therefore, isochlorogenic acid was not depicted (Giner et al., 1992; Mañez et al., 1994). Both stereochemistry and linkage type of sugar moieties, especially those of xylosides and arabinosides, were in many cases insufficiently elucidated in the consulted literature. Hence, the abbreviated forms of the regarding substituents are marked with * when the exact stereochemistry was not provided by the authors. In case of glucose moieties often the linkage type, as well as the stereochemistry was partially stated. Due to the general domination of β-D-glucopyranoside in specialised metabolites, substances are stated as such if information on both stereochemistry and linkage type were partially provided by the authors.

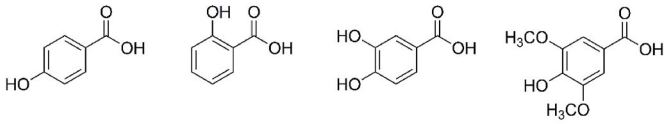
Fraisse et al. (2011) detected chlorogenic acid in their investigation of 18 taxa from the Asteraceae, which was stated as 3-caffeoylquinic acid. Current IUPAC numbering however translates chlorogenic acid to 5-caffeoylquinic acid (Clifford and Abrankó, 2017).

The review is divided into three main parts: 1) ethnopharmacology, 2) phytochemistry, and 3) bioactivities for species of the genera *Hieracium* and *Pilosella*.

3. Ethnopharmacology

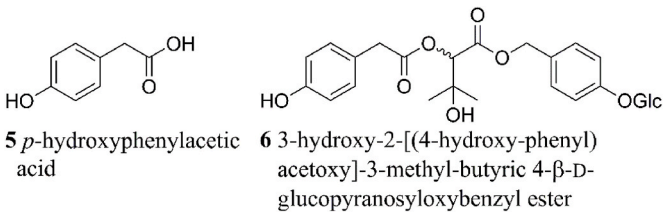
3.1. Pre-Linnean mentions of Hieracium and Pilosella: properties and uses

According to Pliny, the name *Hieracium* L. (hawk in Greek) is related to the use of this species' juice by the hawks to avoid blindness (Teixidor y Cos, 1871). Lonitzer (1551) mentioned that two species of *Hieracium* (Fig. 1): *H. majus* [UR] and *H. minus* [UR] exhibit refreshing and moderate astringent properties. According to this author, the distilled water (*aqua stillatitia*) of *Hieracium*, prepared with three or four tablespoons of the herb, was used internally to treat sores and fiery fevers. It also mitigates body aches and coughs and calms the heat. The *H. majus* juice was also used to stop the heartburn. The distilled water and juice of this plant were used to clean and heal the macules of the eyes, to cleanse



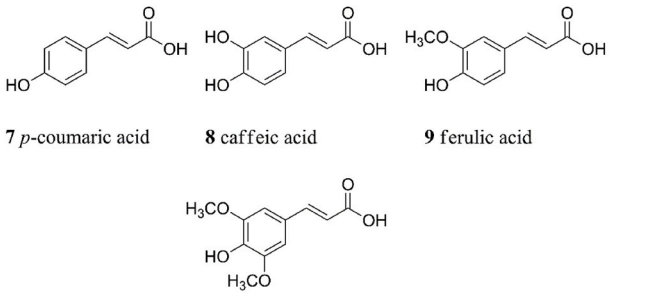
1 *p*-hydroxybenzoic acid **2** salicylic acid **3** protocatechuic acid **4** syringic acid

Fig. 2. Phenylmethanoids.



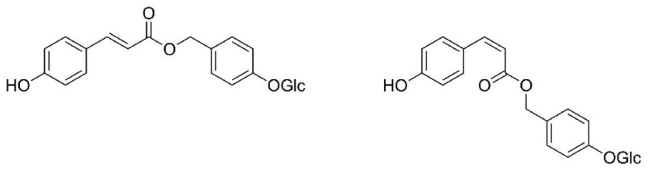
5 *p*-hydroxyphenylacetic acid **6** 3-hydroxy-2-[(4-hydroxy-phenyl) acetoxy]-3-methyl-butyric 4-β-D-glucopyranosyloxybenzyl ester

Fig. 3. Phenylethanoids.



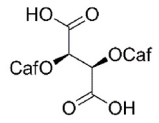
7 *p*-coumaric acid **8** caffeic acid **9** ferulic acid

10 sinapic acid



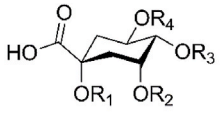
11 4-hydroxy-*E*-cinnamomic acid 4-β-D-glucopyranosyloxybenzyl ester **12** 4-hydroxy-*Z*-cinnamomic acid 4-β-D-glucopyranosyloxybenzyl ester

Fig. 4. Phenylpropanoids.



13 cichoric acid

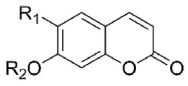
Fig. 5. Caffeoyl derivatives: cichoric acid.



14 R_1= R_2 = R_3= H, R_4= Caf; chlorogenic acid
15 R_1= R_2= H, R_3= R_4= Caf; 4,5-dicaffeoyl quinic acid
16 R_1= Caf, R_2= R_3= H, R_4= Caf; 1,5-dicaffeoyl quinic acid
17 R_1= H, R_2= Caf, R_3= H, R_4= Caf; 3,5-dicaffeoyl quinic acid
18 R_1= H, R_2= R_3= Caf, R_4= H; 3,4-dicaffeoyl quinic acid

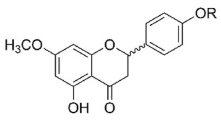
Fig. 6. Caffeoyl derivatives: chlorogenic acid and related compounds.

wrinkles and to treat the lack of visual acuity. However, Lonitzer (1551) pointed out that the juice was somewhat weaker. According to this author, the crushed leaves or the above-mentioned distilled water impregnated in fine linen are able to heal the black and inflamed pustules of the skin in any part of the body. The translation of Dioscorides made by Fuchs (1557) mentions that *H. parvum* [NV] has remarkable astringent and bitter properties. Moreover, this author cites Pliny and says that the juice is mixed with womens' milk in order to heal the eye's



19 R_1= R_2= H; umbelliferone
20 R_1= H, R_2= Glc; skimmin
21 R_1= OH, R_2= Glc; cichoriin
22 R_1= OCH_3, R_2= H; scopoletin

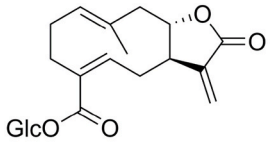
Fig. 7. Umbelliferone and related compounds.



23 R= H; sakuranetin
24 R= CH_3; naringenin 7,4'-*O*-methyl ether

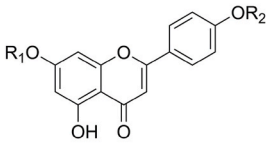
Fig. 8. Flavanones.

illnesses. The root, hanging from the neck, removes the darkness of the sight. In the translation of the Dioscorides *De Materia Médica* made by Laguna (1563) there are mentions of the medicinal properties of *H. majus* and *H. minus*. Both species are mentioned to be useful against inflammations and stomach pain. Also, a plaster made from the whole plant (including roots) is externally applied to treat scorpion stings. Matthiole (1572) also mentioned the properties to cure the eyes by these plants (Fig. 1) taking the stems and making a juice. This author also pointed out that this plant is an excellent remedy to cure the eye's

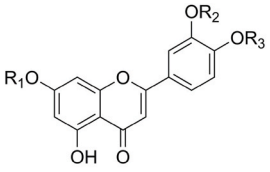


54 germacra-7H-1(10)*E*,4*Z*,11(13)-trien12,8-olide-15-oic acid (15→1)-D-glucopyranosyl ester

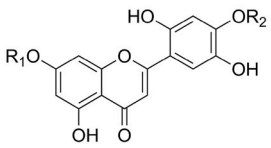
Fig. 11. Sesquiterpene lactones: 12,8-germacranolides.



25 R_1= R_2= H; apigenin
26 R_1= H, R_2= Glc; apigenin 4'-*O*-glucoside
27 R_1= H, R_2= Glu; apigenin 4'-*O*-glucuronide
28 R_1= R_2= CH_3; apigenin 7,4'-*O*-methyl ether
29 R_1= Ara*, R_2= H; apigenin 7-*O*-arabinoside
30 R_1= Glc, R_2= H; apigenin 7-*O*-glucoside
31 R_1= Glu*, R_2= H; apigenin 7-*O*-glucuronide
32 R_1= Rut*, R_2= H; apigenin 7-*O*-rutinoside

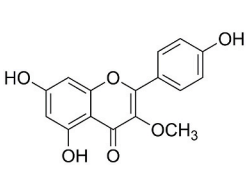


33 R_1= R_2= R_3= H; luteolin
34 R_1= R_2= H, R_3= CH_3; luteolin 4'-*O*-methyl ether
35 R_1= R_2= H, R_3= Ara*; luteolin 4'-*O*-arabinoside
36 R_1= R_2= H, R_3= Glc; luteolin 4'-*O*-glucoside
37 R_1=R_2=H, R_3=Glu; luteolin 4'-*O*-glucuronide
38 R_1= H, R_2= CH_3, R_3= H; luteolin 3'-*O*-methyl ether
39 R_1= Ara*, R_2= R_3= H; luteolin 7-*O*-arabinoside
40 R_1= Glc, R_2= R_3= H; luteolin 7-*O*-glucoside
41 R_1= Glu*, R_2= R_3= H; luteolin 7-*O*-glucuronide
42 R_1= Rha*, R_2= R_3= H; luteolin 7-*O*-rhamnoside
43 R_1=Rut, R_2=R_3=H; luteolin 7-*O*-rutinoside
44 R_1=Rha*(1→6)-Glc, R_2=R_3=H;
luteolin 7-*O*-β-D-xylosyl(1→6)-β-D-glucoside
45 R_1=Xyl*(1→6)-Glc, R_2=R_3=H;
luteolin 7-*O*-β-D-xylosyl(1→6)-β-D-glucoside

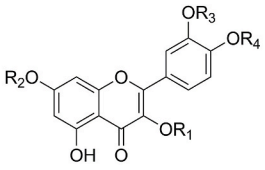


46 R_1= R_2= H; isoetin
47 R_1= H, R_2= Glc; isoetin 4'-*O*-glucoside
48 R_1= H, R_2= Glu; isoetin 4'-*O*-glucuronide
49 R_1= Glc, R_2= H; isoetin 7-*O*-glucoside

Fig. 9. Flavones.

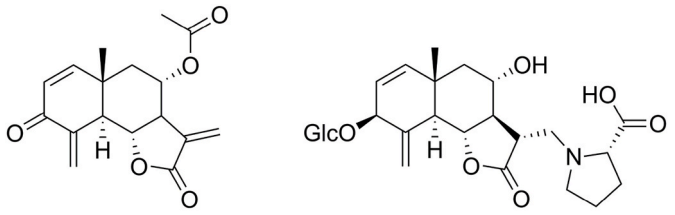


50 kaempferol 3-methyl ether (isokaempferide)



51 R_1= R_2= R_3= R_4= H; quercetin
52 R_1= R_2= H, R_3= CH_3, R_4= H; quercetin 3'-methyl ether (isorhamnetin)
53 R_1= Glc, R_2= R_3= R_4= H; quercetin 3-O-glucoside (isoquercetin)

Fig. 10. Flavonols.



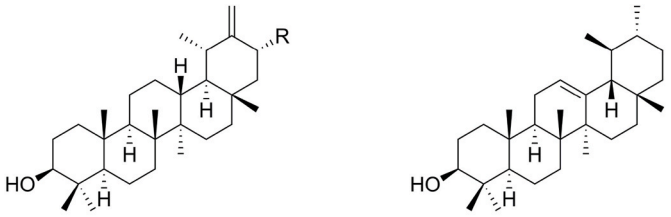
55 irazunolide **56** calophyllamine B

Fig. 12. Sesquiterpene lactones: eudesmanolides.

illnesses. Finally, Lemery (1714) stated that *H. minus*, among other Compositae named *dens leonis,* had several beneficial properties. It is written that *Hieracium* (*Hieracium dentis leonis folio obtuso majus C. B. Pit. Tourn..; Hieracium longius radicatum, Ger. Park. Raii. hift.* and *Hieracium macrorhizon* Tab.) contains a lot of phlegm and oil, poorly essential, and fixed salts. The medicine is used mainly from its root: it is humectant, refreshing and slightly astringent.

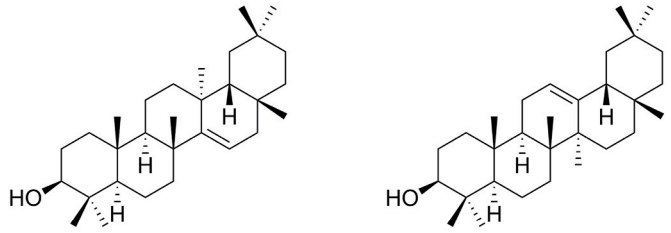
3.2. *Pilosella officinarum* Vaill.

The use of *P. officinarum* is quite ancient as it was revealed by the literature research. The first mention of *Hieracium pilosella* L. [SAN: *Pilosella officinarum* Vaill.] appears in the 12th Century by the German Benedictine abbess Saint Hildegard of the Rhine as a cardiotonic (Mulet, 1991). It has been also cited in the Myrepsos' *Dynameron*, a Byzantine medical compendium written in the 13th Century and containing remedies mostly inherited from the ancient classic Greek and imperial Roman periods (Valiakos et al., 2017): *H. pilosella* was prepared in a multi-plant refreshing beverage. Scopoli (1760) mentioned the medicinal properties of the decoction to treat joint problems and to heal hernia in children. The use of this species was extended in Europe along the Middle Age (Chevallier, 2000; Dal Cero, 2016), the Renaissance, Modern and Contemporary times (Dal Cero, 2016). It is currently included in the European (within the formulae of tinctures and mother tinctures), French and British Pharmacopoeias. It was introduced in the European Union market of medicinal herbs in 1986 (http://www.ema.europa.eu/) and it has become a popular commercial herbal remedy to treat urinary pathologies (Darias et al., 2008). Currently, it has a wide diffusion as a dietary supplement for slimming as well in Europe and South America (Bilia et al., 2007; Hurrell and Puentes, 2013). Preparations of this plant



64 R= H; taraxasterol
65 R= OH; 21α-hydroxy-taraxasterol
66 α-amyrin

Fig. 14. Pentacyclic terpenoids: ursane type.



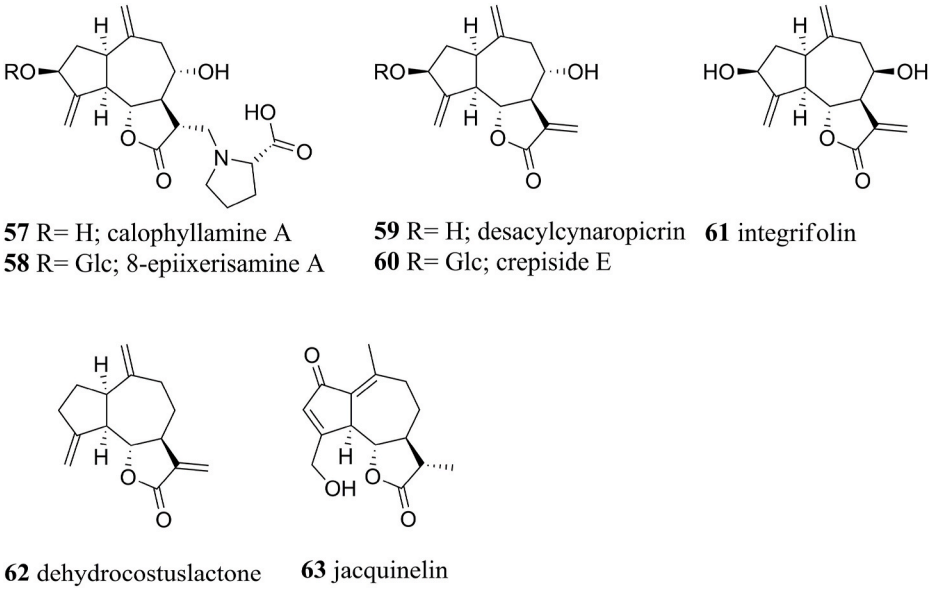
67 taraxerol **68** β-amyrin

Fig. 15. Pentacyclic terpenoids: oleane type.

are legally sold under different marketing formats all over the world: for instance, herbal tea for oral use, both in solid or liquid dosages, hydroalcohol extract, tinctures, hard and powdered herbs e.g. in capsules (Beaux et al., 1999; Bilia et al., 2007; Hurrell and Puentes, 2013; Becker et al., 2017; http://www.ema.europa.eu/). According to the therapeutic properties of *P. officinarum*, a wide array of ailments is treated with this species in traditional medicine. Among them, urinary diseases (including some renal troubles), skin problems, and gastric and intestinal illnesses are the most cited.

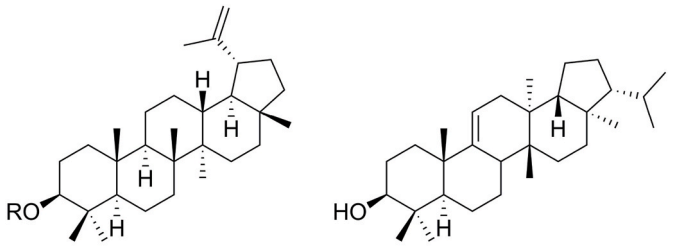
3.2.1. *Diuretic effect and its relation to urinary tract illnesses*

Font Quer (1981) compiled the remarkable diuretic properties of



57 R= H; calophyllamine A
58 R= Glc; 8-epiixerisamine A
59 R= H; desacylcynaropicrin
60 R= Glc; crepiside E
61 integrifolin
62 dehydrocostuslactone
63 jacquinelin

Fig. 13. Sesquiterpene lactones: 12,6-guaianolides.



69 R= H; lupeol
70 R= Ac; lupeol acetate

71 fern-7-en-3β-ol

Fig. 16. Pentacyclic terpenoids: lupane type.

H. pilosella infusion in its *Dioscorides Renovado*: 'According to doctor Leclerc the amount of urine can be doubled or tripled by the influence of this plant, along with the increase of chloride and urea eliminated. This is not influenced by the absorbed water with the decoction or infusion because little amounts of its liquid extract exert the same results. Therefore, it is a plant given against hydropathy, nephritis, ascites, edema, etc., and, in general, whenever it is convenient to rid the organism of waste products without irritating the renal epithelium'. The diuretic effect of the whole plant has been widely recorded in folk medicine in different points of the European geography such as the Spanish Regions of Extremadura, taken as infusion of aerial parts (Vázquez, 2008), in Aragonese Pyrenees taken as cold infusion (Villar et al., 1987), and in Forcall (Valencian Region) taken as a 150 mL decoction of the aerial parts at 3% one or two times per day (Mulet, 1991). In Campania Region, Italy (Guarino et al., 2008), the infusion of blooming plants is used as diuretic and to cause resorption of ascitic effusions of cardiac origin. In Southern Bosnia and Herzegovina, roots and aerial parts of *H. pilosella* are very appreciated in the treatment of kidney problems (to dissolve kidney stones) and urinary system diseases (mainly infections and inflammation processes such as prostate inflammation) or generally to improve urination (Redžić, 2010), as well as in Arkhangelsk Oblast, Northern Russia (Astrologova and Feklistov, 2002). In Deliblato Sand (Serbia) it is used to treat uremia taken as a tea of the fresh root, leaves and fruits prepared by boiling 10 g of herb in 100 g of water (Popović et al., 2014). In Bulgaria, Ivancheva and Stantcheva (2000) found its use as diuretic, taken as the infusion of aerial parts. Also, Efremov and Shreter (1996) reported its use to treat uremia and urolithiasis diseases in this country. The usual way to prepare the medicine in Bulgaria is taking the aerial parts or the whole blooming plant and prepare an infusion to be drunk (Ivancheva and Stantcheva, 2000; Leporati and Ivancheva, 2003; Astrologova and Feklistov, 2002; Redžić, 2007; Guarino et al., 2008; Popović et al., 2014). In German folk medicine, the alcoholic tincture of herbs is taken to treat stones in the kidney and bladder. In Turkey it is used as diuretic (U.S. Department of Agriculture, Agricultural Research Service, 1992–2016.).

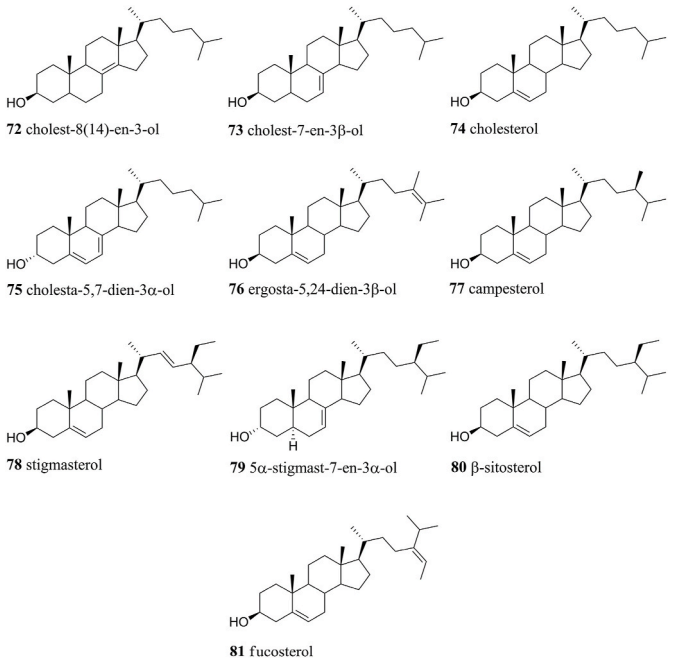


Fig. 17. Phytosterols.

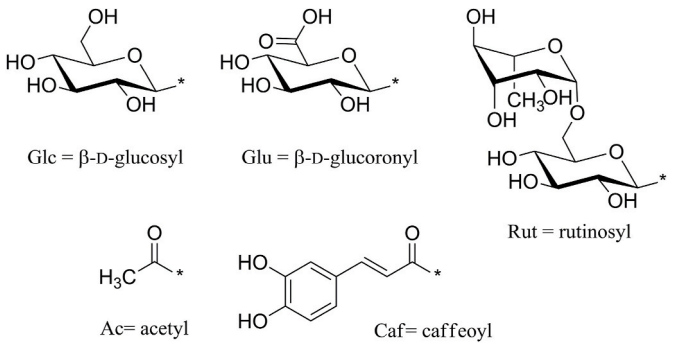


Fig. 18. Sugar moieties and substituents.

3.2.2. Skin problems

Different kind of skin problems are treated with *P. officinarum* preparations. An infusion of the whole plant is mentioned to be useful to heal extrenal and internal wounds in Font Quer (1981). Fresh leaves are directly applied (or after smashing them) to the skin in order to heal wounds in Liguria (Maccioni et al., 2004), Lombard Stelvio National Park in Alta Valtellina Region (Vitalini et al., 2015) and Waldensian valleys of the Western Alps (Bellia and Pieroni, 2015), all three places in Italy. Crushed leaves are also directly applied to heal wounds in Embún, Aragonese Pyrenees of Spain (Villar et al., 1987). To treat skin problems there are some other preparations reported: an infusion of the aerial parts is applied to heal wounds in Prokletije Mountains in Montenegro (Menković et al., 2011); a powder of the aerial part is prepared to treat and heal wounds and ulcers in Arkhangelsk Region, Russia (Astrologova and Feklistov, 2002). In Deliblato Sand (Serbia) a fresh juice of the whole plant is used to treat wounds (Popović et al., 2014). Also, mentions of the dermatological properties of the whole plant were found in Extremadura, Spain (Vázquez, 2008) but the mode of preparation and administration was not explained.

3.2.3. Gastric and intestinal illnesses

According to Font Quer (1981) *H. pilosella* has a strong astringent power and it is used against diarrhea and intestinal worms. It has been reported to be useful against dysentery, stomach and cholera spills, bloody sputum, and intestinal breaks. The infusion of the aerial part is employed as astringent in Bulgaria (Ivancheva and Stantcheva, 2000) and Spain (Rivera and Obón, 1993; Vázquez, 2008). It has also been reported that *H. pilosella* decoction is prepared against diarrhea using the whole plant in the Arkhangelsk Region of Russia (Astrologova and Feklistov, 2002). The Haudenosaunee natives (Iroquouis) of the New York State of the United States of America also used hawkweed against other general gastrointestinal ailments (Frey and Meyers, 2010). In the Balkans it was recorded that a tea made from aerial parts was used to treat diarrhea (Šarić-Kundalić et al., 2010). More specifically in this area, it is reported that an infusion from the whole plant is used against diarrhea in Deliblato Sand, Serbia (Popović et al., 2014) or in Eastern Serbia (Zlatović and Bogosavljević, 2014). Also, in Morocco *H. pilosella* is used to treat chronic diarrhea (Mas y Guindal, 1933). Sõukand and

Raal (2008) reported that it is a bitter herb with constringent activity and also increases salivation and biliary secretion. In Turkey it is used as astringent (U.S. Department of Agriculture, Agricultural Research Service, 1992–2016). However, the latter three sources did not specify the way of preparation and the plant organ used.

3.2.4. Respiratory and vascular ailments

Popović et al. (2014) compiled from Deliblato Sand in Serbia the antihemorrhagic and mucolytic properties of the whole's plant infusion (10 g herb per 100 g boiling water) used to treat bronchial catarrh and heavy bleeding. Šarić-Kundalić et al. (2010) stated that a tea of the aerial parts is used to treat pulmonary ailments in Bosnia-Herzegovina, and Zlatović and Bogosavljević (2014) reported the same for Eastern Serbia. A multi-herb remedy with hypotensive properties was reported in the traditional medicine of West Azerbaijan (Iran) by Miraldi et al. (2001). The preparation is made from glycerin extracts of *Chelidonium majus* L. dried herb 0.5 g, *Eupatorium cannabinum* L. dried herb 2.5 g, *Fumaria officinalis* L. dried herb 2.5 g, *H. pilosella* dried herb 3 g, *Frangula alnus* Mill. dried bark 3 g, glycerin 40 g, water up to 200 mL, and taken in doses of one teaspoonful before meals. In Extremadura (Spain), the whole plant was cited as useful to treat bronchitis (Vázquez, 2008) but the mode of preparation was not compiled. The following references include its therapeutic value but neither the part of the plant used, nor the mode of preparation and administration is mentioned in the original sources. In Cantalojas, Guadalajara (Spain) it was reported to be used as spasmolytic and expectorant (Gil, 1995). Astrologova and Feklistov (2002) found its use against tuberculosis in Arkhangelsk, Russia. Sõukand and Raal (2008) compiled that it is spasmolytic and expectorant, and it is internally employed in the treatment of asthma, bronchitis and cough and stops internal bleeding. In Pallars, Catalonia (Spain), it has been reported for its antigangrenous properties by Agelet and Vallès (2003) and in Morocco *H. pilosella* is used against passive hemorrhage (Mas y Guindal, 1933). In Turkey, it is cited to be used as expectorant, depurative, and haemostatic (U.S. Department of Agriculture, Agricultural Research Service, 1992–2016).

3.2.5. Uses against microorganisms

Font Quer (1981) stated that the most important property of *H. pilosella* is its antibiotic power. According to this author, it is used against Malta fever (brucellosis) and its pathogens. In this regard, the author also mentioned that the antibiotic substance has a powerful diffusive power and passes quickly to the serum and the urine, where it acts with great efficiency, specially in septicemia. Sõukand and Raal (2008) also mentioned that it is an antibiotic herb. Agelet et al. (2000) found that *H. pilosella* was grown in homegardens to be used as antimycotic in Montseny area of Catalonia (Spain). However, any of these works mentioned the part of the plant and the mode of preparation and administration. Internally, the leaf infusion has also been reported to be useful as buccopharyngic antiseptic in Catalonia (Bonet et al., 1999; Rigat et al., 2017).

3.2.6. Other uses in folk medicine

Some antiviral uses have been recorded. Rigat et al. (2017) found that a tisane was taken internally to treat measles in the Catalan Pyrenees (Ripollès County). Also, Gras et al. (2018) reported that a tisane was taken internally to treat chickenpox in Alt Empordà (Catalonia, Spain). However, any other information was not recorded by the authors in their ethnobotanical campaigns.

Finally, other punctual references include a diverse cast of uses for this species. Astrologova and Feklistov (2002) reported from Arkhangelsk Region in Russia its use against liver diseases (jaundice, tumors), stomach hyposecretion, against anemia, ascites and gynecological diseases and general metabolic disorders. In Ukraine, the leaves were used to reduce fever (Kolosova, 2005). The antipyretic properties were also mentioned by Leporati and Ivancheva (2003) from Italy. Font Quer (1981) mentioned that *H. pilosella* is useful to stop women's flow. A 150 mL decoction of the aerial parts at 2%, associated with *Urtica urens* L. (Urticaceae) and taken two or three times per day was recorded to be antipyretic in Besassal, Valencian Region, Spain (Mulet, 1991). In the Styrian Alps (Austria) it is used to wash the eyes (Lamprecht, 2012). The same application is recorded in Deliblato Sands in Serbia where the fresh juice of the whole plant serves not only for eye inflammation, but also for mouth rinsing and inflammation and almost all ailments of internal organs (Popović et al., 2014). It is also recorded that an infusion of inflorescence has a tonic effect (Efremov and Shreter, 1996). The same authors also pointed out that in German folk medicine an alcoholic tincture of this herb is taken at spermatherapy. The only citation that referred to its uses in the psycho-neuronal area is found in Denmark (Jäger et al., 2006) where an extract made from *H. pilosella* decoction in wine was reported to be useful against epilepsy. An infusion of the aerial part is also supplied to treat diabetes in Prokletije Mountains, Montenegro (Menković et al., 2011). Externally, an extract of *P. officinarum* is used to prepare a lotion to be applied in the bone fracture treatments (Heinrich and Jäger, 2015) and Adams et al. (2011) recorded that it was also externally used against malaria in the Renaissance. Finally, Sõukand and Raal (2008) compiled that it is known in folk medicine as an antiphlogistic, thus reducing inflammation. In Italy, Leporati and Ivancheva (2003) also cited it as anti-inflammatory. Vázquez (2008) mentioned its uses as antihelmintic and emenagogue in Extremadura (Spain).

The reported ways of preparation and dosage are quite diverse as well: from fresh plant preparations, infusions, and decoctions to more or less complex mixtures for internal use are documented. Font Quer (1981) recommends the use of fresh plants to prepare an infusion made from 100 g of the plant added to 1 L of boiled water. Then, the herb is macerated until the water gets cold. This preparation is sweetened with honey and taken three or four times per day for internal use. Popović et al. (2014) reported the use of fresh roots, leaves and fruits to prepare a tea (10 g of herbs and 100 g of boiled water). Fresh juice is also used as a remedy for eye and mouth inflammations and wounds, and for almost all ailments of internal organs, including mouth rinsing. Infusions and decoctions are mentioned by Efremov and Shreter (1996): an infusion of herbs is prepared with 10 g of crushed raw materials per 0.5 L of boiling water. Afterwards, a 1/4 glass of cooled infusion is taken 2–3 times a day. Finally, complex mixtures for internal use made from several medicinal plants are explained in section 3.3.4.

3.3. Other species

In this subsection, other species of *Hieracium* and *Pilosella* are reviewed and listed alphabetically, whereas non-identified plants at species levels are collectively exposed at the end. Whenever possible, the field of application and the part of the plant used as well as the mode of preparation and dosage were compiled (Table 1).

3.4. References from unidentified species

Mustafa et al. (2012) reported the topical use of the whole fresh plant of an unidentified *Hieracium* sp., locally named *bari i majasilit të lë kurës* ("leaves of Maya grass leaf"), mixed with milk cream and honey to treat the eczema in Gollak region of Kosovo. Also, leaves from an unidentified *Hieracium* taxon are directly applied to heal wounds in Asturias, Spain (San Miguel, 2004). Finally, a mixture of an unidentified *Hieracium* species along with *Rudbeckia* sp. was employed by Cherokee for "deer" disease (Shemluck, 1982) but neither the part of the plant was mentioned nor the mode of preparation and administration. The author also recorded that the juice made from two or three non determined plants of *Hieracium* was used as a chewing gum. An unidentified species of *Hieracium* from the peruvian Andes (Ancash, Perú) is traditionally used by the Quechua-speaking community to treat intestinal cramps, liver troubles, and stomach problems. The preparation that consists of boiled roots and leaves, with addition of some lime juice and alcohol is

Table 1
Traditional uses of *Hieracium* and *Pilosella* taxa in different countries/regions of the world.

Species	Part used	Traditional uses	Country/Region	References
Hieracium abscissum Less.	Not stated	Heal wounds	Mexico	Rodríguez-Chávez et al. (2017)
	Whole plant	Heal infected wounds	Mexico, Veracruz (Astacinga)	Navarrete et al. (2002)
H. adenocephalum (Sch.Bip.) Arv.-Touv	Not stated	Fodder	Perú (Apillapampa Andean Community)	Thomas et al. (2008)
H. amplexicaule L.	Leaves	An infusion is prepared to treat stomach pain and irritation as well as menstrual pain. It it used as anti-verrucous, healing, analgesic and anti-inflamatory (for dislocations, blows, etc.): a poultice is prepared by mixing up leaves with goat butter; this preparation is heated up to the boiling point and was externally applied.	Spain, Andalusia (Granada)	González-Tejero (1989)
H. aurantiacum L. [SAN: *Pilosella aurantiaca* (L.) F.W.Schultz & Sch.Bip.]	Not stated	Traditionally cultured in homegardens on farms	Austria (Eastern Tyrol)	Vogl-Lukasser and Vogl (2004)
	Flowers and leaves	Heart and eye problems (not mentioned mode of preparation and administration)	Austria (Styrian Alps)	Lamprecht (2012)
H. avilae Kunth	Leaves and stems	Leaves and stems are prepared by infusion or decoction to be taken as a diuretic. It is used to treat pain but any mention is made on the part of the plant, mode of preparation and administration for this use.	Colombia, Boyacá (Sogamoso)	Galvis and Torres (2017)
H. boliviense (Wedd.) Sch.Bip.	Not stated	Fodder	Perú (Apillapampa Andean Community)	Thomas et al. (2008)
H. caesium Fr.	Not stated	Antiepileptic	Denmark	Adams et al. (2012)
H. echioides Lumn. [SAN: *Pilosella echiodies* (Lumn.) F.W.Schultz & Sch.Bip.)]	Not stated	Emetic	Russia	Hapayev and Hapayeva (2015)
H. fendleri Sch.Bip.	Not stated	To treat urinary diseases	Mexico (Navajo Indians)	Wyman and Harris (1951)
	Not stated	A cold infusion of plant is prepared by hunters for anuria	Mexico (Tribe Ramah of Navajo Indians)	http://naeb.brit.org/uses/17171/
	Not stated	A tea made from a herbal mixture contanining this plant (along with *Agoseris aurantica* (Hook.) Greene, *Grindelia aphanactis* Rydb., *Ratibida* Raf. and *Thelesperma* Less.) is used as diuretic to treat veneral diseases, hematuria, pelvic pain, bladder stones and anuria. Also, another mixture of this species along with *Besseya plantaginea* (James) Rydb. is recorded to be used as diuretic.	Mexico (Navajo Indians)	Shemluck (1982)
	Leaves	Symbolic plant to give good luck in hunting by chewing leaves	Mexico (Navajo Indians)	Shemluck (1982)
H. gronovii L.	Leaves	Bruised leaves by allopathic physicians are applied topically for the removal of warts.	Not stated	Lemay (2004)
	Not stated	Stimulant	Not stated	Lemay (2004)
	Not stated	Medicinal	Cherokee indians	Cozzo (2004)
H. jalapensis (probably a mistake and it is *H. jalapense* Standl. & Steyerm. [UR: *H. irasuense* Benth.])	Not stated	Veterinary drug	Guatemala	https://phytochem.nal.usda.gov
H. lactucella Wallr. [SAN: *Pilosella lactucella* (Wallr.) P.D.Sell & C.West]	Not stated	Antiepileptic	Denmark	Adams et al. (2012)
H. lagopus D.Don.	Roots and leaves	To treat kidneys	Peru, Santiago de Chuco (Cachicadán)	Alipio (2019)
H. maculatum Schrank	Not stated	A decoction is prepared to heal wounds, cuts, and ulcers, as well as a laxative in cases of chronic constipation in old people. The infusion of this plant, combined with other species such as *Plantago major* L., has been also applied to treat tuberculosis, chronic bronchitis, and to quell stomach pains	Russia (Veps' Community living between Lake Ladoga, Lake Onega, and the White Sea)	Barnaulov and Barnaulov (2018)
H. mandonii (Sch.Bip.) Arv.-Touv.	Leaves, flowers and roots	To treat vesicle, stomach and matrix pains.	Bolivia, Cochabamba (Chorojo)	Hensen (1992)
	Not stated	Fodder	Bolivia, Cochabamba (Chorojo)	Hensen (1992)
	Not stated	To heal wounds in rural communities	Peru (Peruvian Andes)	Chang et al. (2014)
	Whole plant	Astringent	Argentina	Chang et al. (2014)
H. murorum L. s.l.	Not stated	An infusion is taken for pulmonary tuberculosis, bronchitis, jaundice, hepatitis, cholecystitis, gastritis, anemia, renal and cardiac edema	Russia	Hapayev and Hapayeva (2015)
	Leaves	Crushed leaves of this species are used externally as corticostatic and wound healing agent	Russia	Hapayev and Hapayeva (2015)
	Not stated	To treat epilepsy	Denmark	Adams et al. (2012)
H. neo-herrerae Zahn	Not stated	A decoction is applied topically as antiseptic for wounds and anti-gonorrhoea. The infusion is also taken to treat respiratory and renal affections.	Peru (Paruro Province, Cusco)	De Feo and Urrunaga Soria (2012)
H. pannosum Boiss.	Roots	The root of the plant is suspended in the sun, the resulting liquid (the milk) is dried up and the root is chewed for oral and dental health.	Turkey	Ari et al. (2015).

(*continued on next page*)

Table 1 (*continued*)

Species	Part used	Traditional uses	Country/Region	References
H. pazense S.F.Blake	Not stated	Fodder	Peru (Apillapampa Andean Community)	Thomas et al. (2008)
H. peruanum Fr.	Flowers and leaves	Used to clean infected wounds and pimples with pus by rural communities. 10 g of flowers and leaves of this species are prepared as infusion to clean the affected area, or a plaster is made by grinding the herb in a stone fuller to be applied in the affected area with clean tissue. For both cases, the treatment is applied twice per day during 3 days	Peru (Cajamarca)	Ayay (2017); Cueva (2019)
H. pilosissimum Friv. [*H. chalcidicum* subsp. *divaricatum* (Fr.) Greuter]	Not stated	To treat skin problems	Albania	González-Tejero et al. (2008)
	Fresh leaves	Fresh leaves are externally applied as haemostatic.	Albania (Northern Albanian Alps)	Pieroni et al. (2005)
H. pilosum Willd. ex Steud	Not stated	To treat jaundice	Russia	Hapayev and Hapayeva (2015)
H. plumulosum A.Kern. [SAN: *H. waldsteinii* subsp. *plumulosum* (A.Kern.) Freyn]	Not stated	For healing wounds	Montenegro (Prokletije)	Petrović et al. (1996)
H. pseudopilosella (Ten.) Nägeli & Peter [SAN: *Pilosella pseudopilosella* (Ten.) Soják]	Aerial parts	A decoction is prepared to treat externally hemorroids (baths), and it was also drunk to treat diarrhea and intestinal worms	Spain, Jaen (Cazorla Mountains)	Guzmán (1997).
H. scabrum Michx.	Leaves	Chewed leaves, or leaves prepared as a tea, were useful against diarrhea	USA (tribes of Rappahannock County)	Shemluck (1982); Toupal (2006); http://naeb.brit.org/uses/17174/
H. scabrum Michx. var. *scabrum*	Leaves	Used as an anti-diarrheal remedy in which the treatment involved either chewing the leaves or steeping them and drinking the "broth".	USA (Virginia State; Powhatan Indians)	Morgan and Perry (2010)
H. scouleri Hook.	Leaves and roots	The infusion of leaves and roots is taken as a general tonic	USA (Okanagan-Colville Native American Tribe)	http://naeb.brit.org/uses/17170/
H. sherwalii Abedin & Zamarrud (NV)	Fresh aerial parts	As a wild fodder: cattles were fed with fresh aerial parts of this species, among other plants	Pakistan (Gilgit)	Abbas et al. (2014)
H. tandilense Sleumer	Not stated	Astringent	Argentina	Barboza et al. (2009)
H. umbellatum L. (including *H. canadense* Michx.)	Leaves and roots	Against lung tuberculosis, hemeerolopia ("night blindness"), for strengthening the gums, and against rabies and conjunctivitis. A decoction is prepared to treat dermatoses. The infusion of rhizomes is used as an astringent and haemostatic. The leaves were employed to heal wounds. Poultices are prepared as analgesic for rheumatism and to treat tumors	Russia (Arkhangelsk Region)	Astrologova and Feklistov (2002)
	Not stated	External use to treat hernia and inflammations	Russia	Hapayev and Hapayeva (2015)
	Sprouts	Sprouts of this species are cooked as seasonal vegetables in traditional buddhist food, where it is also recorded due to its medicinal uses to treat urinary tract infections, stomach ache, dysentery, furuncles, tuberculosis, cough and also for detoxification	Korea	Kim et al. (2006) and references therein
	Roots, stems or flowers	Milky roots, stems or flowers were nibbled on by hunters to prepare a hunting lure (sometimes along with charming rituals), to mimic suckling fawns and to attract does by Northern Tribes	USA and Canada (pre-Columbian Amerindian tribe Ojibwe)	Smith (1932); Shemluck (1982)
H. venosum L.	Roots and leaves	To treat haemoptysis and chronic catarrh due to its mild astringent and expectorant properties. A warm infusion of the leaves is prepared to treat sore eyes. To treat bowel complaints a tea is made from a mixture of the *H. venosum* and *Mitchella repens* L. roots. It was also given against scrofula and amenorrhea, but it is stated that is not especially powerful in this regard. It was registered to have reputed power in curing the bites of venomous snakes.	North America (Cherokee tribes)	Eglesfeld (1847)
		To treat tuberculosis both in humans and in cattle		Endersby (2012)
	Not generally stated	A decoction of *H. venosum*, *Aureolaria flava* (L.) B. Boivin and *Eupatorium purpureum* L. was useful to treat milky urine. Roots were employed against diarrhea in a mixture of unidentified plants	North America (Cherokee tribes)	Cozzo (2004)
	Not stated	Antidiarrheal	USA, Virginia (Pouhatan Indians)	Morgan and Perry (2010)
	Not stated	To treat polyps from the nose	USA	https://phytochem.nal.usda.gov
	Leaves	The fresh juice of leaves is used in veterinary to remove warts	Not stated	Wynn and Fougère (2007)
H. cf. *virosum* Pall.	Not stated	Aperient and vulnerary	Spain	https://phytochem.nal.usda.gov
	Not stated	Medicinal	India	http://medicinalplants.in/showfulllist/folk

(*continued on next page*)

Table 1 (*continued*)

Species	Part used	Traditional uses	Country/Region	References
H. vulgatum Fr [SAN: *H. lachenalii* C.C. Gmel. s.l.]	Not stated	The young plant is eaten as vegetable and also considered as blood purifier, whereas adult plants are used as fodder	Pakistan, Gilgit-Baltistan (Astore Valley)	Noor et al. (2012)
	Not stated	Medicinal	India	http://medicinalplants.in/showfulllist/folk
Pilosella capitata (Arv.-Touv.) Mateo [probably *P. capillata* (Arv.-Touv.) Mateo which is a synonym of *P. tardans* (Peter) Soják]	Not stated	It was recorded a popular name as "margarita" (marigold) but any specific use was not stated	Spain (Segura and Alcaraz Mountains)	Verde et al. (1998)

used in case of intestinal spasms (Gonzales de la Cruz et al., 2014). Finally, there are some references to the use of unidentified *Hieracium* materials by Native American Tribes in the Native American Ethnobotany database (http://naeb.brit.org/). Iroquois prepared a poultice of *Hieracium* sp. roots to be applied to sores close to the bone and to treat tuberculosis by means of consumption of a decoction made from plants. The tribe Thompson prepared a gummy juice to be chewed to cleanse the mouth, or to chew for pleasure, and roots were used as a charm for unspecified purpose. Leaves of *Hieracium* sp. are gathered as leafy vegetables for salads in Styria, Austria (Schunko and Vogl, 2010) or to feed the cattle in Azuay, Ecuador (Jijón, 2015). Also, an infusion made from *Hieracium* sp. leaves were used as a drink or to have shower in Central Andes, Peru (Pancorbo-Olivera et al., 2020) but the specific purpose or property was not stated.

4. Specialised metabolites (Figs. 2–18)

Hieracium and *Pilosella* are firmly nested within the Cichorieae tribe of the Asteraceae family and thus also share the main phytochemical features of this tribe: occurrence of various types of phenolic acids, flavonoids aglyca and glycosides, simple coumarins, sesquiterpene lactones, and triterpenes (Kilian et al., 2009; Zidorn et al., 2002; Sareedenchai and Zidorn, 2010). In this section, we detail the natural compounds that are described in both genera. So far, specialised metabolites have been reported by means of HPLC, HPLC-DAD, TLC, NMR, NMR-HRMS and LC-MS; more than 50 were identified only by GC-MS (Feulner et al., 2009, 2011; Ugur et al., 2010), and more than 30 were detected but not determined.

4.1. Phenolic compounds

Several reports on the phytochemistry of *Hieracium* and *Pilosella* are focused on phenolics; phenolics have been reported from more than 80 Central and Eastern European taxa and other territories such as the Iberian Peninsula, New Zealand, etc. The most common phenolic compounds found in these genera are: chlorogenic; 3,5-dicaffeoylquinic; 1,5-dicaffeoylquinic and 4,5-dicaffeoylquinic acids. For more detailed information on the phenolic composition of the *Hieracium* and *Pilosella* complex see Tables 2 and 3.

4.2. Coumarins

Biogenetically closely related to phenolic acids are coumarins which have been studied in 30 taxa of *Hieracium* by Bate-Smith et al. (1968). Umbelliferone was found in *H. pilosella*, *P. hoppenana* (Schult.) F.W. Schultz & Sch.Bip., and *P. peleteriana* (Mérat) F.W.Schultz & Sch.Bip., as well as in 6 intermediate taxa. Giner et al. (1992) obtained only trace amounts of scopoletin in *H. compositum* Lapeyr. More recently, umbelliferone 7-*O*-β-glycopyranoside (skimmin) and esculetin 7-*O*-β-glycopyranoside (cichoriin) were obtained from *P. officinarum* (Gawrońska-Grzywacz and Krzaczek, 2009). Umbelliferone was found in low amounts in different plant extracts made from the whole plant of *H. pilosella* [SAN: *P. officinarum*] by Stanojević et al. (2009) and in acetone:water extracts by Mertens et al. (2018). In a previous study Stanojević et al. (2008) obtained the highest amount of umbelliferone in a dichloromethane:methanol extract of *H. pilosella* [SAN: *P. officinarum*].

4.3. Flavonoids

According to Sareedenchai and Zidorn (2010), the most common flavonoids in the Cichorieae are luteolin 7-*O*-glucoside, luteolin, luteolin 7-*O*-glucuronide, luteolin 4′-*O*-glucoside, apigenin 7-*O*-glucoside, apigenin 4′-*O*-glucuronide and apigenin. As expected these compounds are also widespread in *Hieracium* and *Pilosella* (Tables 4 and 5). So far, the flavonoid composition in these genera is quite well known for Eastern and Central European taxa, and some citations are done for materials studied in Canada, Iberian Peninsula, France, etc. as it is shown in Tables 4 and 5, respectively. In the supplementary data of a study on the diuretic activity of a dietary supplement (XANADREN MD®, Promopharma SPA) *P. officinarum* is mentioned to contain vitexin, an apigenin derivative (Perna et al., 2020). However, as any further information on the identification on this substance is missing, it is not included in the respective tables.

4.4. Sesquiterpene lactones

Sesquiterpene lactones (SL) have also been found in the genus *Hieracium*: the eudesmanolide irazunolide (Fig. 12) has been reported from the Costa Rican taxon *H. irasuense* Benth. [AN] (Hasbun et al., 1982), and a germacranolide (germacra-7αH-1(10)*E*,4Z,11(13)-trien-12,8α-olide-15-oic acid (15 → 1)-β-D-glucopyranosyl ester) in *H. murorum* (Zidorn et al., 2001). Also, desacylcynaropicrin was isolated from the chloroform extract of aerial parts of *H. bectauatensis* Kupr. [NCT] (Kanafin et al., 2015) and jacquinelin from the same species by Adekenov (2015). Finally, Milutinović et al. (2018a) isolated four SLs from methanol extract of *H. calophyllum* R.Uechtr. flowering heads and performed qualitative and quantitative analysis of theses SLs in methanol extracts from aerial flowering parts of 28 *Hieracium* species from the Balkan Peninsula (the studied species are listed in Tables 2 and 4). The authors found the guaianolide crepiside E in all species, except in *H. orieni* A.Kern. [SAN: *H. gymnocephalum* Griseb. ex Pant.] and *H. macrodontoides* (Zahn) Zahn, in variable amounts but in 21 of them it was the most abundant SL. Also, three previously undescribed amino acid-SLs conjugates were found. Firstly, the eudesmanolide calophyllamine B was detected in 14 species but in very low amounts, generally. Secondly, two guaianolides (calophyllamine A and 8-epiixerisamine A) were identified in all samples but in *H. orieni*, *H. mokragorae* (Nägeli & Peter) Freyn [SAN: *H. pannosum* subsp. *mokragorae* Nägeli & Peter], *H. albopellitum* (Zahn) Niketić [SAN: *H. thapsiformoides* subsp. *albopellitum* (Zahn) Greuter], *H. tommassinianum* K.Malý and *H. macrodontoides* they were found in traces. Finally, integrifolin was described from *P. officinarum* commercial material by Mertens et al. (2018).

4.5. Terpenoids

The triterpenes α- and β-amyrin as well as 21α-hydroxy-taraxasterol (18α,19α-urs-20(30)-en-3β,21α-diol) were present in *H. gymnocephalum* aerial flowering parts chloroform extract (Petrović et al., 1999a). Lupeol

Table 2
Phenolic composition of the different reviewed species of *Hieracium* L. The solvents used to prepare the extracts are, as follows: **CH_3OH**: methanol; **$(CH_3)_2CO$:** acetone; **H_2O:** distilled water; **CH_2Cl_2:** dichloromethane; **n-BuOH**: n-butanol; **C_2H_5OH:** ethanol; **$(C_2H_5)_2O$**: diethyl ether; **$C_4H_8O_2$:** ethyl ethanoate.

Species	Extraction solvent	Plant organ	Compounds	References
Hieracium albopellitum (Zahn) Niketić [SAN: *H. thapsiformoides* subsp. *albopellitum* (Zahn) Greuter]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. alpinum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. amplexicaule L.	$CH_2Cl_2/CH_3OH/(C_2H_5)_2O$/*n*-BuOH + C_2H_5OH	aerial parts	chlorogenic acid; isochlorogenic acid; dicaffeoylquinic acid; protocatechuic acid	Mañez et al. (1994)
H. amplexicaule	CH_3OH	aerial parts	chlorogenic acid; isochlorogenic acid; 3,4-dicaffeoylquinic acid; protocatechuic acid	Giner et al. (1992)
H. amplexicaule	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. anastrum (Degen & Zahn) Niketić [SAN: *H. pichleri* subsp. *anastrum* (Degen & Zahn) Zahn]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. atratum Fr.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. bifidum Koch subsp. *caesiiflorum* (Norrl.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. blecicii Niketić [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid, 1,5-dicaffeoylquinic acid, caffeic acid	Petrović et al. (1999b)
H. blecicii	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. bocconei Griseb. subsp. *bocconei* [SAN: *H. bocconei* Griseb.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. bornmuelleri Freyn [SAN: *H. pannosum* subsp. *bornmuelleri* (Freyn) Murr & Zahn]	CH_3OH/H_2O	aerial parts and root	chlorogenic acid	Bakar et al. (2015)
H. borsanum Zahn ex Mráz	CH_3OH	Leaves	chlorogenic acid; 3,5-dicaffeoylquinic acid	Švehlíková et al. (2002)
H. brevifolium Tausch	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. calophyllum R.Uechtr.	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. coloriscapum Rohlena & Zahn	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; caffeic acid	Petrović et al. (1999b)
H. coloriscapum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. compositum Lapeyr.	$CH_2Cl_2/CH_3OH/(C_2H_5)_2O$/*n*-BuOH + C_2H_5OH	aerial parts	chlorogenic acid; isochlorogenic acid; dicaffeoylquinic acid; protocatechuic acid	Mañez et al. (1994)
H. compositum	CH_3OH	aerial parts	chlorogenic acid; isochlorogenic acid; 3,4-dicaffeoylquinic acid; protocatechuic acid	Giner et al. (1992)
H. dentatum s.l. Hoppe	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. durmitoricum (Rohlena & Zahn) Niketić [SAN: *H. stirovacense* subsp. *durmitoricum* (Rohlena & Zahn) Greuter]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. glabratum Willd. ex Froel.	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid	Milutinović et al. (2018b)
H. glaucinum Jord.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. glaucinum subsp. *basalticum* (Sch.Bip.) J.Duvign.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. glaucinum subsp. *heteroschistum* (Zahn) Soó	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. gorfenianum Bornm. & Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. guentheri-beckii Zahn	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; caffeic acid 1,5-dicaffeoylquinic acid;	Petrović et al. (1999b)
H. guentheri-beckii	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. gymnocephalum Griseb. ex Pant.	CH_3OH	aerial flowering parts	chlorogenic acid; caffeic acid; 1,5-dicaffeoylquinic acid; 3,5-dicaffeoylquinic acid	Petrović et al. (1999a,b)

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Table 2 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
H. gymnocephalum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. inuloides Tausch subsp. *tridentatifolium* (Zahn) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. jurassicum Griseb.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. kofelicum Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. kuekenthalianum (Zahn) Zahn [SAN: *H. tephrosoma* subsp. *kuekenthalianum* (Zahn) Zahn]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. laevigatum Willd. subsp. *laevigatum* [SAN: *H. laevigatum* Froel.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. lycopifolium Froel. subsp. *lycopifolium* [SAN: *H. lycopifolium* Froel.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. macilentum Fr. [SAN: *H. froelichianum* subsp. *macilentum* (Fr.) Gottschl. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. macrodontoides (Zahn) Zahn	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. maculatum subsp. *commixtum* (Jord.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. maculatum Schrank subsp. *maculatum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. mirificissimum Rohlena & Zahn [SAN: *H. stirovacense* subsp. *mirificissimum* (Rohlena & Zahn) Greuter]	CH_3OH	aerial flowering parts	chlorogenic acid; caffeoylquinic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid	Milutinović et al. (2018b)
H. mokragorae (Nägeli & Peter) Freyn [SAN: *H. pannosum* subsp. *mokragorae* Nägeli & Peter]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. murorum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	4,5-O-dicaffeoylquinic acid	Zidorn et al. (2002)
H. naegelianum Pančić	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeic acid	Petrović et al. (1999b)
H. naegelianum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. neilreichii Beck [SAN: *H. pallescens* Waldst. & Kit. subsp. *neilreichii* (Beck) Greuter]	CH_3OH	aerial flowering parts	chlorogenic acid; caffeoylquinic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid	Milutinović et al. (2018b)
H. onosmoides subsp. *crinigerum* (Fr.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. orieni A. Kern. [SAN: *H. gymnocephalum* Griseb. ex Pant.]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. oxyodon subsp. *muretii* (Gremli) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. pannosum Boiss.	CH_3OH	flowers, root and leaf	chlorogenic acid; caffeic acid	Gökbulut et al. (2017)
H. pannosum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. paratrichum Niketić [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. picroides Vill.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. piliferum Hoppe subsp. *piliferum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. pilosum Schleich. ex Froel.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. pilosum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. plumulosum A.Kern. [SAN: *H. waldsteinii* Tausch subsp. *plumulosum* (A.Kern.) Freyn]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. porrifolium L. subsp. *porrifolium*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. pospichalii Zahn subsp. *pospichalii*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. prenanthoides subsp. *bupleurifolioides* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. pseudocaesium Degen & Zahn	CH_3OH	leaves	chlorogenic acid; 3,5-dicaffeoylquinic acid	Švehlíková et al. (2002)

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Table 2 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
H. pseudoschenkii (Rohlena & Zahn) Niketić [SAN: *H. bupleuroides* bellarf. ex Willd. subsp. *pseudoschenkii* Rohlena & Zahn]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. pyricephalum Niketić [NV]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. racemosum Waldst. & Kit. ex Willd.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. ratezaticum (Nyáz. & Zahn) Mráz [UR]	CH_3OH	leaves	chlorogenic acid; 3,5-dicaffeoylquinic acid	Švehlíková et al. (2002)
H. rohacsense Kit ex. Kit	CH_3OH	leaves	chlorogenic acid; 3,5-dicaffeoylquinic acid	Švehlíková et al. (2002)
H. rotundatum Kit. ex Schult. [SAN: *H. transylvanicum* Heuff.]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeic acid	Petrović et al. (1999b)
H. sabaudum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. saxifragum subsp. *vulpii* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. scheppigianum Freyn	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid; dicaffeoylquinic acid	Milutinović et al. (2018b)
H. schmidtii subsp. *graniticum* (Sch.Bip.) Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. scorzonerifolium Vill.	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. sommerfeltii Lindeb.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. sparsum subsp. *vierhapperi* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. spirocaule Niketić [NV]	CH_3OH	aerial flowering parts	chlorogenic acid; caffeoylquinic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid	Milutinović et al. (2018b)
H. suborieni (Zahn) P.D.Sell & C.West. [SAN: *H. waldsteinii* Tausch subsp. *suborieni* Zahn]	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeic acid	Petrović et al. (1999b)
H. tommasinianum K.Malý	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. umbellatum L. subsp. *umbellatum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. valdepilosum Vill. s.l.	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. venostorum (Zahn) Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. vetteri Ronniger	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. villosum Jacq.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)
H. villosum	CH_3OH	aerial flowering parts	chlorogenic acid; 3,5-dicaffeoylquinic acid; 1,5-dicaffeoylquinic acid; caffeoylquinic acid	Milutinović et al. (2018b)
H. wiesbaurianum subsp. *semicinerascens* Bornm. & Zahn [SAN: *H. hypochoeroides* subsp. *semicinerascens* (Bornm. & Zahn) Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid; 3,5-dicaffeoylquinic acid; 4,5-dicaffeoylquinic acid	Zidorn et al. (2002)

[lup-20(29)-en-3β-ol], a pentacyclic lupane-type triterpene, was found in *P. officinarum* (Gawrońska-Grzywacz and Krzaczek, 2007). Petrović et al. (1996) isolated the triterpenoids lupeol acetate and β-amyrin from the refined chloroform extract of *H. plumulosum* A.Kern. [SAN: *H. waldsteinii* subsp. *plumulosum* (A.Kern.) Freyn]. Gawrońska-Grzywacz and Krzaczek (2007) studied the triterpenoid composition in herb, inflorescences, and rhizomes with roots of *H. pilosella* extracted with petroleum ether and found the following triterpenoids: α- and β-amyrin, taraxerol, taraxasterol, and fern-7-en-3β-ol. Taraxasterol was dominant in inflorescences, whereas β-amyrin was in herb and rhizomes with roots. Ugur et al. (2010) identified the terpenoid caryophyllene oxide and the monoterpenoid carvacrol as a major component in the chloroform extract of *P. sandrasica* Hartvig & Strid [SAN: *P. auriculoides* (Láng) Arv.-Touv.]. Additionally, these authors also found the cycloaromadendrane sesquiterpenoid aromadendrene epoxide. Milutinović et al. (2020) detected α- and β-amyrin, their respective acetates, as well as lupeol acetate in the dichloromethane extract of the aerial flowering parts of *H. scheppigianum* Freyn.

4.6. Phytosterols

Sterol acetates and free sterols were investigated in detail in inflorescences extracted with petroleum ether of *H. pilosella* by Gawrońska-Grywacz and Krzaczek (2006). Cholesterol, fucosterol and β-sitosterol were dominant whereas cholest-8(14)-en-3β-ol, cholesta-5,7-dien-3β-ol, cholest-7-en-3β-ol, ergosta-5,24-dien-3β-ol, campesterol, stigmasterol, 5α-stigmast-7-en-3α-ol were identified in lesser amounts (<10% total fraction). According to these authors, the inflorescences of this species were the richest part in sterols (0.26%) whereas the content decreased in herb up to 0.24% and in roots up to 0.16% (Krzaczek et al.,

Table 3
Phenolic composition of the different reviewed species of *Pilosella* Hill. The solvents used to prepare the extracts are, as follows: **CH_3OH**: methanol; **$(CH_3)_2CO$:** acetone; **H_2O:** distilled water; **CH_2Cl_2:** dichloromethane; **n-BuOH**: n-butanol; **C_2H_5OH:** ethanol; **$(C_2H_5)_2O$**: diethyl ether; **$C_4H_8O_2$:** ethyl ethanoate.

Species	Extraction solvent	Plant organ	Compounds	References
Pilosella hoppeana subsp. *testimonialis* (Nägeli ex Peter) Soják [SAN: *P. testimonialis* (Nägeli ex J.Hofm.) Gottschl.]	CH_3OH/H_2O	aerial parts and root	chlorogenic acid	Bakar et al. (2015)
P. hoppeana subsp. *testimonialis*	CH_3OH	aerial parts	syringaldehyde, sinapic acid, benzoic acid	Aliyazicioğlu et al. (2019)
P. officinarum Vaill.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	chlorogenic acid, 3,5-dicaffeoylquinic acid and 4,5-dicaffeoyl-quinic acid	Zidorn et al. (2005)
P. officinarum	C_2H_5OH/H_2O	aerial parts	3,5-dicaffeoylquinic acid; chlorogenic acid; 1,5-dicaffeoyl-quinic acid; 4,5-dicaffeoylquinic acid	Fraisse et al. (2011)
P. officinarum	C_2H_5OH	whole plant	caffeic acid; ferulic acid; *p*-hydroxybenzoic acid; *p*-hydroxyphenylacetic acid; protocatechuic acid; *p*-coumaric acid; sinapic acid; salicylic acid; syringic acid	Dombrowicz et al. (1992)
P. officinarum	$(CH_3)_2CO/H_2O$	not specified	chlorogenic acid; 3,4-dicaffeoylquinic acid; 3,5-dicaffeoyl-quinic acid; 4,5-dicaffeoylquinic acid; caffeic acid	Mertens et al. (2018)
P. officinarum	CH_3OH	whole plant	caffeoylquinic acid and derivatives (chlorogenic acid)	Borisova-Jan et al. (2017)
P. officinarum	CH_3OH; C_2H_5OH; H_2O; CH_2Cl_2, CH_2Cl_2/CH_3OH; $C_4H_8O_2$	flowering heads	chlorogenic acid	Stanojević et al. (2008, 2009)

2002).

4.7. Other compounds (identified by GC-MS)

Feulner et al. (2009) studied the floral scent of 27 species of *Hieracium* (currently adscribed to the genus *Pilosella*). Firstly, these authors found the following monoterpenes: D-limonene and (*E*)-β-ocimene in all studied taxa except in *H. densiflorum* subsp. *cymosiforme* Nägeli & Peter [NV] and *H. lactucella* Wallr. [SAN: *Pilosella lactucella* (Wallr.) P.D.Sell & C.West] respectively; (*Z*)-β-ocimene in all samples but in *H. cymosum* L. subsp. *cymosum* [SAN: *P. cymosa* (L.) F.W.Schultz & Sch.Bip.] and *H. lactucella*. Other monoterpenes identified in this study are α-phellandrene in *H. piloselloides* subsp. *praealtum* (Vill. ex Gochnat) [NV], *H. densiflorum* subsp. *ochrocephaloides* (Harz & Zahn) [SAN: *P. densiflora* subsp. *ochrocephaloides* (Harz & Zahn) Gottschl.], *H. densiflorum* subsp. *umbelliferum* (Nägeli & Peter) Gottschl. [SAN: *P. densiflora* (Tausch) Soják], *H. bauhini* Schult. subsp. *hispidissimum* (Rehmann ex Nägeli & Peter) Zahn [SAN: *Pilosella bauhini* subsp. *bauhini*], *H. cymosum* subsp. *cymosum, H. lactucella, H. fallacinum* F.W.Schultz [SAN: *P. fallacina* (F.W. Schultz) F.W.Schultz], *H. spurium* subsp. *tubulatum* (Vollm.) Zahn [NV]; β-pinene in *H. densiflorum* subsp. *umbelliferum*, *H. bauhini* subsp. *hispidissimum, H. calodon* Tausch ex Peter subsp. *phyllophorum* Nägeli & Peter [SAN: *P. auriculoides* (Láng) Arv.-Touv.], *H. calodon* subsp. *pseudofallax* Touton, *H. cymosum* subsp. *cymosum*, *H. lactucella*, *H. schneidii* Schack & Zahn [SAN: *P. schneidii* (Schack & Zahn) S.Bräut. & Greuter]. L-Fenchone was found in *H. densiflorum* subsp. *umbelliferum, H. densiflorum* subsp. *bauhinifolium* Nägeli & Peter [NV] and *H. spurium* subsp. *tubuluatum,* while linalool was present in *H. densiflorum* subsp. *ochrocephaloides, H. densiflorum* subsp. *cymosiforme*. D-Verbenone was only found in *H. spurium* subsp. *tubuluatum.* The occurrence of eucalyptol was restricted to low amounts in *H. cymosum* subsp. *cymosum.* Myrthenal was only found in *H. bauhini* subsp. *hispidissimum.* Also, 3 unidentified monoterpenes were detected in low amounts in this study.

Secondly, these authors found ylangene and α-copaene as the most abundant sesquiterpenes in the studied samples. They also found β-bourbonene, (*Z*)-jasmone, (*E*)-β-carophyllene, (*E*)-α-bergamotene, α-gurjunene, aromadendrene, γ-muurolene, germacrene D, guaiene, α-selinene, amorphene, β-selinene, δ-cadinene and γ-cadinene, but in most cases they were present only in traces or very low amounts (<7%). Finally, 17 sesquiterpenes, present in only low amounts within the studied samples, remained unidentified.

Thirdly, they identified the following benzenoids: methyl salicylate in all studied samples except in *H. echioides* Lumn. subsp. *echioides* [SAN: *P. echioides* subsp. *echioides* (Lumn.) F.W.Schultz & Sch.Bip.], *H. lactucella* Wallr. and *H. spurium* subsp. *tubulatum* (Vollm.) Zahn; benzyl alcohol in *H. caespitosum* Dumort. subsp. *caespitosum*, *H. bauhinii* subsp. *hispidissimum* (Rehm.) Zahn, *H. echioides* subsp. *echioides*, *H. cymosum* subsp. *cymosum*, *H. fallacinum*, *H. aurantiacum* L. subsp. *aurantiacum* [SAN: *P. aurantiaca* (L.) F.W.Schultz & Sch.Bip.]; 4-methoxybenzaldehyde in *H. caespitosum* subsp. *caespitosum*, *H. glomeratum* Froel. subsp. *glomeratum* [SAN: *P. glomerata* (Froel.) Fr.], *H. zizianum* subsp. *adenocymigerum* [SAN: *P. ziziana* (Tausch) F.W.Schultz & Sch. Bip.] and *H. aurantiacum* subsp. *aurantiacum*. The occurrence of benzeneacetaldehyde was restricted to *H. lactucella*.

Finally, Feulner et al. (2009) found (*E*)-4,8-dimethyl-1,3,7-nonatriene (an irregular terpene) in all studied samples except in *H. lactucella, H. fallacinum* and *P. officinarum*.

In a second study, Feulner et al. (2011) studied the floral scent volatiles of 37 *Hieracium* taxa by GC-MS. The analysis revealed linalool, limonene, and (*E*)-β-ocimene as the most abundant monoterpenes in the investigated species. Limonene was present in all samples but only in traces in *H. wiesbaurianum* subsp. *jenzigense* Bornm. et Zahn [SAN: *H. hypochoeroides* subsp. *jenzigense* (Bornm. & Zahn) Greuter], while linalool was present in all taxa except *H. glaucinum* subsp. *oegocladum* (Jord. ex Boreau) Soó (which is not stated in the World Flora Online database unlike a similar named taxon, *H. glaucinum* subsp. *oigocladum* Soó) and *H. onosmoides* Fr. (*E*)-β-Ocimene was more widespread then its configurational isomer (*Z*)-β-ocimene. Both were not detected in *H. bifidum* subsp. *basicuneatum* (Zahn) Zahn, *H. bifidum* Kit. ex Hornem grex *bifidum* [NV], *H. caesium* Fr., *H. caesium* Fr. subsp. *caesium* [NV], *H. harzianum* Zahn, *H. onosmoides*, *H. umbellatum*, and *H. schmidtii* subsp. *comatulum* (Boreau) O.Bolòs & Vigo. However, (*E*)-β-ocimene was further only absent in *H. glaucinum* subsp. *medium* (Jord.) O.Bolòs & Vigo [SAN: *H. glaucinum* subsp. *petiolare* (Jord.) O.Bolòs & Vigo] and *H. franconicum* (Griseb.) Zahn. [SAN: *H. glaucomorphum* subsp. *franconicum* (Griseb.) Greuter], while the occurrence of (*Z*)-β-ocimene was mostly restricted to *H. euwiesbaurianiforme* (Schack & Zahn) Jochen Müll [SAN: *H. hypochoeroides* subsp. *wiesbaurianiforme* Greuter], and *H. laevigatum* Willd. [AN], as well as traces in *H. bupleuroides* C.C.Gmel. subsp. *bupleuroides* [NCT], *H. franconicum*, *H. glaucinum* subsp. *medium*, *H. vulgatum* Fr. [SAN: *H. lachenalii* C.C.Gmel. s.l.], *H. wiesbaurianum* subsp. *apertorum* Bornm. & Schack ex Zahn [SAN: *H. hypochoeroides* subsp. *apertorum* (Zahn) Greuter], and *H. wiesbaurianum* subsp. *jenzigense*. β-Pinene was also widespread in the investigated taxa, however the authors detected noteworth amounts (i.e. of more than 3% relative amounts) of the monoterpene only in the following species: *H. bupleuroides* subsp. *bupleuroides*, *H. caesium* Fr. subsp. *caesium*, *H. franconicum*, *H. glaucinum* grex *cinerascens* (Jord.) Zahn [NCT], *H. glaucinum* subsp.

Table 4
Flavonoid composition of the different studied species of *Hieracium* L. The solvents used to prepare the extracts are, as follows: **CH_3OH**: methanol; **$(CH_3)_2CO$:** acetone; **H_2O:** distilled water; **CH_2Cl_2:** dichloromethane; **n-BuOH**: n-Butanol; **C_2H_5OH:** ethanol; **$(C_2H_5)_2O$**: Diethyl ether; **$C_4H_8O_2$:** ethyl ethanoate.

Species	Extraction solvent	Plant organ	Compounds	References
Hieracium albertinum Farr [SAN: *H. scouleri* Hook.]	CH_3OH/C_2H_5OH + $C_4H_8O_2$/n-BuOH	whole plants	apigenin; apigenin 4′-*O*-glucoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; chrysoeriol; luteolin 7-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Guppy and Bohm (1976)
H. albiflorum Hook.	CH_3OH/C_2H_5OH + $C_4H_8O_2$/n-BuOH	whole plants	apigenin; apigenin 4′-*O*-glucoside; apigenin 7-*O*-glucoside; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Guppy and Bohm (1976)
H. albopellitum (Zahn) Niketić [SAN: *H. thapsiformoides* subsp. *albopellitum* (Zahn) Greuter]	CH_3OH	aerial flowering parts	apigenin; luteolin acylhexoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; quercetin 3-*O*-glucoside; apigenin hexosilpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; luteolin; diosmetin	Milutinović et al. (2018b)
H. alpinum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide, luteolin, luteolin 4′-*O*- glucoside, luteolin 7-*O*-glucoside, luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. amplexicaule L.	$CH_2Cl_2/CH_3OH/(C_2H_5)_2O$/*n*-BuOH and C_2H_5OH	aerial parts	apigenin; apigenin-7-glucoside; luteolin; luteolin-7-glucoside; luteolin-7-rhamnoside; quercetin; quercetin-3-glucoside	Mañez et al. (1994)
H. amplexicaule	$(CH_3)_2CO$	leaves	naringenin 7-methyl ether (sakuranetin); naringenin 7,4′-dimethyl ether; apigenin 7,4′-dimethyl ether	Wollenweber et al. (1997)
H. amplexicaule	CH_3OH	aerial parts	apigenin; apigenin 7-*O*-glucoside; luteolin; diosmetin; luteolin 7-*O*-glucoside; luteolin 7-*O*-rhamnoside	Giner et al. (1992)
H. amplexicaule	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. anastrum (Degen & Zahn) Niketić [SAN: *H. pichleri* subsp. *anastrum* (Degen & Zahn) Zahn]	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide	Milutinović et al. (2018b)
H. arvicola Nägeli & Peter [*Pilosella erythrochrista* (Nägeli & Peter) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. atratum Fr.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin, luteolin 4′-*O*-glucoside, luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. aurantiacum L. [SAN: *P. aurantiaca* (L.) F.W. Schultz & Sch.Bip.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. auriculoides subsp. *trichocymum* Touton & Zahn [SAN: *P. auriculoides* (Láng) Arv.-Touv.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. bauhinii subsp. *bauhini* [SAN: *P. piloselloides* subsp. *bauhinii* (Schult.) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. bifidum subsp. *caesiiflorum* (Almq. ex Norrl.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. blecicii Niketić [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	CH_3OH	aerial flowering parts	apigenin 7-*O*-β-glucoside; luteolin; luteolin 7-*O*-β-glucoside; luteolin 7-*O*-α-L-rhamnosyl(1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside	Petrović et al. (1999b)
H. blecicii	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; diosmetin hexosylpentoside; quercetin 3-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. bocconei Griseb. subsp. *bocconei*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. borsanum Mráz	CH_3OH	leaves	apigenin 4′-*O*-glucuronide; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoside	Švehlíková et al. (2002)
H. bornmuelleri Freyn [SAN: *H. pannosum* subsp. *bornmuelleri* (Freyn) Murr & Zahn]	CH_3OH/H_2O	aerial parts	apigenin	Bakar et al. (2015)
H. brachiatum Bert. ex DC.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. caespitosum Dumort. subsp. *caespitosum* [SAN: *P. caespitosa* (Dumort.) P.D.Sell & C. West]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
	$CH_3OH/(CH_3)_2CO/H_2O$	Flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)

(*continued on next page*)

Table 4 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
Hieracium caespitosum subsp. *colliniforme* (Peter) P.D.Sell [SAN: *P. caespitosa* subsp. *colliniformis* (Peter) P.D.Sell & C.West]				
H. calodon subsp. *pseudofallax* Touton [NV]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. calophyllum R.Uechtr.	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide.	Milutinović et al. (2018b)
H. coloriscapum Rohlena & Zahn	CH_3OH	aerial flowering parts	apigenin 7-*O*-β -glucoside; luteolin; luteolin 7-*O*-β-glucoside; luteolin 7-*O*-α-L-rhamnosyl(1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside	Petrović et al. (1999b)
H. coloriscapum	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide.	Milutinović et al. (2018b)
H. compositum Lapeyr.	$CH_2Cl_2/CH_3OH/(C_2H_5)_2O$/*n*-BuOH and C_2H_5OH	aerial parts	apigenin; apigenin-7-glucoside; diosmetin; luteolin; luteolin-7-glucoside; luteolin-7-rhamnoside	Mañez et al. (1994)
H. compositum	CH_3OH	aerial parts	apigenin; apigenin 7-*O*-glucoside; luteolin; diosmetin; luteolin 7-*O*-glucoside; luteolin 7-*O*-rhamnoside	Giner et al. (1992)
H. cymosum L. subsp. *cymosum* [SAN: *P. cymosa* (L.) F.W.Schultz & Sch.Bip.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin, luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. cynoglossoides Arv.-Touv. [SAN: *H. scouleri* Hook.]	CH_3OH; C_2H_5OH	whole plants	apigenin; apigenin 4′-*O*-glucuronide; apigenin 4′-*O*-glucoside; apigenin 7-*O*-glucoside; chrysoeriol; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Guppy and Bohm (1976)
H. dentatum Hoppe s.l.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside.	Milutinović et al. (2018b)
H. derubellum Gottschl. & Schuhw. [SAN: *P. derubella* (Gottschl. & Schuhw.) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. durmitoricum (Rohlena & Zahn) Niketić [SAN: *H. stirovacense* subsp. *durmitoricum* (Rohlena & Zahn) Greuter]	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin acylhexoside; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin hexosylpentoside; luteolin 7-*O*-glucoxyloside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide	Milutinović et al. (2018b)
H. fallacinum F.W. Schultz subsp. *fallacinum* [SAN: *P. fallacina* (F.W.Schultz) F.W. Schultz]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. fallax Willd. subsp. *durisetum* Nägeli & Peter [SAN: *P. setigera* Fr.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. fuscum subsp. *chrysanthes* Nägeli & Peter [NV]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. glabratum Willd.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. glaucinum Jord.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. glaucinum subsp. *basalticum* (Sch.Bip.) J. Duvign.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. glaucinum subsp. *heteroschistum* (Zahn) Soó	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. glomertaum Froel. [SAN: *P glomerata* (Froel.) Fr.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. gorfenianum Bornm. & Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads whole plants	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)

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Table 4 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
H. gracile Hook. [SAN: *H. triste* Willd. ex Spreng.]	$CH_3OH + C_2H_5OH + C_4H_8O_2$/n-BuOH		apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; apigenin 4′-*O*-glucoside; apigenin 7-*O*-glucoside; chrysoeriol; luteolin; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Guppy and Bohm (1976)
H. guentheri-beckii Zahn	CH_3OH	aerial flowering parts	apigenin 7-*O*-β-glucoside; luteolin; luteolin 7-*O*-β-glucoside; luteolin 7-*O*-α-L-rhamnosyl (1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside	Petrović et al. (1999b)
H. guentheri-beckii	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexosylpentosid; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. guthnikianum subsp. *rubrisabinum* (Nägeli) Zahn [SAN: *P. guthnickiana* (Hegetschw.) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. gymnocephalum Griseb. ex Pant.	CH_3OH	aerial flowering parts	apigenin 7-*O*-β-glucoside; luteolin; luteolin 7-*O*-β-D-glucoside; luteolin 7-*O*-α-L-rhamnosyl (1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside,	Petrović et al. (1999a, b)
H. gymnocephalum	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin acylhexoside; luteolin; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin hexosylpentoside; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide	Milutinović et al. (2018b)
H. hoppeanum subsp. *hoppeanum* [SAN: *P. hoppeana* (Schult.) F.W.Schultz & Sch.Bip.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. hypeuryum Peter [SAN: *P. hypeurya* (Peter) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. inuloides subsp. *tridentatifolium* (Zahn) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. jurassicum Griseb.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. kalksburgense Wiesb. [SAN: *P. kalksburgensis* (Wiesb.) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. kofelicum Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. kuekenthalianum (Zahn) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. lactucella Wallr. subsp. *lactucella* [SAN: *P. lactucella* (Wallr.) P.D.Sell & C.West]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. laevigatum Willd. subsp. *laevigatum* [SAN: *H. laevigatum* Willd.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. leptophyton Nägeli & Peter [SAN: *P. leptophyton* (Nägeli & Peter) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. leptophyton subsp. *polyanthemoides* Zahn [SAN: *P. leptophyton* subsp. *polyanthemoides* (Zahn) Gottschl.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. lycopifolium Froel. subsp. *lycopifolium*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. macilentum Fr.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. macranthelum Nägeli & Peter [SAN: *P. macranthela* (Nägeli & Peter) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. macrodontoides (Zahn) Zahn	CH_3OH	aerial flowering parts	apigenin 7-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-glucoside; apigenin	Milutinović et al. (2018b)
H. macrostolonum Gus.Schneid. [SAN:*P. macrostolona* (Gus.Schneid.) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. maculatum subsp. *commixtum* (Jord.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. maculatum Schrank subsp. *maculatum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. mirificissimum Rohlena & Zahn	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; luteolin; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucuronide; luteolin hexosylpentoside; quercetin 3-*O*-	Milutinović et al. (2018b)

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Table 4 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
			glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	
H. mokragorae (Nägeli & Peter) Freyn	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin; diosmetin; diosmetin hexoside; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. murorum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	apigenin 4′-*O*-β-D-glucuronide	Zidorn et al. (2002)
H. murorum subsp. *grandidens* var. *minoriceps* Zahn [NV]	$(C_2H_5)_2O$; $(C_2H_5)_2O$ + $C_4H_8O_2$; $C_4H_8O_2$; CH_3OH + $C_4H_8O_2$	flowering heads* leaves**	apigenin**; luteolin**; luteolin 7-*O*-glucoside*; unspecified luteolin 7-*O*-diglycoside**	Haag-Berrurier and Duquénois (1969)
H. naegelianum Pančić	CH_3OH	aerial flowering parts	luteolin 7-*O*-glucoside; luteolin; luteolin 7-*O*-α-L-rhamnosyl (1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside; luteolin 7-*O*-β-glucoside	Petrović et al. (1999b)
H. naegelianum	CH_3OH	aerial flowering parts	luteolin hexosylpentoside; luteolin 7-*O*-glucoxyloside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; luteolin acylhexoside; apigenin 7-*O*-glucuronide	Milutinović et al. (2018b)
H. neilreichii Beck [SAN: *H. pallescens* Waldst. & Kit. subsp. *neilreichii* (Beck) Greuter]	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin acylhexoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-glucoside; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide	Milutinović et al. (2018b)
H. onosmoides subsp. *crinigerum* (Fr.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. orieni A.Kern.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin acylhexoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. oxyodon subsp. *muretii* (Gremli) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. pallidiflorum subsp. *huteri* (Hausm. ex Bamb.) Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. pannosum Boiss.	CH_3OH	flowers, root and leaf	luteolin; luteolin 7-*O*-glucoside; apigenin	Gökbulut et al. (2017)
H. pannosum	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; luteolin 4′-*O*-glucoside; luteolin	Milutinović et al. (2018b)
H. paratrichum Niketić [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide	Milutinović et al. (2018b)
H. peleterianum Mérat subsp. *peleterianum* [SAN: *P. peleteriana* (Mérat) F.W.Schultz & Sch.Bip.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. picroides Vill.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. piliferum Hoppe subsp. *piliferum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. piloselloides Vill. [SAN: *P. piloselloides* (Vill.) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. piloselloides var. *obscurum* (Rchb.) Zahn. [SAN: *P. piloselloides* subsp. *praealta* (Gochnat) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. pilosum Schleich. ex Froel.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. pilosum	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; quercetin 3-*O*-	Milutinović et al. (2018b)

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Table 4 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
			glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; diosmetin	
H. piloselloides subsp. *subcymigerum* (Nägeli & Peter) Zahn [SAN: *P. piloselloides* subsp. *praealta* (Gochnat) S.Bräut. & Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. piloselloides subsp. *themariense* Bornm. & Zahn [SAN: *P. piloselloides* (Vill.) Soják subsp. *piloselloides*]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. plumulosum A.Kern.	CH_3OH	aerial flowering parts	apigenin; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin 7-*O*-rutinoside; luteolin hexosylpentoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin; diosmetin	Milutinović et al. (2018b)
H. porrifolium L. subsp. *porrifolium*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. pospichalii Zahn subsp. *pospichalii*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. prenanthoides subsp. *bupleurifolioides* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. pseudocaesium Degen & Zahn	CH_3OH	leaves	apigenin 4′-*O*-glucuronide; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoside	Švehlíková et al. (2002)
H. pseudoschenkii (Rohlena & Zahn) Niketić [SAN: *H. bupleuroides* subsp. *pseudoschenkii* Rohlena & Zahn]	CH_3OH	aerial flowering parts	apigenin 7-*O*-glucuronide; luteolin acylhexoside; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; quercetin 3-*O*-glucoside; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside; luteolin; diosmetin; apigenin	Milutinović et al. (2018b)
H. pyricephalum Niketić [NV]	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin hexosylpentoside; luteolin; luteolin 7-*O*-glucuronide; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoside; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin acylhexoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; diosmetin; quercetin 3-*O*-glucoside	Milutinović et al. (2018b)
H. racemosum Waldst. & Kit. ex Willd.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. ratezaticum (Nyáz. & Zahn) Mráz	CH_3OH	leaves	apigenin 4′-*O*-glucuronide; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoside	Švehlíková et al. (2002)
H. rohacsense Kit.	CH_3OH	leaves	apigenin 4′-*O*-glucuronide; luteolin 4′-*O*-glucuronide; luteolin 7-*O*-glucoside	Švehlíková et al. (2002)
H. rothianum Wallr. subsp. *rothianum* [SAN: *P. rothiana* (Wallr.) F.W.Schultz & Sch.Bip.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. rotundatum Kit. ex Schult. [SAN: *H. transylvanicum* Heuff.]	CH_3OH	aerial flowering parts	apigenin; luteolin; luteolin 7-*O*-glucoside	Petrović et al. (1999b)
H. rubriflorum Zahn [SAN: *P. substoloniflora* (Peter) Soják]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. sabaudum L.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. saxifragum subsp. *vulpii* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. scheppigianum Freyn	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucuronide; apigenin hexosylpentoside; luteolin; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoside; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin acylhexoside; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; diosmetin; diosmetin hexoside	Milutinović et al. (2018b)
H. schmidtii subsp. *graniticum* (Sch.Bip.) Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. sciadophorum subsp. *tridentinum* Nägeli & Peter [SAN: *P. corymbulifera* (Arv.-Touv.) Arv.-Touv.]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. scorzonerifolium Vill. s.l.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; apigenin 7-*O*-rutinoside; apigenin hexosylpentoside; luteolin; luteolin 7-*O*-glucoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin acylhexoside; luteolin hexosyldeoxyhexoside; diosmetin hexoside; quercetin 3-*O*-glucoside	Milutinović et al. (2018b)
H. sommerfeltii Lindab.	$CH_3OH/(CH_3)_2CO/H_2O$		luteolin; luteolin 7-*O*-glucoside	Zidorn et al. (2002)

(*continued on next page*)

Table 4 (*continued*)

Species	Extraction solvent	Plant organ	Compounds	References
		flowering heads		
H. sparsum subsp. *vierhapperi* Zahn	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. sphaerocephalum Froel.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. spirocaule Niketić [NV]	CH_3OH	aerial flowering parts	apigenin; diosmetin; luteolin 4′-*O*-glucuronide; luteolin; luteolin hexosylpentoside; luteolin 7-*O*-glucoxyloside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide; apigenin hexosylpentoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucoside apigenin 7-*O*-glucuronide; luteolin 7-*O*-rutinoside;	Milutinović et al. (2018b)
H. suborienii (Zahn) P.D.Sell & C.West.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-β- glucoside; luteolin; luteolin 7-*O*-β-glucoside; luteolin 7-*O*-α-L-rhamnosyl (1 → 6)-β-D-glucoside; luteolin 7-*O*-β-D-xylosyl (1 → 6)-β-D-glucoside	Petrović et al. (1999b)
H. tommasinianum K.Malý	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucuronide; apigenin hexosylpentoside; luteolin; luteolin 7-*O*-glucoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin acylhexoside; luteolin hexosylpentoside; diosmetin; diosmetin hexoside	Milutinović et al. (2018b)
H. umbellatum L.	$CH_3OH + C_2H_5OH + C_4H_8O_2$/n-BuOH	whole plants	apigenin; apigenin 7-*O*-arabinoside; apigenin 4′-*O*-glucoside; apigenin 7-*O*-glucoside; apigenin 7-*O*-glucuronide; chrysoeriol; luteolin; luteolin 4′-*O*-arabinoside; luteolin 7-*O*-arabinoside; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide; quercetin 3-*O*-glucoside	Guppy and Bohm (1976)
H. umbellatum L. subsp. *umbellatum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin, luteolin 4′-*O*-glucoside, luteolin 7-*O*-glucoside, luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. valdepilosum Vill. s.l.	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucoside; apigenin 7-*O*-rutinoside; apigenin 7-*O*-glucuronide; luteolin, luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 4′-*O*-glucuronide; luteolin hexosylpentoside; luteolin hexosyldeoxyhexoside; quercetin 3-*O*-glucoside; diosmetin	Milutinović et al. (2018b)
H. venostorum (Zahn) Gottschl.	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. vetteri (Zahn) Ronniger	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside	Zidorn et al. (2002)
H. villosum Jacq. subsp. *villosum*	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
H. villosum	CH_3OH	aerial flowering parts	apigenin; apigenin 7-*O*-glucuronide; diosmetin; luteolin; luteolin 4′-*O*-glucuronide; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoxyloside; luteolin 7-*O*-glucoside; luteolin hexosyldeoxyhexoside; luteolin 7-*O*-rutinoside; luteolin 7-*O*-glucuronide; diosmetin hexoside; quercetin 3-*O*-glucoside, apigenin 7-*O*-rutinoside, apigenin 7-*O*-glucoside	Milutinović et al. (2018b)
H. wiesbaurianum Uechtr. subsp. *semicinerascens* Bornm. & Zahn [SAN: *H. hypochoeroides* subsp. *semicinerascens* (Bornm. & Zahn) Greuter]	$CH_3OH/(CH_3)_2CO/H_2O$	flowering heads	luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)

oegocladum, *H. murorum*, *H. onosmoides*, and *H. wiesbaurianum* subsp. *niphanthodes* Bornm. & Zahn [SAN: *H. hypochoeroides* subsp. *niphanthodes* (Bornm. & Zahn) Greuter]. Other than that, the authors detected γ-terpinene, (*E*)-linalool oxide (furanoid), (*Z*)-linalool oxide (furanoid), (*E*)-linalool oxide (pyranosid), (*Z*)-linalool oxide (pyranosid), verbenone, terpinolene, α-terpineol, myrthenal, and carvone. Except (*E*)-lianolool oxide furanosid in *H. bupleuroides* subsp. *bupleuroides* and *H. wiesbaurianum* subsp. *arnoldianum* Zahn [NCT], those compounds were detected in rather low relative amounts (not more than 3%) if present in the samples. Feulner et al. (2011) further reported 29 sesquiterpenes of which 17 remained unidentified. α-Copaene, the most abundant sesquiterpene, was present in all investigated species. Silphin-1-ene was not detected in *H. bupleuroides* subsp. *bupleuroides*, *H. glaucinum* subsp. *medium*, *H. glaucinum* subsp. *prasiophaeum*, *H. lachenalii*, and *H. murorum* subsp. *sylvularum* (Boreau) Zahn, while α-isocomene was absent *H. lachenalii*, and *H. murorum* subsp. *sylvularum*. Other detected sesquiterpenes comprised (*E*)-β-caryophyllene, γ-amorphene, thujopsene, aromadendrene, allo-aromadendrene, γ-gurjunene, germacrene d, α-muurolene, α-cedrene, α-selinene, β-selinene (most likely in the second part of the table wrongly stated as α-selinene), γ-cadiene, δ-cadiene, and lilial, which however were mostly present in low amounts of less than 2%. (*E*)-4,8-Dimethyl-1,3,7-nonatriene was detected in all studied species. In addition, the authors detected a total of five benzenoids, i.e. *p*-methylanisole, that was restricted to low amounts in *H. franconicum* and *H. glaucum* subsp. *isaricum* (Nägeli ex J. Hofm.) Nägeli et Peter (listed neither in the Plant List nor World Flora Online unlike the accepted taxon *H. glaucum* subsp. *isariciforme* Murr), and more abundant in *H. bupleuroides* subsp. *bupleuroides*, benzeneacetaldehyde, which was not detected in *H. bifidum* subsp. *stenolepis* var. *valdefloccosum* (Vollm.) Zahn [NV], *H. bupleuroides* subsp. *bupleuroides*, *H.* [*sommerfeltii*] *crinicaesium* (Schack et Zahn) Joch.Müll.[SAN: *H. hypochoeroides* subsp. *crinicaesium* (Schack & Zahn) Greuter], *H. euwiesbaurianiforme*, *H. glaucinum* grex *cinerascens*, *H. glaucum* subsp. *isaricum, H. glaucinum* subsp. *oegocladum*, *H. glaucinum* subsp. *prasiophaeum*, *H. laevigatum*, *H. murorum*, *H. murorum* subsp. *silvularum*, *H. umbellatum*, *H.* [*wiesbaurianum*] *parvimaculatum* Joch.Müll. [SAN: *H. hypochoeroides* subsp. *parvimaculatum* (Joch.Müll.) Greuter], *H. saxifragum* Fr. subsp. *dufftii* Zahn [NV], *H. wiesbaurianum* s.l., *H. wiesbaurianum* subsp. *apertorum*, *H.*

Table 5
Flavonoid composition of the different studied species of *Pilosella* Hill. The solvents used to prepare the extracts are, as follows: **CH_3OH**: methanol; **$(CH_3)_2CO$:** acetone; **H_2O:** distilled water; **CH_2Cl_2:** dichloromethane; **n-BuOH**: n-butanol; **C_2H_5OH:** ethanol; **$(C_2H_5)_2O$**: diethyl ether; **$C_4H_8O_2$:** ethyl ethanoate.

Species	Extraction solvent	Plant organ	Compounds	References
Pilosella hoppeana subsp. *testimonialis* [SAN: *P. testimonialis* (Nägeli ex J.Hofm.) Gottschl.]	CH_3OH/H_2O	aerial parts	apigenin; luteolin	Bakar et al. (2015)
P. hoppeana subsp. *testimonialis*	CH_3OH	aerial parts	quercetin	Aliyazicioğlu et al. (2019)
P. officinarum Vaill.	C_2H_5OH	flowering heads	apigenin; luteolin; luteolin 7-glycoside; isorhamnetin	Haag-Berrurier and Duquenois (1962, 1963) and Shelyuto et al. (1977)
P. officinarum	CH_3OH	flowering heads and leaves	isoetin; luteolin	Harborne (1978)
P. officinarum	CH_3OH/ $(CH_3)_2CO$/ H_2O	flowering heads	isoetin 4′-*O*-glucuronide; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-glucoside; luteolin 7-*O*-glucuronide	Zidorn et al. (2002)
P. officinarum	CH_3OH/ $(CH_3)_2CO$/ H_2O	flowering heads	isoetin 4′-*O*-β-D-glucuronide	Zidorn et al. (2005)
P. officinarum	CH_3OH	whole plant	apigenin-7-*O*-glucoside (apigetrin)	Stanojević et al. (2008, 2009)
P. officinarum	CH_3OH	aerial parts	apigenin; luteolin; luteolin 4′-*O*-glucoside; luteolin 7-*O*-β-glucopyranoside; isoetin 7-*O*-β-glucopyranoside; isoetin 4′-*O*-glucuronide; kaempferol 3-methyl ether; apigenin 7-*O*-β-glucopyranoside	Gawrońska-Grzywacz and Krzaczek (2009)
P. officinarum	CH_3OH	flowering heads	isoetin 4′-*O*-β-D-glucopyranoside	Gawrońska-Grzywacz et al. (2011)
P. officinarum	$(CH_3)_2CO$/ H_2O	not specified	apigenin; luteolin	Mertens et al. (2018)

wiesbaurianum subsp. *arnoldianum*, *H. wiesbaurianum* subsp. *jenzigense*, *H. wiesbaurianum* subsp. *niphanthodes*, and *H. wiesbaurianum* subsp. *semicinerascens*, as well as phenylethyl alcohol, which was not detected in *H.* [*wiesbaurianum* subsp. *jenzigense*] *var. euwiesbaurianiforme*, *H. glaucinum* subsp. *oegocladum*, *H. murorum* subsp. *silvularum*, *H.* [*wiesbaurianum*] *parvimaculatum*, and *H. schmidtii* subsp. *comatulum*. Methyl salicylate was present in all taxa, while 4-methoxybenzaldehyde was not observed in *H.* [*wiesbaurianum*] *parvimaculatum*. Finally, the authors detected eight fatty acid derivatives.

Ugur et al. (2010) found hexahydro farnesylacetone (ketone compound) in the chloroform extract of *P. sandrasica* as well as the sesquiterpene alcohol cedrane-8,13-diol in the chloroform extract in the same species.

4.8. 4-Hydroxybenzyl alcohol derivatives

The methanol extract of the air-dried, sub-aerial parts of *H. murorum* gave two 4-hydroxybenzyl alcohol derivatives: 4-hydroxy-cinnamic acid 4-β-D-glucopyranosyloxybenzyl ester and 3-hydroxy-2-[(4-hydroxy-phenyl) acetoxy]-3-methyl-butyric 4-β-D-glucopyranosyloxybenzyl ester (Zidorn et al., 2001).

5. Bioactivities

The literature research provided reports on bioactivities of *Hieracium* and *Pilosella* species that comprise investigations on the antidiabetic (Table 6), anti-inflammatory (Table 7), antimicrobial (Table 8), antioxidant (Table 9), antiviral (Table 10), cytotoxic and antiproliferative (Table 11), diuretic (Table 12), and gastroprotective (Table 13) activities. In addition, in Table 14 reports of investigations on bioactivites that cannot be linked to reported ethnopharmaceutical usage are compiled. The reviewed literature comprised both *in vitro* and *in vivo* testing, with the latter being mostly restricted to investigations on the anti-inflammatory, diuretic, and gastroprotective activities.

5.1. Antidiabetic activity

Efforts to prevent or delay the onset of diabetes are an urgent public health priority with health, social, and economic benefits (Aziz et al., 2015). Plants continue to play an important role in the treatment of diabetes, particularly in developing countries where most people have limited resources and do not have access to modern treatment (Ali et al., 2006). Gökbulut et al. (2017) studied the antidiabetic capacity of

Table 6
Compiled antidiabetic assays conducted on *Hieracium* species.

Species	Organ	Extraction solvent	Test Model	Dosis tested	Inhibition [%]	Reference
Hieracium pannosum Boiss.	F	CH_3OH	α-amylase inhibitory activity	0.3 mg/mL	not active	Gökbulut et al. (2017)
				1 mg/mL	8.65 ± 1.71	
				3 mg/mL	21.05 ± 3.29	
			α-glucosidase inhibitory activity	3 mg/mL	5.82 ± 0.91	
	L	CH_3OH	α-amylase inhibitory activity	0.3 mg/mL	not active	
				1 mg/mL	not active	
				3 mg/mL	32.11 ± 0.91	
			α-glucosidase inhibitory activity	3 mg/mL	7.21 ± 2.66	
	R	CH_3OH	α-amylase inhibitory activity	0.3 mg/mL	not active	
				1 mg/mL	7.36 ± 0.68	
				3 mg/mL	37.90 ± 1.58	
			α-glucosidase inhibitory activity	3 mg/mL	9.24 ± 1.24	

Abreviations used: R roots, F flowering heads, L leaves.

Table 7
Compiled antiinflammatory assays conducted on *Hieracium* and *Pilosella* species.

Species	Organ	Extraction solvent	Test Model	Dosis tested/ concentration	Results	Reference
Hiercium albiflorum Hook. as part of nine plant mixture (containing additional equals of licorice, beefsteak plant, fenugreek, skullcap and food extracts of black pepper, green tea, tumeric, fermented soybeans paste)	n.s.	C_2H_5OH	TMA induced contact hypersensitivity in BALB/c mice	250 mg/kg BW	reduced earthickness ($p < 0.01$) IgE levels in serum suppressed ($p < 0.05$) IL-1β in inflamed ear tissue reduced ($p < 0.01$) IL-4 and IL-1β in splenocytes reduced ($p < 0.05$)	Bae et al. (2013)
			OVA-sensitizied BALB/c mice	250 mg/kg BW	OVA-specific IgE decreased ($p < 0.01$) IFN-γ, IL-2 increased ($p < 0.01$) IL-4 supressed ($p < 0.01$) IL-10 not enhanced	
			treatment of splenocytes of OVA-sensitizied BALB/c mice with NPM-9; ELISA on cytokine levels (IL-4 and IFN-γ/IL-4)	n.s.	IC_{50} for IL-4 12.7 μg/mL IFN-γ/IL-4 ratio 4.80	
H. albiflorum	n.s.	C_2H_5OH	treatment of splenocytes of OVA-sensitizied BALB/c mice with extract; ELISA on cytokine levels (IL-4 and IFN-γ/IL-4)	n.s.	IC_{50} for IL-4208 μg/mL IFN-γ/IL-4 ratio 0.15	
H. calophyllum R.Uechtr.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	carrageenan induced rat paw edema test, evaluating paw withdrawal thresholds with an electric Von Frey anesthesiometer and the increase of the paw volume with a plethysmometer	200 mg/kg p.o.	38.1% antihyperalgesic effect after 60 min; no significant reduction of the carrageenan induced rat paw edema	Milutinović et al. (2020)
H. gymnocephalum Griseb. ex Pant.	AP + F	CH_2Cl_2	carrageenan induced rat paw edema test	25 mg/kg p.o. 50 mg/kg p.o. 100 mg/kg p.o. 200 mg/kg p.o.	5.9 ± 0.4% 11.7 ± 1.3% 31.2 ± 8.0% 44.1 ± 16.3% anti-inflammatory effect	Petrović et al. (2008)
H. glabratum Willd.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	carrageenan induced rat paw edema test, evaluating paw withdrawal thresholds with an electric Von Frey anesthesiometer and the increase of the paw volume with a plethysmometer	50–200 mg/kg p.o.	25.3–51.6% antihyperalgesic effect after 60 min; ED_{50} = 211.6 ± 70.6 mg/kg; no significant reduction of the carrageenan induced rat paw edema	Milutinović et al. (2020)
			Rotarod test	200 mg/kg p.o.	no effect on the motor ability	
H. scheppigianum Freyn	AP + F	CH_2Cl_2	carrageenan induced rat paw edema test, evaluating paw withdrawal thresholds with an electric Von Frey anesthesiometer and the increase of the paw volume with a plethysmometer	50–200 mg/kg p.o.	26.9–56.2% antihyperalgesic effect after 60–90 min; ED_{50} = 163.0 ± 26.5 mg/kg; no significant reduction of the carrageenan induced rat paw edema	
			Rotarod test	200 mg/kg p.o.	no effect on the motor ability	
Pilosella hoppeana subsp. *testimonialis* [SAN: *P. testimonialis* (Nägeli ex J. Hofm.) Gottschl.]	AP	CH_3OH	increase of NO concentration in cells	12.5 25 50 100 250 μg/mL	1.98 μmol/g protein ($p < 0.05$) 5.24 μmol/g protein 7.08 μmol/g protein ($p < 0.05$) 13.66 μmol/g protein ($p < 0.05$) 32.48 μmol/g protein ($p < 0.05$)	Aliyazicioğlu et al. (2019)
			inhibition of COX1 and COX2	500 μg/mL	65% inhibition COX1 73% inhibition COX2	
			increase of heme oxygenase in cells	25 50 100 250 500 μg/mL	53% of control ($p < 0.05$) 70% of control 107% of control ($p < 0.05$) 111% of control ($p < 0.05$) 133% of control	
			increase of MMP-9, JNK, TNF-α, Nrf-2, p38, IL-10 and IL-1β	25, 50, 100 μg/mL	n.s.	

Abreviations used: n.s. not stated, WP whole plant, AP aerial parts, F flowers.

methanol extracts *in vitro* using flowering heads, leaves, and roots of *H. pannosum* Boiss. The extracts were assayed for their α-amylase and α-glucosidase inhibitory activity. The root extract displayed the highest activity among the investigated extracts (α-amylase 37.9 ± 1.6 and 7.4 ± 0.7% inhibition at 3 and 1 mg/mL; α-glucosidase 9.2 ± 1.2% inhibition at 3 mg/mL). However, the results were considerably lower than the inhibtion obtained by acarbose, an α-amlylase and α-glucosidase inhibitor used as positive control (α-amylase 44.7 ± 2.8 at 1 mg/mL; α-glucosidase 98.9 ± 0.1 at 1 mg/mL). Results as obtained by Gökbulut et al. (2017) are stated in Table 6.

5.2. Anti-inflammatory activity

Inflammation is clinically defined as a pathophysiological process characterized by redness, edema, fever, pain, and loss of function. Although the currently used steroidal anti-inflammatory drugs and

Table 8
Compiled antimicrobial assays conducted on *Hieracium* and *Pilosella* species.

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
Hieracium sp.	WP	CH_3OH	Disc diffusion	10 µL (1/1 w/v)	Ec, Psp, Pa, Se, Sd, Sty, Sa, Sf, Ca	33.3% inhibited microorganisms	–	Barbour et al. (2004)
				20 µL (1/1 w/v)	Ec, Psp, Pa, Se, Sd, Sty, Sa, Sf, Ca	88.8% inhibited microorganisms	–	
			MIC	1:2–1:4 (w/v)	Ec	Sensitive	1:2.0	
					Psp	Sensitive	1:2.0	
					Pa	Sensitive	1:2.0	
					Sd	Sensitive	1:2.0	
					Se	Sensitive	1:2.0	
					Sty	Sensitive	1:2.0	
					Sa	Sensitive	1:2.0	
					Sf	not effetive	–	
					Ca	Sensitive	1:2.0	
H. caespitosum Dumort. [SAN: *Pilosella caespitosa* (Dumort.) P.D. Sell & C.West]	WP	CH_3OH	Disc diffusion (over night, 35 °C)	20 and 30 µL of extract	Sch	Resistant	–	Booth et al. (2012)
					Sa	Resistant	–	
H. umbellatum L.	S	CH_3OH:H_2O (1:1)	disk diffusion (18 h, 37 °C)	50 µL	Ec-ATCC8677	Resistant	–	Borchardt et al. (2008)
					Pa-ATCC9721	Resistant	–	
					Sa-ATCC12600	Resistant	–	
					Ca-ATCC10231	Resistant	–	
	St	C_6H_{14}	Disc diffusion (24 h, 37 °C)	paper disc immersion in C_6H_{14} extract for 5 min	Ec-ATCC25922	Resistant	–	Kuluev et al. (2019)
					Kp-181210171-2	Resistant	–	
					Pa-ATCC27853	Resistant	–	
					Sa-ATCC206 USA	Resistant	–	
					Ca-181210169-1	Resistant	–	
Pilosella echioides (Lumn.) F.W. Schultz & Sch. Bip.	R	C_6H_{14}	Disc diffusion (24 h, 37 °C)	paper disc immersion in C_6H_{14} extract for 5 min	Ec-ATCC25922	Resistant	–	Kuluev et al. (2019)
					Kp-181210171-2	Resistant	–	
					Pa-ATCC27853	Resistant	–	
					Sa-ATCC206 USA	Resistant	–	
					Ca-181210169-1	Resistant	–	
P. officinarum Vaill.	WP	CH_3OH	Disc diffusion including MIC (Bacteria 18 h, 37 °C; fungi 48 h, 25 °C)	70 µL extract	Ec-ATCC25922	Sensitive	11.75 mg/mL	Stanojević et al. (2008)
					Kp-ATCC13883	Sensitive	23.5 mg/mL	
					Pa-ATCC9027	Sensitive	23.5 mg/mL	
					Se-ATCC13076	Sensitive	23.5 mg/mL	
					Bs-ATCC6633	Sensitive	23.5 mg/mL	
					Sa-ATCC6538	Sensitive	23.5 mg/mL	
					An-ATCC16404	Sensitive	23.5 mg/mL	
					Ca-ATCC10231	Resistant	–	
		CH_2Cl_2:CH_3OH (9:1)	Disc diffusion including MIC (Bacteria 18 h, 37 °C; fungi 48 h, 25 °C)	70 µL extract	Ec-ATCC25922	Sensitive	14.87 mg/mL	Stanojević et al. (2008)
					Kp-ATCC13883	Sensitive	29.75 mg/mL	
					Pa-ATCC9027	Sensitive	14.87 mg/mL	
					Se-ATCC13076	Sensitive	7.44 mg/mL	
					Bs-ATCC6633	Sensitive	7.44 mg/mL	
					Sa-ATCC6538	Sensitive	14.87 mg/mL	
					An-ATCC16404	Sensitive	29.75 mg/mL	
					Ca-ATCC10231	Resistant	–	
		CH_2Cl_2	Disc diffusion including MIC (Bacteria 18 h, 37 °C; fungi 48 h, 25 °C)	70 µL extract	Ec-ATCC25922	Sensitive	25.16 mg/mL	Stanojević et al. (2008)
					Kp-ATCC13883	Sensitive	30.19 mg/mL	
					Pa-ATCC9027	Sensitive	25.16 mg/mL	
					Se-ATCC13076	Sensitive	20.12 mg/mL	
					Bs-ATCC6633	Sensitive	20.12 mg/mL	
					Sa-ATCC6538	Sensitive	20.12 mg/mL	

(*continued on next page*)

Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Resistant	–	
		$C_4H_8O_2$	Disc diffusion including MIC (Bacteria 18 h, 37 °C; fungi 48 h, 25 °C)	70 µL extract	Ec-ATCC25922	Sensitive	10.66 mg/mL	Stanojević et al. (2008)
					Kp-ATCC13883	Sensitive	10.66 mg/mL	
					Pa-ATCC9027	Sensitive	10.66 mg/mL	
					Se-ATCC13076	Sensitive	10.66 mg/mL	
					Bs-ATCC6633	Sensitive	10.66 mg/mL	
					Sa-ATCC6538	Sensitive	10.66 mg/mL	
					An-ATCC16404	Sensitive	10.66 mg/mL	
					Ca-ATCC10231	Resistant	–	
	L	CH_2Cl_2	Disc diffusion (18 h, 37 °C; *P. acnes*, *Cl. sporogens* 48 h, 37 °C, anaerobic conditions; yeasts 48 h, 25 °C; moulds 96 h, 25 °C)	15 µL (20% w/V)	Ec-ATCC25922	Resistant	–	Nostro et al. (2000)
					Kp-ATCC13883	Resistant	–	
					Pv-ATCC13315	Resistant	–	
					Pa-ATCC9027	Resistant	–	
					Se (clinical isolate)	Resistant	–	
					Sma-ATCC19980	Resistant	–	
					Ba-ATCC6633	Sensitive	9 mm	
					Cs-ATCC10404	Resistant	–	
					Lm-ATCC7644	Resistant	–	
					Pac-ATCC6919	Sensitive	10 mm	
					Sa-ATCC6538P	Sensitive	7 mm	
					Af (wild type)	Resistant	–	
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Resistant	–	
					Ctr (clinical isolate)	Resistant	–	
					Fo (wild type)	Resistant	–	
					Pen (wild type)	Resistant	–	
	L	CH_2Cl_2:CH_3OH (9:1)	Disc diffusion (18 h, 37 °C; *P. acnes*, *Cl. sporogens* 48 h, 37 °C, anaerobic conditions; yeasts 48 h, 25 °C; moulds 96 h, 25 °C)	15 µL (20% w/V)	Ec-ATCC25922	Resistant	–	Nostro et al. (2000)
					Kp-ATCC13883	Resistant	–	
					Pv-ATCC13315	Resistant	–	
					Pa-ATCC9027	Resistant	–	
					Se (clinical isolate)	Resistant	–	
					Sma-ATCC19980	Resistant	–	
					Ba-ATCC6633	Sensitive	9 mm	
					Cs-ATCC10404	Sensitive	9 mm	
					Lm-ATCC7644	Resistant	–	
					Pac-ATCC6919	Sensitive	14 mm	
					Sa-ATCC6538P	Sensitive	7 mm	
					Af (wild type)	Resistant	–	
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Resistant	–	
					Ctr (clinical isolate)	Resistant	–	
					Fo (wild type)	Resistant	–	
					Pen (wild type)	Resistant	–	
	L	$(C_2H_5)_2O$ (diethyl ether layer of an aqueous extract pretreated by acidification to pH 2.0, incubation at 37 °C for 30 min, neutralisation to pH 7.0)	Disc diffusion (18 h, 37 °C; *P. acnes*, *Cl. sporogens* 48 h, 37 °C, anaerobic conditions; yeasts 48 h, 25 °C; moulds 96 h, 25 °C)	15 µL (20% w/V)	Ec-ATCC25922	Resistant	–	Nostro et al. (2000)
					Kp-ATCC13883	Resistant	–	
					Pv-ATCC13315	Sensitive	8 mm	
					Pa-ATCC9027	Resistant	–	
					Se (clinical isolate)	Resistant	–	
					Sma-ATCC19980	Resistant	–	
					Ba-ATCC6633	Sensitive	16 mm	
					Cs-ATCC10404	Sensitive	11 mm	
					Lm-ATCC7644	Sensitive	10 mm	

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Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					Pac-ATCC6919	Sensitive	28 mm	
					Sa-ATCC6538P	Sensitive	20 mm	
					Af (wild type)	Sensitive	12 mm	
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Sensitive	16 mm	
					Ctr (clinical isolate)	Sensitive	12 mm	
					Fo (wild type)	Sensitive	7 mm	
					Mc (clinical isolate)	n.s.	–	
					Mg (clinical isolate)	n.s.	–	
					Pen (wild type)	Sensitive	10 mm	
					Tm (clinical isolate)	n.s.	–	
	L	$(C_2H_5)_2O$ (diethyl ether layer of an aqueous extract pretreated by acidification to pH 2.0, incubation at 37 °C for 30 min, neutralisation to pH 7.0)	MIC as agar dilution method (up to 3 weeks, 30 °C)	0.006–0.2% w/V	Ec-ATCC25922	n.t.	–	Nostro et al. (2000)
					Kp-ATCC13883	n.t.	–	
					Pv-ATCC13315	n.t.	–	
					Pa-ATCC9027	n.t.	–	
					Se (clinical isolate)	n.t.	–	
					Sma-ATCC19980	n.t.	–	
					Ba-ATCC6633	Sensitive	0.1% w/V	
					Cs-ATCC10404	n.t.	–	
					Lm-ATCC7644	n.t.	–	
					Pac-ATCC6919	Sensitive	0.1% w/V	
					Sa-ATCC6538P	Sensitive	0.05% w/V	
					Af (wild type)	Sensitive	0.2% w/V	
					An-ATCC16404	n.t.	–	
					Ca-ATCC10231	Sensitive	0.1% w/V	
					Ctr (clinical isolate)	Sensitive	0.1% w/V	
					Fo (wild type)	n.t.	–	
					Mc (clinical isolate)	Sensitive	0.05% w/V	
					Mg (clinical isolate)	Sensitive	0.1% w/V	
					Pen (wild type)	n.t.	–	
					Tm (clinical isolate)	Sensitive	0.1% w/V	
	L	H_2O	Disc diffusion (24 h, 37 °C)	10 µL (100 mg/mL)	Ec-PI No.336	Resistant	–	Frey and Meyers (2010)
					St-PI No.381	Resistant	–	
					Sa-PI No.4651	Sensitive	9.0 ± 0.6 mm	
					Sl-PI No.525	Resistant	–	
	L	CH_3OH	Disc diffusion (18 h, 37 °C; *P. acnes*, *Cl. sporogens* 48 h, 37 °C, anaerobic conditions; yeasts 48 h, 25 °C; moulds 96 h, 25 °C)	15 µL (20% w/V)	Ec-ATCC25922	Resistant	–	Nostro et al. (2000)
					Kp-ATCC13883	Resistant	–	
					Pv-ATCC13315	Resistant	–	
					Pa-ATCC9027	Resistant	–	
					Se (clinical isolate)	Resistant	–	
					Sma-ATCC19980	Resistant	–	
					Ba-ATCC6633	Resistant	–	
					Cs-ATCC10404	Sensitive	10 mm	
					Lm-ATCC7644	Resistant	–	
					Pac-ATCC6919	Sensitive	15 mm	
					Sa-ATCC6538P	Resistant	–	
					Af (wild type)	Resistant	–	
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Resistant	–	
					Ctr (clinical isolate)	Resistant	–	
					Fo (wild type)	Resistant	–	
					Pen (wild type)	Resistant	–	
	L	petroleum ether	Disc diffusion (18 h, 37 °C; *P. acnes*, *Cl. sporogens* 48 h, 37 °C, anaerobic conditions; yeasts 48 h, 25 °C; moulds 96 h, 25 °C)	15 µL (20% w/V)	Ec-ATCC25922	Resistant	–	Nostro et al. (2000)
					Kp-ATCC13883	Resistant	–	
					Pv-ATCC13315	Resistant	–	

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Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					Pa-ATCC9027	Resistant	–	
					Se (clinical isolate)	Resistant	–	
					Sma-ATCC19980	Resistant	–	
					Ba-ATCC6633	Sensitive	10 mm	
					Cs-ATCC10404	Sensitive	16 mm	
					Lm-ATCC7644	Resistant	–	
					Pac-ATCC6919	Sensitive	12 mm	
					Sa-ATCC6538P	Sensitive	9 mm	
					Af (wild type)	Resistant	–	
					An-ATCC16404	Resistant	–	
					Ca-ATCC10231	Resistant	–	
					Ctr (clinical isolate)	Resistant	–	
					Fo (wild type)	Resistant	–	
					Pen (wild type)	Resistant	–	
	L	H_2O	MIC as 96-Well plate assay (24 h, 37 °C)	3.125–100 mg/mL	Ec-PI No.336	n.t.	–	Frey and Meyers (2010)
					St-PI No.381	n.t.	–	
					Sa-PI No.4651	Sensitive	12.5 mg/mL	
					Sl-PI No.525	n.t.	–	
	St	H_2O	Disc diffusion (24 h, 37 °C)	10 µL (100 mg/mL)	Ec-PI No.336	Resistant	–	Frey and Meyers (2010)
					St-PI No.381	Sensitive	9.1 ± 0.6 mm	
					Sa-PI No.4651	Resistant	–	
					Sl-PI No.525	Resistant	–	
	St	H_2O	MIC as 96-Well plate assay (24 h, 37 °C)	3.125–100 mg/mL	Ec-PI No.336	n.t.	–	Frey and Meyers (2010)
					St-PI No.381	Sensitive	3.125 mg/mL	
					Sa-PI No.4651	n.t.	–	
					Sl-PI No.525	n.t.	–	
	F	H_2O	Disc diffusion (24 h, 37 °C)	10 µL (100 mg/mL)	Ec-PI No.336	Resistant	–	Frey and Meyers (2010)
					St-PI No.381	Resistant	–	
					Sa-PI No.4651	Sensitive	8.1 ± 0.6 mm	
					Sl-PI No.525	Resistant	–	
	F	H_2O	MIC as 96-Well plate assay (24 h, 37 °C)	3.125–100 mg/mL	Ec-PI No.336	n.t.	–	Frey and Meyers (2010)
					St-PI No.381	n.t.	–	
					Sa-PI No.4651	Sensitive	12.5 mg/mL	
					Sl-PI No.525	n.t.	–	
	F	isoetin 4′-*O*-β-D-glucopyranoside	Agar well diffusion (preincubated 1 h at RT, 24 h 37 °C bacteria, 48 h 25 °C yeasts)	40 µL (1 mg/mL)	Ec-ATCC25922	Resistant	–	Gawrońska-Grzywacz et al. (2011)
					Kp-ATCC13883	Resistant	–	
					Pa-ATCC9027	Sensitive	7 mm	
					Pm-ATCC12453	Resistant	–	
					Bc-ATCC10876	Resistant	–	
					Bs-ATCC6633	Resistant	–	
					Ml-ATCC10240	Resistant	–	
					Sa-ATCC6538	Resistant	–	
					Sa-ATCC25923	Resistant	–	
					Sep-ATCC12228	Resistant	–	
					Ca-ATCC10231	Resistant	–	
					Cp-ATCC22091	Resistant	–	
			Micro-dilution broth (24 h, 35 °C)	15.6–500 µg/mL	Pa-ATCC9027	Sensitive	125 µg/mL	
	n.s.	Aqueous	n.s.	n.s.	Bm	Sensitive	n.s.	Greib and Duquénois (1960)
					Bab	Sensitive	n.s.	
					Bsu	Sensitive	n.s.	
	n.s.	C_2H_5OH:H_2O (65:35)	Agar well diffusion (24 h; 20 °C *Carnobacterium* spec., *P. fragi*, *Brochothrix*; *E. coli*, *Enterococcus* spec. 37 °C; all other 30 °C)	60 µL	Ec	Sensitive	9.77 mm	Bonomo et al. (2020)
					Hf	Sensitive	–	
					Pf	Sensitive	–	
					Pp	Sensitive	–	
					Bt	Sensitive	–	
					Cd	n.s.	–	
					Cm	n.s.	–	

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Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					Eca	Sensitive	–	
					Ed	Sensitive	–	
					Ef	Sensitive	–	
					Efa	Sensitive	–	
					Eg	Sensitive	–	
					Eh	Sensitive	–	
					Ls	Resistant	–	
					Seq strain I	Sensitive	–	
					Seq strain II	Low/resistant	–	
					Seq strain III	n.s.	–	
					Ss	Sensitive	–	
					Sx	Low/resistant	–	
					Wci	n.s.	–	
					Wco	Sensitive	–	
					Wh	n.s.	–	
					Wm	Sensitive	–	
					Wp	n.s.	–	
					Wv	n.s.	–	
			MIC by agar well diffusion (24 h)	1–120 μg/mL	Ec	n.t.	–	
					Hf	n.t.	–	
					Pf	n.t.	–	
					Pp	n.t.	–	
					Bt	Sensitive	40 ± 0.45 μg/mL	
					Cd	n.t.	–	
					Cm	Sensitive	40 ± 0.34 μg/mL	
					Eca	Sensitive	5 ± 0.28 μg/mL	
					Ed	n.t.	–	
					Ef	Sensitive	5 ± 0.31 μg/mL	
					Efa	n.t.	–	
					Eg	Sensitive	40 ± 0.77 μg/mL	
					Eh	n.t.	–	
					Ls	n.t.	–	
					Seq strain I	Sensitive	40 ± 0.38 μg/mL	
					Seq strain II	n.t.	–	
					Seq strain III	n.t.	–	
					Ss	n.t.	–	
					Sx	n.t.	–	
					Wci	n.t.	–	
					Wco	n.t.	–	
					Wh	n.t.	–	
					Wm	n.t.	–	
					Wp	n.t.	–	
					Wv	n.t.	–	
P. sandrasica Hartvig & Strid [SAN: *P. auriculoides* (Láng) Arv.-Touv.]	AP	C_6H_{14}	Disc diffusion	20 μL (25 mg/mL)	Ea-RSKK720	Resistant	–	Ugur et al. (2010)
					Ec-ATCC25922	Resistant	–	
					Pa-ATCC27853	Resistant	–	
					Sma-MU23	n.t.	–	
					Sma-MU25	n.t.	–	
					Sma-MU52	n.t.	–	
					Sma-MU53	n.t.	–	
					Sma-MU63	n.t.	–	
					Sma-MU64	n.t.	–	
					Sma-MU69	n.t.	–	
					Sma-MU94	n.t.	–	
					Sma-MU99	n.t.	–	
					Sma-MU136	n.t.	–	
					Sma-MU137	n.t.	–	
					Bs-ATCC6633	Resistant	–	
					Ml-NRRLB-4375	Resistant	–	
					Sa-ATCC25923	Resistant	–	
					Sm-CNCTC8/77	Resistant	–	
					Sa-MU38	n.t.	–	
					Sa-MU40	n.t.	–	
					Sa-MU46	n.t.	–	
					Sc-MU27	n.t.	–	
					Sep-MU30	n.t.	–	
					Sle-MU43	n.t.	–	
					Ssp-MU28	n.t.	–	
					Sx-MU34	n.t.	–	

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Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					Sx-MU35	n.t.		
					Sx-MU37	n.t.	–	
					Sx-MU42	n.t.	–	
					Sle-MU43	n.t.	–	
					Ca-ATCC10239	Resistant	–	
					Ct-RSKK665	Resistant	–	
	AP	$CHCl_3$	Disc diffusion	20 µL (25 mg/ mL)	Ea-RSKK720	Sensitive	12 mm	Ugur et al. (2010)
					Ec-ATCC25922	Sensitive	10 mm	
					Pa-ATCC27853	Sensitive	13 mm	
					Sma-MU23	Resistant	–	
					Sma-MU25	Resistant	–	
					Sma-MU52	Resistant	–	
					Sma-MU53	Resistant	–	
					Sma-MU63	Resistant	–	
					Sma-MU64	Resistant	–	
					Sma-MU69	Resistant	–	
					Sma-MU94	Resistant	–	
					Sma-MU99	Resistant	–	
					Sma-MU136	Resistant	–	
					Sma-MU137	Resistant	–	
					Bs-ATCC6633	Resistant	–	
					Ml-NRRLB-4375	Resistant	–	
					Sa-ATCC25923	Resistant	–	
					Sm-CNCTC8/77	Resistant	–	
					Sa-MU38	n.t.	–	
					Sa-MU40	n.t.	–	
					Sa-MU46	n.t.	–	
					Sc-MU27	n.t.	–	
					Sep-MU30	n.t.	–	
					Sle-MU43	n.t.	–	
					Ssp-MU28	n.t.	–	
					Sx-MU34	n.t.	–	
					Sx-MU35	n.t.	–	
					Sx-MU37	n.t.	–	
					Sx-MU42	n.t.	–	
					Ca-ATCC10239	Resistant	–	
					Ct-RSKK665	Resistant	–	
	AP	$C_4H_8O_2$	Disc diffusion	20 µL (25 mg/ mL)	Ea-RSKK720	Resistant	–	Ugur et al. (2010)
					Ec-ATCC25922	Resistant	–	
					Pa-ATCC27853	Resistant	–	
					Sma-MU23	n.t.	–	
					Sma-MU25	n.t.	–	
					Sma-MU52	n.t.	–	
					Sma-MU53	n.t.	–	
					Sma-MU63	n.t.	–	
					Sma-MU64	n.t.	–	
					Sma-MU69	n.t.	–	
					Sma-MU94	n.t.	–	
					Sma-MU99	n.t.	–	
					Sma-MU136	n.t.	–	
					Sma-MU137	n.t.	–	
					Bs-ATCC6633	Resistant	–	
					Ml-NRRLB-4375	Resistant	–	
					Sa-ATCC25923	Resistant	–	
					Sm-CNCTC8/77	Resistant	–	
					Sa-MU38	n.t.	–	
					Sa-MU40	n.t.	–	
					Sa-MU46	n.t.	–	
					Sc-MU27	n.t.	–	
					Sep-MU30	n.t.	–	
					Sle-MU43	n.t.	–	
					Ssp-MU28	n.t.	–	
					Sx-MU34	n.t.	–	
					Sx-MU35	n.t.	–	
					Sx-MU37	n.t.	–	
					Sx-MU42	n.t.	–	
					Ca-ATCC10239	Resistant	–	
					Ct-RSKK665	Resistant	–	
	AP	C_2H_5OH	Disc diffusion	20 µL (25 mg/ mL)	Ea-RSKK720	Sensitive	11 mm	Ugur et al. (2010)
					Ec-ATCC25922	Sensitive	10 mm	
					Pa-ATCC27853	Sensitive	14 mm	
					Sma-MU23	Sensitive	11 mm	

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Table 8 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Organism tested	Results	MIC/Inhibition zone	Reference
					Sma-MU25	Sensitive	13 mm	
					Sma-MU52	Sensitive	11 mm	
					Sma-MU53	Sensitive	15 mm	
					Sma-MU63	Sensitive	10 mm	
					Sma-MU64	Sensitive	14 mm	
					Sma-MU69	Sensitive	10 mm	
					Sma-MU94	Sensitive	14 mm	
					Sma-MU99	Sensitive	15 mm	
					Sma-MU136	Sensitive	17 mm	
					Sma-MU137	Sensitive	14 mm	
					Bs-ATCC6633	Resistant	–	
					Ml-NRRLB-4375	Resistant	–	
					Sa-ATCC25923	Sensitive	21 mm	
					Sm-CNCTC8/77	Sensitive	11 mm	
					Sa-MU38	Sensitive	18 mm	
					Sa-MU40	Sensitive	15 mm	
					Sa-MU46	Sensitive	16 mm	
					Sc-MU27	Resistant	–	
					Sep-MU30	Sensitive	16 mm	
					Sle-MU43	Sensitive	13 mm	
					Ssp-MU28	Resistant	–	
					Sx-MU34	Sensitive	13 mm	
					Sx-MU35	Sensitive	18 mm	
					Sx-MU37	Sensitive	17 mm	
					Sx-MU42	Sensitive	19 mm	
					Ca-ATCC10239	Resistant	–	
					Ct-RSKK665	Sensitive	12 mm	

Abreviations used: n.t. not tested, WP whole plant, AP aerial parts, R roots, F flowering heads, L leaves, S seeds, St stems. Abbreviations of microorganisms Bm *Brucella melitensis*, Bab *B. abortus bovi*, Bsu *B. suis*, Ec *Escherichia coli*, Ea *Enterobacter aerogenes*, Kp *Klebsiella pneumoniae*, Pm *Proteus mirabilis*, Psp *Proteus* sp., Pv *P. vulgaris*, Pa *Pseudomonas aeruginosa*, Pf *P. fragi*, Pp *P. proteamaculans*, Se *Salmonella enteridis*, Sty *S. typhi*, St *S. typhimurium*, Sma *Serratia marcescens*, Sd *Shigella dysenteriae*, Sma *Stenotrophomonas maltophilia*, Bc *Bacillus cereus*, Ba *B. subtilis*, Bt *Brochothrix thermosphacta*, Cd *Carnobacterium divergens,* Cm *C. maltaromaticum*, CM *Clostridium sporogens*, Eca *Enterococcus casseliflavus*, Ed *E. durans*, Ef *E. faecalis*, Efa *E. faecium*, Eh *E. hirae*, Eg *E. gallinarum*, Ls *Lactobacillus sakei*, Li *Listeria innocua*, Lm L. *monocytogenes*, Ml *Micrococcus luteus*, Pac *Propionibacterium acnes*, Sa *Staphylococcus aureus*, Sc *S. capitis*, Sch *S. choleraesius*, Sep *S. epidermidis*, Seq *S. equorum*, Sle *S. lentus*, Ss *S. succinus*, Ssp *Staphylococcus* sp., Sx *S. xylosus*, Sf *Streptococcus faecalis*, Sl *S. lactis*, Sm *S. mutans*, Wci *Weissella cibaria*, Wco *W. confusa*, Wh *W. hellenica*, Wm *W. minore*, Wp *W. paramesenteroides*, Wv *W. viridescens*, Af *Aspergillus fumigatus*, An *A. niger*, Ca *Candida albicans*, Cp *C. parapsilosis*, Ct *C. tropialis*, Ctr *C. tropicalis*, Fo *Fusarium oxysporum*, Mc *Microsporum canis*, Mg *M. gypseum*, Pen *Penicillium* sp., Tm *Trichophyton mentagrophytes*.

nonsteroidal anti-inflammatory drugs treat acute inflammatory disorders, these conventional drugs have not been successfully administred to cure chronic inflammatory disorders such as rheumatoid arthritis nor atopic dermatitis (Kim et al., 2004). Bae et al. (2013) studied in an *in vivo* model the effect of an ethanolic extract of a nine-plants mixture containing *H. albiflorum* on allergic skin inflammation while understanding the underlying mechanism. Therefore, mice were sensitizied by either TMA or OVA and several parameters (earthickness, serum IgE levels; IFN-γ, IL-1β, IL-2, IL-4, IL-10 secreted from splenocytes) were evaluated. Additionally, splenocytes of OVA-sensitizied mice were treated with each plant extract separately to evaluate the IC_{50} of IL-4 as well as the ratio of IFN-γ/IL-4. While both treatment regimes comprised a solvent control group (OVA: saline and 2.5% ethanol; TMA: acetone and isopropyl myristate (4:1, v/v)), the usage of prednisolone as a positive control was restricted to sensitization with TMA. NPM-9 significantly decreased serum IgE production in TMA treated mice, IL-1β in the ear tissure and IL-4 as well as IL-1β, both secreted from splenocytes. Treatment with NPM-9 of OVA sensitized mice led to significantly decreased OVA-specific IgE as well as IL-4, whereas IFN-γ and IL-2 significantly increased. IL-10 values of the NMP-9 treated mice did not significantly differ from naïve and untreated groups. Treatment of splenocytes from OVA sensitized mice with the ethanolic extract of *H. albiflorum* displayed an $IC_{50} = 208$ μg/mL, thus being the second least active out of the tested extracts, while the resulting IFN-γ/IL-4 ratio was also the second lowest (together with turmeric which displayed the same ratio). However, the authors did not state the concentrations tested *ex vivo*. The authors concluded that NPM-9 supresses the T-helper cells 2 mediated allergic response, which they assumed is linked to a possible induction of T-helper cells 1. Additionally, the authors stated that the natural product mixture (NPM-9) has been patented in Korea (Patent number 10–1141191).

Another *in vivo* study carried out by Petrović et al. (2008) analysed the anti-inflammatory activity of *H. gymnocephalum* Griseb. ex Pant. extracts (aerial blooming parts/CH_2Cl_2) by means of the reduction of the carrageenan induced edema in rats' paw. The authors observed anti-inflammatory effects of 5.9, 11.7, 31.2 and 44.1% at doses of 25, 50, 100 and 200 mg/kg, respectively. The authors stated that the highest doses were comparable to the effects of indomethacin, which was applied as reference. In a previous study, the triterpenols α- and β-amyrin were isolated from the chloroform extract of the aerial parts of *H. gymnocephalum* (Petrović et al., 1999a) which were found to possess anti-inflammatory activity (Akihisa et al., 1996). Thus, the authors concluded that the triterpenols were the cause of the anti-inflammatory activity. Milutinović et al. (2020) tested three *Hieracium* species in the carrageenan-induced localised inflammation model in rats. The dichloromethane extract of *H. scheppiginaum* Freyn and the pretreated methanol extract of *H. glabratum* Willd. (according to The Plant List *H. glabratum* Willd. ex Froel.) both achieved antihyperalgesic effects of more than 50% (calculated on the averaged differences observed in the control group) at the highest tested dose (200 mg/kg p.o.). Both extracts did not influence the motoric ability as tested in the rotarod test in rats (in the dose 200 mg/kg p.o.) and proved to be non-toxic in mice in a two-week span after administering oraly the tenfold of the dosis used to investigate the antihyperalgesic effect. The effective dose of *H. scheppigianum* was determined as $ED_{50} = 163.0 \pm 26.5$ mg/kg, the one of *H. glabratum* as $ED_{50} = 211.6 \pm 70.6$ mg/kg. The third tested extract, derived from the aerial flowering parts of *H. calophyllum* R.Uechtr., was less active (38.1%). Ibuprofene was used as a reference drug (100 mg/kg). None of the tested extracts displayed a significant reduction of the edema. Based on their conducted literature search the authors

considered α- and β-amyrin as well as lupeol acetate in the extract of *H. scheppigianum* and flavonoids of the luteolin and apigenin type in the methanolic extracts of *H. glabratum* and *H. calophyllum* as active principles responsible for the antihyperalgesic effect (Milutinović et al., 2020). Aliyazicioğlu et al. (2019) reported on the effect of a methanolic extract of the aerial parts of *P. hoppeana* subsp. *testimonialis* [SAN: *P. testimonialis* (Nägeli ex J.Hofm.) Gottschl.] on the NO concentration, the heme oxygenase activity in cells, and the inhibition of both COX1 and COX2. Further, typical parameters involved with inflammation such as MMP-9, JNK, TNF-α, Nrf-2, p38, IL-10 and IL-1β were investigated by means of a Western blot. However, results of the Western blot were presented as figures, allowing only the interpretation of the overall trend: the tested extract led to an increase of the tested parameters. Only IL-1β did not increase at the two lower tested concentrations (50, 25 μg/mL) in comparison to the negative control. Significance was not stated for the results of the Western blot. HPLC analyses of the methanolic extract revealed the presence of syringaldehyde (stated as shiringaldehyde), sinapic acid, benzoic acid, and quercetin. The authors concluded that the extract has wound healing abilities due to the demonstrated anti-inflammatory activities. Further information on the tested plant organs, extracts, tested doses and obtained results are displayed in Table 7.

5.3. Antibacterial activity

The resistance of bacteria expanded due to the indiscriminate use of antibiotics for the treatment of infectious diseases. This situation has led to increased efforts in the search of new antimicrobial compounds from diverse sources including medicinal plants (Bauer et al., 1966; Cheesman et al., 2017). A variety of techniques have been reported for determining the antimicrobial activity of plant materials. The most frequently *in vitro* used techniques include the agar well diffusion method and the dilution method based on incorporation of plant samples in the media prior to inoculation. Out of the investigated taxa, a *Hieracium* species (determination was performed only at the level of the genus by the authors) (Barbour et al., 2004), *P. sandrasica [SAN: P. auriculoides (Láng) Arv.-Touv.]* (Ugur et al., 2010) and *P. officinarum* Stanojević et al. (2008); Frey and Meyers (2010); Nostro et al. (2000); Greib and Duquénois (1960); Bonomo et al. (2020) displayed antimicrobial activity in various screenings. Further, isoetin 4′-*O*-β-D-glucopyranoside, a flavonoid isolated from the flowering heads of *P. officinarum*, was slightly active against *Pseudomonas aeruginosa* (MIC = 125 μg/mL). The antimicrobial activity of *P. sandrasica* focussed on an ethanolic extract while the respective chloroform extract was active against less species. The antimicrobial activity as compiled from the available literature neither focussed on gram-positive nor gram-negative strains and was not restricted to plant organs nor extracts. Table 8 provides a more detailed overview about the compiled literature.

Stanojević et al. (2008) performed antimicrobial tests subjecting extracts of different polarity prepared from the whole plant of *P. officinarum* using the disc diffusion test. However, neither positive nor negative controls were included in this work. Frey and Meyers (2010) studied the effect of the aqueous extracts of *P. officinarum* using both the disc diffusion as well as a serial dilution assay. Both assays comprised sterile water as negative and ampicillin as positive controls. The linearity of the obtained results by the serial dilution assay was demonstrated by correlation coefficients $R^{2=}$0.89 for flowering heads, 0.95 for leaf extracts, and 0.63 for steam extracts. Nostro et al. (2000) investigated the antimicrobial activity of the leaves of *P. officinarum*. Extracts of different polarity were evaluated in the disc diffusion test with DMSO as negative and vancomycin, amoxicillin, and amphotericin as positive controls. The authors did not establish the MICs of compounds with a diameter of less than 12 mm in the initial testing. In the following investigations *Escherichia coli* was noted not to be tested due to the diameter being less than 12 mm. In fact, *E. coli* was stated to be inactive in the initial screening unlike *Proteus vulgaris* which was inhibited by the diethyl ether extract (8 mm diameter inhibition zone). It seems likely that the authors confused the notification attached to *E. coli* with *P. vulgaris*.

Greib and Duquénois (1960) tested the effect of aqueous extracts derived from *P. officinarum* against three *Brucella* species both *in vitro* and *in vivo*. In the *in vitro* assay, the extracts could cut the microorganisms' growth. The authors also found that the treatment was easily tolerated, non-toxic and effective (even in cases of chronic brucellosis) after administration to the animals. However, the authors did not state what plant organ had been extracted nor how the experiment was conducted. Finally, Bonomo et al. (2020) screened an ethanolic extract of *P. officinarum*. Highly active extracts were further used to establish MICs of sensitive strains. However, although the extract of *P. officinarum* was found effective against all gram-negative species in the initial testing, the authors investigated only MICs of gram-positive bacteria. The authors did not provide information about the extracted plant organ. In this study five strains of *Lactobacillus sakei* were included but did not differ in hindsight of the results, hence the summarising table does not discriminate between the strains. Gawrońska-Grzywacz et al. (2011) screened isoetin 4′-*O*-β-D-glucopyranoside for its antimicrobial activity using the agar well diffusion and micro-dilution broth method. Wells containing DMSO without test compound were used as negative control, and gentamicin and fluconazole as positive controls.

In an antimicrobial screening of species indigenous to Lebanon, Barbour et al. (2004) investigated a not nearer determined *Hieracium* species. A negative control experiment was conducted with the solvent, but the usage of a positive control was not mentioned. They further did not provide information on the incubation time. Several extracts were prepared of the aerial parts of *P. sandrasica*, an endemic species in Turkey, and screened using the disc diffusion method to identify candidates that were then subjected to multiresistant strains. Although the authors used hexane, chloroform, ethanol, and ethyl acetate as negative controls, any mention is made on the positive controls employed (Ugur et al., 2010). However, further investigations on the composition of the active extracts were restricted to the chloroform extract, revealing monoterpene hydrocarbons, sesquiterpenoids, and diterpenoids (Ugur et al., 2010).

For the methanolic extract prepared by Booth et al. (2012) of *H. caespitosum* [SAN: *Pilosella caespitosa* (Dumort.) P.D.Sell & C.West] the sample was weighed first and only then ground, resulting in a possibly lower concentration than stated. The concentration tested by Borchardt et al. (2008) remains unclear: after extraction of 2 mg of plant material, the solvent was evaporated to a not nearer defined concentration, thus limiting the comparability between the investigated plant species and other studies.

5.4. Antimycotic activity

In many studies screening the antimicrobial activity of *Hieracium* and *Pilosella* extracts moulds and yeasts were included, thus providing an overview about the antimycotic range (Table 8). Stanojević et al. (2008) studied the effect of *P. officinarum* extracts of different polarity on the fungi *Aspergillus niger* and *Candida albicans* using the disc diffusion test method as well as determining the corresponding MIC values. However, neither positive nor negative controls were included in this work. In the screening of extracts of *P. officinarum* conducted by Nostro et al. (2000) the antimycotic activity was studied. Further investigations on the respective MICs were conducted but values were not established for *Fusarium oxysporum* and the *Penicillium* species despite the earlier observed activity in the disk diffusion test. DMSO was used as negative and vancomycin, amoxicillin, and amphotericin as positive controls. Gawrońska-Grzywacz et al. (2011) isolated isoetin 4′-*O*-β-D-glucopyranoside from the flowering heads of *P. officinarum* and subjected it to the agar well diffusion method against two yeasts species. They used DMSO without test compound as negative control and

fluconazole as positive control. The Turkish species *P. sandrasica* was tested against two yeasts by Ugur et al. (2010). They used hexane, chloroform, ethanol, and ethyl acetate as negative controls but any mention is made on the positive control. *H. umbellatum* did not display an inhibition of the growth of *C. albicans* (Borchardt et al., 2008; Kuluev et al., 2019) as well as a hexane extract of the roots of *P. echioides* (Kuluev et al., 2019).

5.5. Antioxidant activity

The reviewed literature on antioxidant activities of *Hieracium* and *Pilosella* species comprised a broad variety of *in vitro* assays based on the free radical scavenging activity (DPPH, ABTS tests), reduction of ferric ions as well as other markers of oxidative stress investigated in tests such as the β-carotene-linoleic acid assay. A complete list of all reviewed studies is compiled in Table 9. Amongst the studied species *P. officinarum* recieved the most attention.

Especially in case of the DPPH assay differences in the methodology between studies were observed. The incubation time ranged from no incubation at all to 4 h while the temperature during the incubation varied between the studies or was not stated at all. To improve comparability, whenever possible the tested concentrations were calculated from the information stated by the authors. In addition, in case of the DPPH assay the results were altered to IC_{50} if synonyms of this value were stated. In only on case the authors investigated the antioxidant capacity of a single compound, isoetin 4′-*O*-β-D-glucopyranoside, isolated from the flowering heads of *P. officinarum* (Gawrońska-Grzywacz et al., 2011). In the remaining studies, crude extracts of different polarity of 39 plant species were investigated, revealing a broad range of antioxidant activity. Detailed results are stated in Table 9.

5.6. Antiviral activity

Both *H. umbellatum* and *P. officinarum* were subject of *in vitro* studies evaluating a potential usage in the treatment of HIV. More detailed information on the two studies is compiled in Table 10. Min et al. (1999) screened methanol extracts of 93 Korean plant species *in vitro* against the HIV-1 protease. Among the tested species was *H. umbellatum*, that however was not considered active due to the low inhibion of the HIV-1 protease (15.0 ± 2.6%) in comparison to the other species tested. The authors performed the experiments using negative controls, i.e., the protease without any extracts, and acetyl pepstatin as positive control (50% inhibitory activity, IC_{50} at 29 μg/mL). A second study investigated the ethanolic and aqueous extracts of *P. officinarum* (Bedoya et al., 2001). The antiviral activity was evaluated using MT-2 NL 4.3 cells infected with HIV-1, simultaneously determining the cytotoxic effect of the extracts by the MTT assay. Ethanolic extracts showed marked cytotoxicity, thus preventing the testing of higher concentrations. The aqueous extract of *P. officinarum* was neither cytotoxic in the evaluated concentration (0–200 μg/mL) nor did the extract show any antiviral effect against HIV. The authors did not state whether they conducted control experiments nor what plant organ was extracted, although they mentioned that plants were collected during the flowering season. It should be noted that although the authors stated 500 μg/mL as highest tested concentration in case of *P. officinarum* the highest tested concentration appears to be 200 μg/mL.

5.7. Cytotoxic and antiproliferative activities

Substantial research has been directed towards discovering compounds with cytotoxic and antiproliferative activities that might be endowed with potential chemopreventive or anticancer applications (Twilley et al., 2020). The antiproliferative effect of isoetin 4′-*O*-β-D-glucopyranoside isolated from *P. officinarum* flowering heads by Gawrońska-Grzywacz et al. (2011) was assayed *in vitro* in two human tumor cell lines derived from lung (A549) and colon (HT-29). Cells were exposed to either the culture medium (negative control) or the tested flavonoid (1–100 μM) for 96 h and their proliferation was determined by means of the MTT method. In case of the HT-29 cell culture, the proliferation was significantly decreased (10–100 μM) in a non-dose dependent manner ($p < 0.05$). Proliferation of A549 cells was not affected by up to 25 μM, however at the highest concentrations (50 and 100 μM) a significant increase was observed ($p < 0.05$). The screening of plant extracts in search of candidates for the treatment of HIV by Bedoya et al. (2001) included the evaluation of the cytotoxic effect of the extracts. The aqueous extract of *P. officinarum* was considered non-toxic in the tested range (0–200 μg/mL) while all investigated ethanolic extracts displayed pronounced cytotoxic activity against MT-2 cells. However, the authors did not state what plant organ was extracted. Le Coguic and Seralini (2019) evaluated a multi component nutraceutical containing amongst other *P. officinarum* in three different cell lines (HEK 293, HepG2, and JEG-3) in a MTT assay. Of the three tested cell lines only JEG-3 cells were affected by concentrations of more than 0.2%, resulting in significantly decreased viability. While the viability of the cells was calculated using untreated cells, a positive control was not mentioned. In an additionally conducted bromodeoxyuridine cell proliferation ELISA assay the nutraceutical containing *P. officinarum* was not included. The methanolic extract of the whole plant of *H. caespitosum* [SAN: *P. caespitosa* (Dumort.) P.D.Sell & C.West] was mildy active in another *in vitro* experiment against HeLa cells. The authors calculated a LC_{50} of 0.67 mg/mL by the least squares regression at doses from 0.6 to 0.06 mg/mL (Booth et al., 2012) and hence the value appears to be extrapolated. Tris buffer was used as a negative control in this work. Aliyazicioğlu et al. (2019) subjected HT29 and L9N29 cells to the methanolic extract of *P. hoppeana* subsp. *testimonialis*. The problematic of the identity of this subspecies has been pointed out above. Treatment in the range of 12.5–250 μg/mL did not reduce the viability more than 25%. It seems that the authors mixed up the order in which the results were stated as the highest tested concentration resulted in the highest viability in both tested cell lines. For more information, see Table 11.

Investigations on the cytoxic activity remain scarce so far. However, especially the findings of Bedoya et al. (2001) indicate that the kind of preparations, i.e., the way of extraction, might influence the cytotoxic effect. Nevertheless, as already pointed out above, reports about side effects of the usage of *P. officinarum* preparations are limited to one single note.

5.8. Diuretic activity

Diuresis is the increased volume of urine depending on high levels of excrete sodium. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. The number of studies investigating the diuretic activity was restricted to three reports. An *in vivo* study by Beaux et al. (1999) investigated the diuretic effect of an ethanolic extract of *P. officinarum* aerial parts after the intra-peritoneal administration of two doses (50 and 200 mg/kg animal) in rats during the following 2–24 h. The negative controls were treated with hypotonic saline solution, while positive controls received hydrochlorothiazide (10 mg/kg). Unfortunately, the authors did not state in what unit the secreted volume of the urine was measured. Another *in vivo* study by Canello et al. (2017) performed a clinical evaluation on the effect of a nutraceutical diet enriched with plants (with *P. officinarum* as the most abundant in a 5-plants mixture) applied to 33 cats suffering from cystitis with evident hematuria, dysuria and/or stranguria. The trial lasted 30 days. The authors obtained a significant restoration of the urine color, turbidity, pH, RBC, WBC, as well as a significant urine weight and protein decrease and a significant decrease of struvite uroliths in all treated cats at the end of the treatment. However, they did not employ positive nor negative controls in this study and the comparisons were made before and after the treatment over the same group of animals. Further missing were statements on the

extracted plant organs and the extraction solvent. Information on the actually carried out feeding regime were missing as well as the authors refer to the instructions of the supplier without providing sufficient information to comprehend that aspect. It was not investigated how the single compounds of the mixture contribute to the observed effects. Perna et al. (2020) investigated the effects of a supplement containing an undefined extract of *P. officinarum* on the bloating sensation and hydration in women. Participants took the mixture diluted in water each morning and results were evaluated after 30 and 60 days. The hydration improved significantly, while the bloating sensation was not significantly improved. Interestingly, according to the composition as stated in the supplementary data the *P. officinarum* extract contains the flavonoid vitexin, a derivative of apigenin, which was so far not reported from this taxon. The study was rather small with no more than 19 participants and did not include a placebo or negative group. The complex mixture of the supplement does not allow to interpretate the contribution of single extracts. More detailed information on the discussed studies is provided in Table 12. For better understanding the differences between T_0 and T_1 as obtained by Canello et al. (2017) were calculated.

5.9. Gastroprotective activity

Ulcers are a usual illness of the gastrointestinal tract. They are open sores that develop on the lining of the stomach. Classical approaches to treat them involve a combination of PPI and antibiotics. Petrović et al. (2008) analysed the gastroprotective activity of *H. gymnocephalum* Griseb. ex Pant. extract (aerial blooming parts/CH_2Cl_2) using the *in vivo* experimental model of indomethacine-induced gastric mucosa lesions. Rats that received the extract of *H. gymnocephalum* (200 mg/kg p.o.) displayed a reduction of lesions (40% less animals with lesions), as well as significantly reduced gastric damage, lesion area and length of gastric lesions ($p < 0.05$ vs control). An anti-inflammatory effect ($p < 0.01$ vs control) was also observed. DMSO was used to treat the control group but no positive control was included. In earlier conducted studies (Petrović et al., 1999a), α- and β-amyrin, triterpene alcohols that possess anti-inflammatory and gastroprotective effects (Akihisa et al., 1996; Navarrete et al., 2002), were isolated from the chloroform extract of the aerial parts of *H. gymnocephalum*. Hence, the authors concluded that these compounds could be responsible for the reduced symptoms observed in the study. Testing conditions are compiled in Table 13.

5.10. Antiepileptic activity

Epilepsy can be caused by imbalance in the GABAnergic system. The GABAA receptor, which is involved in epilepsy, has a binding site for compounds, such as benzodiazepines (Stafford et al., 2005). Thus, a way to determine the antiepileptic potential of plant extracts is to test for affinity to the benzodiazepine site on the GABAA receptor, which enhances the receptor sensitivity for endogenous GABA, preventing epileptic incidences (Jäger et al., 2006). Jäger et al. (2006) tested 42 species traditionally used in the Danish folk medicine to treat epilepsy and convulsions in a flumazenil-binding assay. Total and unspecific binding was determined with buffer or diazepam (1 M, final concentration in assay). In comparison to other tested species (*Primula elatior* Hill, *P. veris* L. and *Tanacetum parthenium* Sch.Bip.) the binding of the tested *P. officinarum* extracts was rather low. However, the ethanolic extracts was slightly more active than the aqueous. Detailed information is provided in Table 14.

5.11. Hypotensive activity

Hypertension is a major contributor to blood vessels–related diseases such as stroke, myocardial infarction, chronic renal failure, and congestive heart failure (Mantero and Boscaro, 1992). Marked hypotensive effect was obtained by some extracts from Bulgarian *P. officinarum* (Petkov, 1986). However, the approach used to study this activity (including controls), the kind of extracts, dose-range tested, effective concentrations and measurements on activity were not mentioned in this work.

5.12. Anti-obesity activity

According to the World Health Organisation, 65% of the world's population live in countries where overweight and obesity kills more people than underweight (World Health Organization, 2011) becoming a first-order problem. Lee et al. (2012) screened the lipase inhibitory activity *in vitro* of methanol extracts from 560 different medicinal plant species, including *H. umbellatum*. Amounts of oleic acid produced in the enzymatic conversion of triolein by the porcine pancreatic lipase (Type II) were measured to determine the inhibitory activity of the plant extracts. In comparison to the most active species (*Desmodium oxyphyllum* DC., with 74.2 ± 0.4%) *H. umbellatum* showed a relatively high activity with 49.8 ± 0.5%. However, there is no mention of the use of control groups (positive or negative) in this work. Table 14 provides more detailed information.

5.13. Arthropodicidal activities with applications in veterinary and agriculture

In a screening of medicinal plant species the methanol extract of the whole plant of an undetermined *Hieracium* species (collected in Kneisseh, Lebanon) significantly lowered the number of alive nymphs of the Cotton Whitefly, *Bemisia tabaci* (Gennadius, 1889), (Hammad et al., 2014). Treatment with the extract of the *Hieracium* species led to oozing in the nymphs, indicating a toxic effect. However, the extract was ineffective against adult whiteflies. A slight acaricidal activity of methanol extracts was reported by Hammad et al. (2017). The extract of the whole plant from another unidentified *Hieracium* species collected in Kneisseh (Lebanon) led to a mortality of *Tetranychus urticae* Koch, 1836 adult mites. This was about half of the strength in comparison to the most active extract (*Lotus carmeli* Boiss., whole plant, 43.6 ± 8.4% mortality). Both studies used 10% methanol or distilled water in control groups. Information on both studies are compiled in Table 14.

5.14. Global periorbital skin rejuvenation

To counter the signs of aging affecting the area around the eye Colvan et al. (2019) investigated whether the daily application of a cosmetic cream containing low molecular weight heparan sulfates and plant extracts bettered the overall appearance. Amongst other the formulation contained low amounts of an undefined extract of *P. officinarum*. However, the number of participants ($n = 15$) was rather low, and it was not evaluated how each component of the cosmetic cream contributed to the observed effects, thus not allowing for an interpretation of the activity exerted by *P. officinarum*. Results are stated in more detail in Table 14.

5.15. Reduction of ruminal ammonia

High amounts of ammonia due to the intake of crude protein can stress the metabolism of cows (Kapp-Bitter et al., 2020). An *in vitro* study investigated whether the intake of plant species could lower the amount of ammonia formation in the rumen, assuming that high amounts of tannins could prevent the crude protein from being decomposed (Kapp-Bitter et al., 2020). It needs to be noted that the values were established for the tested plant species as part of a mixture of plants. Additionally, the plant species were characterized with regard to parameters evaluating the nutrient value that was estimated as the IVOMD as well as the basic chemical composition thus providing data on the content of condensed tannins, non-tannin phenols, total extractable phenols, and total tannis. All three values significantly differed from the respective results achieved by the basal mixture. The authors observed a

Table 9
Compiled antioxidant assays conducted on *Hieracium* and *Pilosella* species.

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
Hieracium albopellitum (Zahn) Niketić [SAN: *H. thapsiformoides* subsp. *albopellitum* (Zahn) Greuter]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	did not reach 50% inhibition of OH radical	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 40.82 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.18 ± 0.14 mmol Fe^{2+}/g extract	
H. anastrum Degen & Zahn [SAN: *H. pichleri* subsp. *anastrum* (Degen & Zahn) Zahn]	AP + F	CH_3OH	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 18.69 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 41.37 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.21 ± 0.18 mmol Fe^{2+}/g extract	
H. aurantiacum L. [SAN: *Pilosella aurantiaca* (L.) F.W.Schultz & Sch.Bip.]	AP + F	C_2H_5OH:H_2O (70:30)	DPPH scavenging activity	no incubation, SIA	0.005–1 mg/mL	IC_{50} = 0.174 mg/mL	Koleckar et al. (2008)
H. blecicii Niketić [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 16.06 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 30.44 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.35 ± 2.21 mmol Fe^{2+}/g extract	
H. bornmuelleri Freyn [SAN: *H. pannosum* subsp. *bornmuelleri* (Freyn) Murr & Zahn]	AP	n.s.	DPPH scavenging activity	30 min at 30 °C	0.0005–0.0333 mg/mL	IC_{50} = 0.939 mg/mL	Bakar et al. (2015)
			TBARS assay	duration not stated	n.s.	MDA = 24.56 nmol/mL	
	R	CH_3OH:H_2O (80:20)	DPPH scavenging activity	30 min at 30 °C	0.0005–0.0333 mg/mL	IC_{50} = 0.461 mg/mL	
			TBARS assay	duration not stated	n.s.	MDA = 37.74 nmol/mL	
H. caespitosum Dumort [SAN: *P. caespitosa* (Dumort.) P.D.Sell & C. West]	AP + F	C_2H_5OH:H_2O (70:30)	DPPH scavenging activity	no incubation, SIA	0.005–1 mg/mL	IC_{50} = 0.129 mg/mL	Koleckar et al. (2008)
H. calophyllum R.Uechtr.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 23.54 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 42.28 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.12 ± 0.11 mmol Fe^{2+}/g extract	
H. cappadocicum Freyn [SAN: *H. chalcidicum* subsp. *cappadocicum* (Freyn) Greuter]	n.s.	CH_3OH	DPPH scavenging activity	30 min at room temperature	n.s.	IC_{50} = 30 ± 0.14 μg/mL	Tepe et al. (2006)
			Linoleic acid oxidation	48 h at room temperature	350 μL (2 g/L)	Inhibition of 55.1 ± 2.33%	
H. coloriscapum Rohlena & Zahn	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 19.95 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 38.94 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.17 ± 0.18 mmol Fe^{2+}/g extract	
H. dentatum s.l. Hoppe	AP + F	CH_3OH	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 22.97 μg/mL	
				30 min	2.5–200 μg/mL	IC_{50} = 33.31 μg/mL	

(*continued on next page*)

Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
			DPPH scavenging activity				
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.22 ± 0.11 mmol Fe^{2+}/g extract	
H. durmitoricum (Rohlena & Zahn) Niketić [SAN: *H. stirovacense* subsp. *durmitoricum* (Rohlena & Zahn) Greuter]	AP + F	CH_3OH	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 17.67 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 31.81 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.24 ± 0.09 mmol Fe^{2+}/g extract	
H. glabratum Willd. ex Froel.	AP + F	CH_3OH	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 12.11 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 14.20 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 2.65 ± 0.19 mmol Fe^{2+}/g extract	
H. guentheri-beckii Zahn	AP + F	CH_3OH	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 15.65 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 27.26 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.39 ± 0.25 mmol Fe^{2+}/g extract	
H. gymnocephalum Griseb. ex Pant.	AP + F	CH_2Cl_2	2-Deoxyribose assay	1 h at 37 °C	n.s.	Inhibition of OH· generation of 35.3%, 39.3%, 30.5%, 35.8% by 1%, 2.5%, 5%, and 10% (w/v)	Petrović et al. (2008)
			DPPH scavenging activity	30 min at 23 °C	0.0625–1.25 μg/mL	IC_{50} = 60 mg/mL	
			TBA test	1 h at 37 °C	0.0167–0.333 μg/mL	Inhibition of Fe^{2+}/ ascorbate induced LP of 7.4%, 16.6%, 4.8%, 3.8%, 12.9% at 0.5%, 1%, 2.5%, 5% and 10% (w/v)	
	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 22.88 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 34.39 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.17 ± 0.19 mmol Fe^{2+}/g extract	
H. laevigatum Froel.	AP + F	C_2H_5OH:H_2O (70:30)	DPPH scavenging activity	no incubation, SIA	0.005–1 mg/mL	IC_{50} = 0.233 mg/mL	Koleckar et al. (2008)
H. macrodontoides (Zahn) Zahn	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 18.06 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 30.65 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.52 ± 0.19 mmol Fe^{2+}/g extract	
H. mirificissimum Rohlena & Zahn [SAN: *H. stirovacense* subsp. *mirificissimum* (Rohlena & Zahn) Greuter]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 14.85 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 21.36 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 2.09 ± 0.38 mmol Fe^{2+}/g extract	
H. mokragorae (Nägeli & Peter) Freyn [SAN:	AP + F		2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	did not reach 50% inhibition of OH radical	

(*continued on next page*)

Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
H. pannosum subsp. *mokragorae* Nägeli & Peter]		CH_3OH (pretreated with CH_2Cl_2)					
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 60.00 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.03 ± 0.18 mmol Fe^{2+}/g extract	
H. murorum L.	AP + F	C_2H_5OH:H_2O (70:30)	DPPH scavenging activity	no incubation, SIA	0.005–1 mg/mL	IC_{50} = 0.132 mg/mL	Koleckar et al. (2008)
H. naegelianum Pančić	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 15.18 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 20.19 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.96 ± 0.25 mmol Fe^{2+}/g extract	
H. neilreichii Beck [SAN: *H. pallescens* subsp. *neilreichii* (Beck) Greuter]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 23.96 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 35.92 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.21 ± 0.05 mmol Fe^{2+}/g extract	
H. orieni A.Kern. [SAN: *H. gymnocephalum* Griseb. ex Pant.]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 18.24 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 35.28 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.24 ± 0.08 mmol Fe^{2+}/g extract	
H. paratrichum [NV, SAN: *H. gymnocephalum* Griseb. ex Pant.]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 21.76 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 34.48 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.29 ± 0.15 mmol Fe^{2+}/g extract	
H. pannosum Boiss.	F	CH_3OH	ABTS scavenging activity	6 min at room temperature	n.s.	IC_{50} = 0.258 ± 0.006 mg/mL	Gökbulut et al. (2017)
			DPPH scavenging activity	10 min	n.s.	IC_{50} = 0.767 ± 0.033 mg/mL	
			Ferric reducing antioxidant power	20 min at 50 °C	0.3, 1, and 3 mg/mL	Absorbances of 2.29 ± 0.04, 1.45 ± 0.06, 0.44 ± 0.01 for 3, 1, and 0.3 mg/mL respectively.	
			Metal chelating activity	not stated	0.3, 1, and 3 mg/mL	Inhibition percentages of 27.5 ± 7.29 at 3 mg/mL	
			Superoxide anion scavenging	5 min at room temperature	0.3, 1, and 3 mg/mL	Inhibition percentages of 56.34 ± 2.66, 33.29 ± 2.47 for 3 and 1 mg/mL respectively.	
	L	CH_3OH	ABTS scavenging activity	6 min at room temperature	n.s.	IC_{50} = 0.240 ± 0.005 mg/mL	
			DPPH scavenging activity	10 min	n.s.	IC_{50} = 0.776 ± 0.021 mg/mL	
			Ferric reducing antioxidant power	20 min at 50 °C	0.3, 1, and 3 mg/mL	Absorbances of 2.34 ± 0.19, 1.46 ± 0.00, 0.48 ± 0.06 for 3, 1, and 0.3 mg/mL respectively.	
			Metal chelating activity	not stated	0.3, 1, and 3 mg/mL	Inhibition percentages of 99.07 ± 6.16, 23.71 ±	

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Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
						2.68 at 3 and 1 mg/mL respectively.	
			Superoxide anion scavenging	5 min at room temperature	0.3, 1, and 3 mg/mL	Inhibition percentages of 48.70 ± 4.15, 14.79 ± 6.63, 9.59 ± 3.02 for 3, 1 and 0.3 mg/mL respectively.	
	R	CH_3OH	ABTS scavenging activity	6 min at room temperature	n.s.	IC_{50} = 0.101 ± 0.005 mg/mL	
			DPPH scavenging activity	10 min	n.s.	IC_{50} = 0.455 ± 0.004 mg/mL	
			Ferric reducing antioxidant power	20 min at 50 °C	0.3, 1, and 3 mg/mL	Absorbances of 2.81 ± 0.03, 1.50 ± 0.11, 0.52 ± 0.02 for 3, 1, and 0.3 mg/mL respectively	
			Metal chelating activity	not stated	0.3, 1, and 3 mg/mL	No inhibition recorded.	
			Superoxide anion scavenging	5 min at room temperature	0.3, 1, and 3 mg/mL	Inhition percentages of 71.76 ± 7.61, 55.12 ± 6.27 for 3 and 1 mg/mL	
H. pannosum s.l.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 24.45 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 56.60 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.05 ± 0.07 mmol Fe^{2+}/g extract	
H. pilosum Schleich. ex Froel.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 18.01 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 29.59 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.67 ± 0.32 mmol Fe^{2+}/g extract	
H. plumulosum A.Kern. [SAN: *H. waldsteinii* subsp. *plumulosum* (A. Kern.) Freyn]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	did not reach 50% inhibition of OH radical	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 39.26 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.19 ± 0.23 mmol Fe^{2+}/g extract	
H. pseudoschenkii (Rohlena & Zahn) Niketić [SAN: *H. bupleuroides* subsp. *pseudoschenkii* Rohlena & Zahn]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 21.65 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 33.95 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.20 ± 0.20 mmol Fe^{2+}/g extract	
H. pyricephalum Niketić [NV]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 22.94 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 40.17 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.19 ± 0.20 mmol Fe^{2+}/g extract	
H. scheppigianum Freyn	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 17.80 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 33.19 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.20 ± 0.16 mmol Fe^{2+}/g extract	

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Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
H. scorzonerifolium Vill. s.l.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 23.68 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 40.84 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.17 ± 0.10 mmol Fe^{2+}/g extract	
H. spirocaule Niketić [NV]	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 22.48 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 38.88 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.16 ± 0.22 mmol Fe^{2+}/g extract	
H. tommasinianum K.Malý	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	did not reach 50% inhibition of OH radical	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 56.82 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.05 ± 0.03 mmol Fe^{2+}/g extract	
H. umbellatum L.	F	C_2H_5OH (80%)	ABTS scavenging activity	10 min	n.s.	RC_{50} = 0.26 ± 0.01 mg/mL	Woo et al. (2010)
			DPPH scavenging activity	30 min at room temperature	n.s.	IC_{50} = 0.22 ± 0.00 mg/mL	
			Ferrous ion chelating	10 min at room temperature	n.s.	RC_{50} = 1.97 ± 0.14 mg/mL	
			Inhibition activity on lipid peroxidation of linoleic acid	stored at 40 °C, 3 min after adding the testing reagents	0.025 mg/mL	Inhibitory rate of 72.16 ± 0.43% on the 4th day; not detected on days 8, 12, 16, 20, 24, 28, 32	
	S	n.s.	DPPH scavenging activity	4 h at 35 °C	n.s.	27.85 μM Trolox/100 g (TE)	Borchardt et al. (2008)
H. valdepilosum Vill. s.l.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 20.58 μg/mL	Milutinović et al. (2018b)
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 35.06 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.20 ± 0.19 mmol Fe^{2+}/g extract	
H. villosum Jacq.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	2-Deoxyribose assay	1 h at 37 °C	0.875–200 μg/mL	IC_{50} = 23.59 μg/mL	
			DPPH scavenging activity	30 min	2.5–200 μg/mL	IC_{50} = 39.19 μg/mL	
			FRAP assay	30 min at 37 °C	16.1 μg/mL	TAA = 1.41 ± 0.21 mmol Fe^{2+}/g extract	
P. caespitosa (Dumort.) P. D.Sell & C.West	AP + F	C_2H_5OH:H_2O (70:30)	DPPH scavenging activity	no incubation, SIA	0.005–1 mg/mL	IC_{50} = 0.134 mg/mL	Koleckar et al. (2008)
P. hoppeana subsp. *testimonialis* [SAN: *P. testimonialis* (Nägeli ex J.Hofm.) Gottschl.]	AP	n.s.	DPPH scavenging activity	30 min at 30 °C	0.0005–0.0333 mg/mL	IC_{50} = 0.864 mg/mL	Bakar et al. (2015)
			TBARS assay	duration not stated	n.s.	MDA = 53.16 nmol/mL	
	R	CH_3OH:H_2O (80:20)	DPPH scavenging activity	30 min at 30 °C	0.0005–0.0333 mg/mL	IC_{50} = 0.231 mg/mL	
			TBARS assay	duration not stated	n.s.	MDA = 3.91 nmol/mL	
P. officinarum Vaill.	AP + F	C_2H_5OH:H_2O (50:50)	DPPH scavenging activity	30 min	9.96 μg/mL	IC_{50} = 44.6 ± 0.8 μg/mL, Antioxidant capacity 11.24 ± 0.20%	Fraisse et al. (2011)

(*continued on next page*)

Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
	F	Isoetin 4′-*O*-β-D-glucopyranoside	DPPH scavenging activity	30 min at room temperature	0.625–6.25 μg/mL	IC_{50} = 3.7 μg/mL	Gawrońska-Grzywacz et al. (2011)
	F	C_2H_5OH (80%)	ABTS scavenging activity	10 min	n.s.	$RC_{50} = 0.34 \pm 0.03$ mg/mL	Woo et al. (2010)
			DPPH scavenging activity	30 min at room temperature	n.s.	$IC_{50} = 0.11 \pm 0.01$ mg/mL	
			Ferrous ion chelating	10 min at room temperature	n.s.	$RC_{50} = 0.90 \pm 0.11$ mg/mL	
			Inhibition activity on lipid peroxidation of linoleic acid	stored at 40 °C, 3 min after adding the testing reagents	0.025 mg/mL	Inhibitory rate of 90.66 ± 0.01, 89.82 ± 0.15, 80.33 ± 0.50, 68.79 ± 0.23, 65.59 ± 0.19, 48.43 ± 0.42% on the 4th, 8th, 12th, 16th, 20th, and the 24th day, respectively; not detected on days 28 and 32	
	L + R	C_2H_5OH:H_2O (50:50)	DPPH scavenging activity	no incubation	0.0012–0.3 mg/mL	$IC_{50} = 0.011 \pm 5 \times 10^{-4}$ mg/mL; 95.17%	Stanojević et al. (2009)
			DPPH scavenging activity	20 min at room temperature	0.0012–0.3 mg/mL	$IC_{50} = 0.007 \pm 10^{-4}$ mg/mL; 95.9%	
			Hydroxyl radical assay (Fenton reaction)	measurement after 5 min	0.2–0.5 mg/mL	$IC_{50} = 0.283 \pm 0.007$ mg/mL	
		CH_3OH:H_2O (80:20)	DPPH scavenging activity	no incubation	0.0012–0.3 mg/mL	$IC_{50} = 0.014 \pm 3 \times 10^{-4}$ mg/mL; 95.14%	
			DPPH scavenging activity	20 min at room temperature	0.0012–0.3 mg/mL	$IC_{50} = 0.009 \pm 10^{-4}$ mg/mL; 95.25%	
			Hydroxyl radical assay (Fenton reaction)	measurement after 5 min	0.2–0.5 mg/mL	$IC_{50} = 0.267 \pm 0.005$ mg/mL	
		H_2O	DPPH scavenging activity	no incubation	0.0012–0.3 mg/mL	$IC_{50} = 0.023 \pm 4 \times 10^{-4}$ mg/mL; 95.2%	
			DPPH scavenging activity	20 min at room temperature	0.0012–0.3 mg/mL	$IC_{50} = 0.011 \pm 2 \times 10^{-4}$ mg/mL; 96.1%	
			Hydroxyl radical assay (Fenton reaction)	measurement after 5 min	0.2–0.5 mg/mL	$IC_{50} = 0.279 \pm 0.012$ mg/mL	
	WP	CH_2Cl_2	DPPH scavenging activity	no incubation	n.s.-0.18 mg/mL	$IC_{50} > 0.18$ mg/mL; 12.7% at 0.18 mg/mL	Stanojević et al. (2008)
			DPPH scavenging activity	20 min	n.s.-0.18 mg/mL	$IC_{50} > 0.18$ mg/mL; 19.83% at 0.18 mg/mL	
		CH_2Cl_2:CH_3OH (9:1)	DPPH scavenging activity	no incubation	n.s.-0.18 mg/mL	$IC_{50} = 0.167$ mg/mL; 51.75% at 0.18 mg/mL	
			DPPH scavenging activity	20 min	n.s.-0.18 mg/mL	$IC_{50} = 0.075$ mg/mL; 87.62% at 0.18 mg/mL	
		$C_4H_8O_2$	DPPH scavenging activity	no incubation	n.s.-0.18 mg/mL	$IC_{50} = 0.079$ mg/mL; 67.7% at 0.18 mg/mL	
			DPPH scavenging activity	20 min	n.s.-0.18 mg/mL	$IC_{50} = 0.058$ mg/mL; 94.54% at 0.18 mg/mL	
		CH_3OH	DPPH scavenging activity	no incubation	n.s.-0.18 mg/mL	$IC_{50} = 0.015$ mg/mL; 95.33% at 0.18 mg/mL	
			DPPH scavenging activity	20 min	n.s.-0.18 mg/mL	$IC_{50} = 0.012$ mg/mL; 95.53% at 0.18 mg/mL	
	n.s.	C_2H_5OH:H_2O (65:35)	Beta carotene bleaching assay	3 h at 50 °C 60 min	n.s. (0.2 mL extract)	AA = 48.59 ± 8.77%	Bonomo et al. (2020)

(*continued on next page*)

Table 9 (*continued*)

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Incubation	Concentration	Results	Reference
			DPPH scavenging activity		n.s. (120 µL extract)	182.21 ± 5.14 mg trolox equivalent/100 mL extract	
			FRAP assay	40 min at 37 °C	n.s. (150 µL extract)	520.88 ± 23.17 mg trolox equivalent/100 mL extract	

Abbreviations used: n.s. not stated, WP whole plant, AP aerial parts, R roots, F flowering heads, L leaves, S seeds.

Table 10
Compiled results from antiviral assays conducted on *Hieracium* and *Pilosella* species.

Species	Organ	Extraction solvent	Test Model	Concentration	Results	Reference
Hieracium umbellatum L.	WP	CH_3OH	inhibition of HIV-1 protease	100 µg/mL	15.0 ± 2.6% (not active)	Min et al. (1999)
Pilosella officinarum Vaill.	n.s.	C_2H_5OH	MT-2 cells infected with HIV-1 NL 4.3 combined with MTT assay	0–200 µg/mL	not active	Bedoya et al. (2001)
		H_2O			not active	

Abreviations used: n.s. not stated, WP whole plant.

negative relationship between the phenol concentration and the ammonia concentration which is in line with the observed effect of *P. officinarum* as this species displayed a low amount of total extractable phenols. Further information and results are stated in Table 14.

5.16. Toxicological data

In *Dioscorides Renovado* (Font Quer, 1981) it is stated that the use of *H. pilosella* (SAN= *P. officinarum*) has the advantage of being innocuous. According to this author 'the plant lacks toxicity for humans and does not even act on the intestinal flora of the healthy person'. In this regard, Greib and Duquénois (1960) reported that this species' aqueous extract could be administered to animals without any sign of toxicity or lesion for several months. Recently, Milutinović et al. (2020) demonstrated that within two weeks after orally administering high doses (2000 mg/kg) of extracts derived from *H. scheppigianum* and *H. glabratum* the behaviour of the tested mice did not alter, nor lead to any signs of toxicity. We could not find any other work concerning the toxicity of the memebers of *Hieracium* and *Pilosella*. The only reported case of side effects was on a 34-year-old-woman that referred to have developed a macular–papular eruption involving the face, neck, arms, and trunk, after a twelve-day treatment for slimming with a tincture made from a mixture composed by *P. officinarum* (Tognetti et al., 2011). However, the authors related the adverse effect to other added compounds in the preparation.

6. Discussion

6.1. - On the pre-Linnean attributions to the Hieracium and Pilosella uses and properties

In spite of the references to some *Hieracium* species before the Linnean nomenclature (e.g. *H. majus*, *H. minus*, *H. parvum*) the iconographies and descriptions found in these texts (Fig. 1) seem not to correspond to the current idea of *Hieracium*, introduced by Linnaeus (1753). Fuchs (1557) attributed the properties of the Dioscorides' *Hieracium parvum* most likely to *Taraxacum* sp. according to the description made and the illustrations provided as this *H. parvum* possesses deeply divided leaves, with acute leaflets. Also, the mentions of *Hieracium* in the Dioscorides *De Materia Medica* (and annotations made by Laguna) seem not to correspond to the Linnean and current idea of this genus' species as Laguna mentioned that people named *H. minus* 'dandelion' among other herbs (*Chondrilla*, *Hedypnois* and *Taraxacum*). According to this, we think that *H. minus* could be a synonym of *H. parvum* and both of them can be, more likely, attributed to the current *Taraxacum* genus. On the contrary, the *Pilosella* species mentioned by Lonitzer (1551) such as *P. major* and *P. minor* could be attributed to current taxa of this genus attending to the described morphological characters and the drawn icononographies. However, the specific correspondence between these binomens and the currently accepted taxa is difficult to determine with these materials and therefore, the medicinal properties cannot be stated.

6.2. - Limitations of the ethnopharmacological compilation and phytochemical research

Out of the more than 850 estimated species of *Hieracium* and *Pilosella*, references to their traditional uses have been only reported from 34 of them. This can be very surprising at first but there are several reasons that may explain the limited ethnopharmacological compilation. The first reason is related to the high degree of polymorphism in the group, that implies difficulties in understanding and identifiying the taxonomical diversity of *Hieracium* and *Pilosella* at the level of species. Nägeli and Peter (1885, 1886–1889) and Zahn (1921–1923) distinguished 'basic species' (Hauptarten) defined as being morphologically unique, from 'intermediate species' (Zwischenarten), which share the morphological characters and combine traits of two or more basic species and are thought to have hybrid origin. This approach significantly contributed to the understanding of the complex. However, an innumerable number of subspecies, varieties and forms affiliated to both basic and intermediate species (either originated by mutations or hybridization processes) has been described. This fact, in turn, opened a complex taxonomical scenario where difficult consensus on the diversity scheme has been traditionally present. The first consequence of this situation would be the identification problem at the level of species in certain taxa with ethnopharmacological interests that can be observed in the literature reviewed in this work (San Miguel, 2004; Aceituno, 2010; Mustafa et al., 2012; Gonzales de la Cruz et al., 2014; Hammad et al., 2014) and the checked electronic databases. The authors also wonder whether these difficulties have sometimes motivated the exclusion of *Hieracium* and *Pilosella* taxa in ethnobiological inventories or publications as reported for other challenging genera (Bebber et al., 2007; Vázquez, 2008). The second consequence of this strong level of taxonomical diversification in both genera is the high degree of rare and

Table 11
Compiled cytotoxic and antiproliferative assays conducted on *Hieracium* and *Pilosella* species.

Species	Organ	Extraction solvent/ Specialised metabolite	Test Model	Dosis tested	Results	Reference
Hieracium caespitosum [SAN: *Pilosella caespitosa* (Dumort.) P.D.Sell & C.West]	WP	CH_3OH	HeLa cells	0.06–0.6 µg/µL	LC_{50} of 0.67 mg/mL	Booth et al. (2012)
H. glabratum Willd.	AP + F	CH_3OH (pretreated with CH_2Cl_2)	Acute oral toxicity in male Swiss Webster mice	2000 mg/ kg p.o.	no behavioural changes, signs of toxicity and lethal outcomes in the 2-week study	Milutinović et al. (2020)
H. scheppigianum Freyn	AP + F	CH_2Cl_2	Acute oral toxicity in male Swiss Webster mice	2000 mg/ kg p.o.	no behavioural changes, signs of toxicity and lethal outcomes in the 2-week study	
Pilosella hoppeana subsp. *testimonialis* [SAN: *P. testimonialis* (Nägeli ex J. Hofm.) Gottschl.]	AP	CH_3OH	HT29	250 100 50 25 12.5 µg/ mL	97.36 ± 0.07 95.18 ± 0.10 89.03 ± 0.08 82.51 ± 0.12 79.18 ± 0.08% viability	Aliyazicioğlu et al. (2019)
					IC_{50} without result	
			L9N29	250 100 50 25 12.5 µg/ mL	99.05 ± 0.13 92.13 ± 0.11 87.12 ± 0.14 82.99 ± 0.20 75.70 ± 0.25% viability	
					IC_{50} without result	
P. officinarum Vaill.	F	isoetin 4′-*O*-β-D-glucopyranoside	MTT (human lung cancer cells A549)	1–100 µM for 96 h	A549: no effect up to 25 µM, 50 and 100 µM significant stimulus of proliferation ($p < 0.05$)	Gawrońska-Grzywacz et al. (2011)
			MTT (human colon cancer cells HT-29)	1–100 µM for 96 h	HT-29: non-dose dependent, significant decrease of proliferation at concentrations of 10–100 µM ($p < 0.05$)	
	n.s.	C_2H_5OH	toxicity on MT-2 cells	0–200 µg/ mL	nontoxic limit concentration not stated	Bedoya et al. (2001)
		H_2O			nontoxic limit concentration 200 µg/mL	
nutraceutical (MER'EMYNCIL BIO) containing *P. officinarum* alongside *Foeniculum vulgare* Mill. juice, *Ananas comosus* (L.) Merr., *A. comosus* concentrate, *Citrus* × *auriantum* L. dry extract *Citrus* × *limon* (L.) Osbeck concentrate juice, *Curcuma longa* L. powder, *Fucus* sp., *Viola tricolor* L., *Sambucus nigra* L. flowers, *Fraxinus excelsior* L. leaves, *Glechoma hederacea* L., *Rosmarinus officinalis* L. leaves, *Levisticum officinale* W.D.J. Koch leaves, *Taraxacum* sp. leaves, sea water, water	n.s.	n.s.	MTT (HEK 293 ECACC 85120602)	0 0.2 1 2 100%	no significantly reduced viability at any tested dose	Le Coguic and Seralini (2019)
			MTT (HepG2 ECACC 85011430)	0 0.2 1 2 100%	no significantly reduced viability at any tested dose	
			MTT (JEG-3 ECACC 92120308)	0 0.2 1 2 100%	above 0.2% decreased viability with significance of $p < 0.05$ at concentrations of 0.2 and 1% and $p < 0.01$ at concentrations of 2 and 100%	
			BrdU (HepG2 ECACC 85011430)	2%	not tested	

Abreviations used: n.s. not stated, WP whole plant, F flowers.

Table 12
Compiled studies conducted on the diuretic activity of *Pilosella* species.

Species	Organ	Extraction solvent	Test Model	Dosis tested	Results	Reference
Pilosella officinarum Vaill.	AP	commercial hydroalcoholic extract (Laboratoire Vernin, France)	intra-peritoneal administration in rats; Reference hydrochlorothiazide	50 and 200 mg/kg animal (diluted in 0.45% hypotonic saline solution)	50 mg/kg: ineffective 200 mg/kg: significantly increased urine volume secretion from 2 to 3 h ($p < 0.05$) and from 4 to 24 h ($p < 0.001$) no significant increase in K^+/Na^+ excretion at 50 nor 200 mg/kg	Beaux et al. (1999)
XANADREN MD® (formulation consisting of 375 mg mannitol by *Fraxinus ornus* L. (mannitol 70%), water, *Ananas comosus* L. concentrated juice (13.87%/100 mL), *Betula pendula* R. dry extract 75 mg (Hyperoside 1%), *Equisetum arvense* L. dry extract 75 mg (minerals silicon 10%), *Urtica dioica* L. dry extract 75 mg (β-sitosterol 4%), *P. officinarum* Vaill. dry extract 75 mg (vitexin 1%), ascorbic acid (1%), citric acid (0.3%), potassium sorbate (0.2%)	n.s.	n.s.	4 and 8 week supplementation in an open lable study on patients with extra cellular water (>45%)	15 mL XANADREN MD® in 500 mL H_2O (before breakfast)	decrease of extra cellular water of 1.97 and 2.30% after 30 and 60 days ($P < 0.01$) increase of 1.60% cellular water decrease of fat mass of 1.58 and 2.21% after 30 and 60 days ($P = 0.057$) basal metabolic rate 46 kcal after 60 days increase of free fat mass of 2.90 kg ($P < 0.05$) nutritional status (by Phase Angle) + 0.41 ($P = 0.05$) and BCMI +0.51 ($P = 0.01$) after 60 days no significant decrease of the waist circumference (0.40 cm), waist to hip ratio, waist and hips ratio, no significant effects concering health-related quality (SF-36) of life and the bloating sensation (bowel symptom questionnaire) ($P = 0.422$) after 60 days interaction time for treatment: extra cellular trend $P = 0.021$ and basal metabolic rate trend $P = 0.025$	Perna et al. (2020)
nutraceutical diet *P. officinarum* (0.0749%) *Urtica dioica* L. (0.0619%) *Lespedeza* spp. (0.0589%) *V. macrocarpon* (0.0372%) *Taraxacum officinale* (L.) Weber ex F.H.Wigg. [SAN: *Taraxacum* sect. Taraxacum Weber ex F.H.Wigg.] (0.0231%) alongside proteins, minerals, and amino acids	n.s.	n.s.	dipstick urinanalysis (multistix 10 SG)	n.s.	Urine color (according Brabson et al., 2015): −2.03 ($p < 0.001$) Turbidity: −0.94 ($p < 0.001$) pH value: −0.92 ($p < 0.001$) urine weight: −19 SG ($p < 0.05$) protein concentration: −27.3 mg/dl ($p < 0.05$) red blood cells: −0.08 mg/dl ($p < 0.001$) white blood cells: −2.4 mg/dl ($p < 0.001$) decrease of struvite uroliths	Canello et al. (2017)

Abbreviations used: n.s. not stated, AP aerial parts.

Table 13
Compiled studies conducted on the gastroprotective activity of *Hieracium* species.

Species	Organ	Extraction solvent	Test Model	Dosis tested	Results	Reference
Hieracium gymnocephalum Griseb. ex Pant.	AP + F	CH_2Cl_2	indomethacine-induced gastric mucosa lesions in rats	200 mg/kg p.o.	40% less animals with lesions significant reduction of the gastric damage score (0.5 ± 0.5), lesion area (0.01 ± 0.1 mm^2), length of gastric lesions (3.7 ± 5.5 mm) ($p < 0.05$ vs control), and anti-inflammatory effect (78.3 ± 21.0%) ($p < 0.01$ vs control)	Petrović et al. (2008)

Abreviations used: AP aerial parts, F flowering heads.

restricted endemic taxa that this complex presents, for example, in Croatia (Nicolić et al., 2020), Greece (Kougioumoutzis et al., 2021) or Spain (Buira et al., 2016). Medicinal plants must be abundant and easy to recognize and harvest as rare species are difficult to find (Leonti, 2011). Therefore, only the most common and widespread *Hieracium* and *Pilosella* species (such as *P. officinarum*, *H. murorum*, *H. umbellatum*, etc.) are likely to take part of the popular knowledge and pharmacopoeias as we found in this review. Rare and restricted endemic species (which constitute an important group in *Hieracium* and *Pilosella*) are therefore not likely to take part of this body of knowledge. Furthermore, the genus concept in *Hieracium-Pilosella* has had different interpretations in the generic and sub-generic circumscription over the years and references to certain taxa such as *P. officinarum*, *H. murorum*, *H. pannosum*, *H. umbellatum,* and *H. venosum* (among others) might not really correspond to the current adscription of the species or the genus. For instance, *H. virosum* was mentioned to be used in Spain (Table 1). However, *H. virosum* sensu stricto is absent from all Central and Western Europe, including Spain (http://www.plantsoftheworldonline.org/) and,

Table 14
Compiled studies conducted on other activities of *Hieracium* and *Pilosella* species.

Activity	Species	Organ	Extraction solvent	Test Model	Doses/concentration tested	Results	Reference
Acaricidal	*Hieracium* sp.	WP	CH_3OH	adult mites of *Tetranychus urticae*	2.5 mL extract (1:10 (w/v) in distilled water)	18.96 ± 5.57% mortality of *T. urticae* adult mites	Hammad et al. (2017)
Antiepileptic	*Pilosella officinarum* Vaill.	AP	C_2H_5OH 96%	^{3}H-Ro 15–1788 (flumazenil) binding assay	10 mg/mL	42 ± 16% binding of flumenazil	Jäger et al. (2006)
					1 mg/mL	70 ± 7% binding of flumenazil	
					0.1 mg/mL	81 ± 2% binding of flumenazil	
					0.01 mg/mL	86 ± 5% binding of flumenazil	
			H_2O		10 mg/mL	72 ± 2% binding of flumenazil	
					1 mg/mL	121 ± 1% binding of flumenazil	
					0.1 mg/mL	104 ± 11% binding of flumenazil	
					0.01 mg/mL	103 ± 1% binding of flumenazil	
Anti-obesity	*H. umbellatum* L.	L	CH_3OH	inhibition of lipase activity	0.5 μg/μL	49.8 ± 0.5% lipase inhibition	Lee et al. (2012)
Hypotensive	*P. officinarum*	n.s.	n.s.	n.s.	n.s.	n.s.	Petkov (1986)
Insecticidal	*Hieracium* sp.	WP	CH_3OH	nymphs and adults of *Bemisia tabaci*	average of 9 mL extract (1:10 (w/v) in distilled water)	3.55 ± 0.47 alive adults after treatment 19.33 ± 3.62 alive nymphs after treatment respect 6.77 ± 0.22 alive adults and 35.1 ± 0.7 alive nymphs in the control group (water) 6.33 ± 0.23 alive adults and 34.11 ± 0.58 alive nymphs after treatment in the control group (10% CH_3OH)	Hammad et al. (2014)
Global periorbital skin rejuvenation	cosmetic cream containing low molecular weight heparan sulfate and extracts of *Tephrosia purpurea* (L.) Pers. seeds (1–4%), *Eupenicillium crustaceum* (1–4%), *P. officinarum* (1–3%), *Bellis perennis* L. flowering heads (1–3%)	n.s.	n.s.	open-lable study: application around the eye area twice a day after cleansing for 12 weeks		self-assessments: 93% reported imporvement in the appearance of dark circles; 93% reported their skin was hydrated after application; 67% reported improvements in coarse wrinkles after 12 weeks of usage; 73% reported improvement in under-eye puffiness after 12 weeks investigator assessment: 53% improvement of under-eye dark circles by one grade or higher; 50% of subjects showed improvement in the appearance of coarse wrinkles after 12 weeks; 87% of subjects showed improvement in the appearance of fine lines; mild improvements of global improvements of 40%, 27% moderate and 20% marked improvements; 100% agreed on an easy use of the cream, that the cream did not dry the skin and application led to a soothing feeling improvement in the appearance of lines and wrinkles around eyes and on the upper eyelids improvements under-eye crepiness reported	Colvan et al. (2019)
Reduction of ammonia concentration in rumen fluid	*P. officinarum*	AP	milled drug	incubation in a Hohenheim Gas Test apparatus with 30 mL rumen fluid (39 °C, 24 h)	200 mg (0.30:0.70 drug:basal diet consisting of *Lolium perenne* L. and *Medicago sativa* L.)	37.8 mL/200 mg dry matter ($P < 0.05$) total gas *in vitro* organic matter digestibility: 487 g/kg organic matter ($P < 0.05$) 14.4 mmol/L ammonia ($P < 0.05$)	Kapp-Bitter et al. (2020)

Abreviations used: n.s. not stated, WP whole plant, AP aerial parts, L leaves

therefore, this reference has to be treated with caution. Ideally, it would be of great ethnopharmacological interests to confirm the currently taxonomical adscription of the taxon considered in this reference. Beyond the species level, references found on *Hieracium* taxa that currently correspond to different genera were excluded from the compilation here presented, but the most interesting for the aim of this review are further commented.

Also, the plant species investigated by Koleckar et al. (2008) named *H. cespitosa* is most likely a typo and hence should correspond to *H. caespitosum* [SAN: *P. caespitosa* (Dumort.) P.D.Sell & C.West]. However, the same study also included *P. caespitosa* and results given for both species are in the same range which makes us think both specimens correspond to the same taxon. Finally, the loss of traditional knowledge on uses of plants is a recognised general problem in ethnopharmacology (Quave et al., 2012). This may also influence the surprisingly low number of references in the *Hieracium* and *Pilosella* traditional uses, as we reviewed. For instance, Cozzo (2004) compiled that the medicinal use of *H. gronovii* was already forgotten by the Cherokee indians when the research was carried out. Also, Vitalini et al. (2015) stated that the use of *P. officinarum* to heal wounds in Alta Valtellina is documented but already abandoned in Lombard Stelvio National Park (Italy). In this regard, it would be of great ethnopharmacological interest to perform specific questions focussed on *Hieracium* and *Pilosella* taxa when performing ethnobotanical fieldwork campaigns, in order to record valuable local uses in understudied regions, thus avoiding their lose as it has been commented above. Furthermore, it would be also beneficial to verify which uses are in current practice in the more prospected territories. Finally, an effort to determine what currently accepted taxon the used specimens correspond to would be desirable in order to gain consistent data.

If we analyse the geographical component in the traditional usage of *Hieracium* and *Pilosella* species in folk medicine, we find references from all continents in the world (except Australia, where they are not native). A vast array of uses is circumscribed to the European countries and this is most probably the reason why *P. officinarum* is present in the British and French Pharmacopoeias. Several references to the popular use of *Hieracium* and *Pilosella* are also circumscribed to the Russian territory such as *P. officinarum*, *H. murorum*, *H. echioides*, *H. umbellatum* and *H. pilosum*. However, none of these species is present in the Russian Pharmacopoeia (Shikov et al., 2014). Another question that would be interesting to resolve is to which extent the current popular use of *P. officinarum* is, in fact, linked to the ancestral traditional use of this species in a given region or whether it was influenced or incorporated from foreign traditions in the last centuries as a result of medical text translations since the Middle Age as documented for Japan (Gordon--Cumming, 1887). It seems reasonable to think that *P. officinarum* has a long tradition of medicinal uses in Central and Southern Europe as revealed in the literature research here performed. However, how traditional its use is in other regions where we found references (such as Russia or another Slavic countries, Asiaand America) seems unclear.

We also found some gaps as far as the phytochemical composition concerns. Phenolic compounds and flavonoids are quite well investigated in these genera, specially in Central Europe and the Balkans (see Tables 2–5). However, most species from other areas (such as the Iberian Peninsula or Turkey) are still not investigated in spite of their richness in *Hieracium* and *Pilosella*. If we take into consideration other specialised metabolites (coumarines, sesquiterpenoids, sesquiterpene lactones, etc.) the current scientific knowledge is rather limited. For instance, eudesmanolides were reported to be often predominant in *Hieracium* and *Pilosella,* whereas guaianolides were dominant in *Crepis* (Zidorn, 2008). However, a more recent study performed by Milutinović et al. (2018a) showed that guaianolides were also dominant in 28 *Hieracium* species from the Balkan Peninsula. Therefore, future research lines should be focused on non-phenolic compounds in order to describe newly identified chemical constituents and for a better understanding of the chemical diversity within these genera.

6.3. - Experimental data to support traditional usage and their correlation to the chemical composition

The first experimental evidence both *in vitro* and *in vivo* attempting to support traditional use is found in the diuretic activity for which, moreover, the responsible constituents are quite clearly identified, as we discuss beneath. However, the number of studies is still low and they present some gaps in order to conclude that diuretic activity is well proven. Research on the diuretic capacity of *P. officinarum* performed by Beaux et al. (1999) related it to the ability of increasing the urine flux. This property seems to be the reason why this species has been also traditionally used to successfully treat different ailments and/or inflammations of the urinary system including prostate and renal ones (Efremov and Shreter, 1996; Redžić, 2007; Popović et al., 2014), to treat obesity, to slim (Hurrell and Puentes, 2013; Becker et al., 2017; de Freitas and de Almeida, 2017) and to resorb ascetic effusions of cardiac origin (Guarino et al., 2008). The diuretic activity of *P. officinarum* has been related to its content in polyphenolic acids (particularly caffeic and chlorogenic acids), tannins, and flavonoids (Moro and Basile, 2000). As *P. officinarum*, practically all *Hieracium* and *Pilosella* chemically studied produce these compounds (Tables 2–5) and this may certainly explain why other species have diuretic properties or are reported to be helpful in urinary diseases treatment in the folk medicine. Examples compiled in this review are *H. fendleri* (Shemluck, 1982), *H. murorum* (Hapayev and Hapayeva, 2015), *H. umbellatum* (Kim et al., 2006), and *H. venosum* (Cozzo, 2004). However, none of them were tested to verify their supposed diuretic activity and it could be interesting to screen whether these taxa show stronger diuretic activity than *P. officinarum*. In any case, although diuretic properties of *P. officinarum* are pointed out experimentally, it would be helpful to perform specific studies and clinical trials to completely support this traditional use and to understand the specific way that it helps in other urinary tract diseases.

Another traditional use supported by experimental research is the anti-inflammatory one, according to the reviewed literature. Dombrowicz et al. (1992) related the use of *P. officinarum* to treat inflammations of the upper parts of the respiratory tract to the presence of salicylic acid. *H. gymnocephalum* tested by Petrović et al. (2008) showed significant anti-inflammatory effects and the authors related this property to the presence of triterpene alcohols (as α- and β-amyrin, as well as taraxasterol derivative) found in previous studies. However, the authors did not specifically test these compounds to verify that the triterpene alcohols are the active principles within *H. gymnocephalum*, exerting the anti-inflammatory activity of this species. In inflammations originated by allergic disorders *H. albiflorum* was very effective to treat them according to Bae et al. (2013). However, this species was not chemically investigated. In any case, chemical differences in natural compounds responsible of the anti-inflammatory activity (presumably salicylic acid and triterpene alcohols) should be further determined. Also, a more-in-depth research on this topic conducted in other species traditionally used as anti-inflammatory (but still lacking tests on bioactivity and thorough investigations of their chemophenetic profile) such as *H. amplexicaule* (González-Tejero, 1989) and *H. umbellatum* (Hapayev and Hapayeva, 2015) will be helpful to characterize the potential use of *Hieracium* and *Pilosella* species to support their suitability to treat inflammations. Unlike the results compiled in this review, Hwang et al. (2014) obtained very low anti-inflammatory activity in *H. coreanum* extracts. However, *H. coreanum* is currently adscribed to *Crepis coreana* (Nakai) H.S.Pak. *Crepis* species lack apigenin and quercetin unlike *Hieracium* and *Pilosella* (Mañez et al., 1994). As both quercetin (Tian et al., 2021) and apigenin (Ginwala et al., 2019) were reported to have strong anti-infammatory activities, the above mentioned differences might be explained by the chemophenetical differences between the genera *Crepis* and *Hieracium-Pilosella*. While antimycotic activities were observed only in the ethanolic extract of *P. sandrasica* (Ugur et al., 2010), as well as in some extracts of *P. officinarum* (Nostro et al., 2000; Stanojević et al., 2008), several *Hieracium* and *Pilosella* extracts

demonstrated antibacterial activities. Dombrowicz et al. (1992) related this property to the high abundance of caffeic acid and *p*-coumaric acid in *P. officinarum*. Various ethnopharmacological references mentioned the usage of preparations derived from *P. officinarum* as antiobiotics (Sõukand and Raal, 2008; Agelet et al., 2000; Bonet et al., 1999). According to Font Quer (1981) *P. officinarum* was used to treat brucellosis, a sickness triggered by *Brucella* species. The findings of Greib and Duquénois (1960) support this application as all three tested *Brucella* species were affected by the treatment with *P. officinarum*. The observed activites of the extracts of *P. officinarum* were not restricted to certain plant organs or polartity ranges making the contribution of various compound classes to the antimicrobial effect likely. In addition, Gawrońska-Grzywacz et al. (2011) related this property to the flavonoid isoetin 4′-*O*-β-D-glucopyranoside for the same species. These compiled evidences may be helpful to support the high number of references on the traditional uses of *P. officinarum* as vulnerary and to treat different types of bacterial and fungal infections, both internally and externally (Table 1). However, specific investigations on antibacterial activity of these species should be performed in order to verify their traditional uses. In addition, active principles exerting such activity were generally not identified in *Hieracium* and *Pilosella* species. Several authors considered whether flavonoids and terpenes present within *P. officinarum* might hold responsible for the antimicrobial action of this species' extracts due to interference with membrane constituents but performed no further testing (Bonomo et al., 2020; Nostro et al., 2020; Stanojević et al., 2008). Finally, Barbour et al. (2004) did not provide information on the composition of the methanolic extract of the undetermined *Hieracium* species they investigated in an antibacterial testing. Based on a literature research they related the observed antibacterial activity to a germacranolide as well as hydroxyenzyl alcohol derivatives, previously isolated from *H. murorum* (Zidorn et al., 2001). However, as Barbour et al. (2004) did not determine the species of the investigated taxon this allocation should be treated with caution. The compiled literature also reported activity against two yeasts (*C. albican*, *C. tropialis*), two *Aspergillus* species as well as *F. oxysporum*, and an undetermined species of *Penicillium*. However, none of the studies conducted further investigations on the composition of the extracts or active principles but it was mentioned that contained flavonoids and terpenes could interfere with the cell membrane and thus were cytotoxic (Nostro et al., 2000; Stanojević et al., 2008). According to Agelet et al. (2000) *P. officinarum* was used in Catalonia, Spain, as an antimycotic preparation.

A remarkable effort has been done in estimating the antioxidant capacity of *Hieracium* and *Pilosella* species during the last two decades (Table 9). These species' extracts have been related to antioxidant properties in several kind of extractants and plant organs according to the assays performed so far, particulatly for *P. officinarum* (Fraisse et al., 2011; Gawrońska-Grzywacz et al., 2011; Stanojević et al., 2008; 2009; Woo et al., 2010), *P. hoppeana* subsp. *testimonialis*, *H. bornmuelleri* (Bakar et al., 2015), *H. pannosum* (Gökbulut et al., 2017), *H. cappadocicum* (Tepe et al., 2006), *H. glabratum, H. mirificissimum,* and *H. naegelianum* extracts (Milutinović et al., 2018b). In most cases, the antioxidant power was attributed to the high phenolic contents, mainly chlorogenic acid and flavonoids (Stanojević et al., 2008; Fraisse et al., 2011; Bakar et al., 2015; Milutinović et al., 2018b) such as isoetin 4′-*O*-β-D-glucopyranoside (Gawrońska-Grzywacz et al., 2011). In contrast, Woo et al. (2010) did not find correlation between phenolic composition and antioxidant activity. However, the main gap concerning all these studies is that all of them were only set up on chemical assays, based on redox reactions performed *in vitro* (DPPH, ABTS, etc.) and none of them carried out additional enzymatic assays as well as *in vivo* models. Although these *in vitro* tests suggest the antioxidant capacity of the studied extracts, due to the lack of more accurate *in vitro* test and *in vivo* experiments we cannot assume the experimental support of the antioxidant bioactivity and its subsequent therapeutic efficacy (Kasote et al., 2015). Moreover, although phenolic compounds and flavonoids may exert protective activities against abiotic (Zidorn et al., 2005) and biotic (Kulbat, 2016) stresses in plants, it is also not proven that these compounds might act in the same way in humans (Harnly, 2017; Kasote et al., 2015), thus making it quite risky to correlate phenolic compounds and health promoting properties due to the antioxidant activity as demonstrated *in vitro*. Therefore, a more comprehensive research on antioxidant activity (including *in vivo* studies) would be beneficial in order to consider these species as promising antioxidant agents. Antidiabetic activity was found for *H. pannosum* extracts in Gökbulut et al. (2017). However, there is no record of traditional uses to treat diabetes for this species. On the contrary, *P. officinarum* was traditionally used in Montenegro to treat diabetes (Menković et al., 2011) but experimental data to support this activity is lacking for this species. Also, the natural product responsible for this activity is still unknown.

The cytotoxic activity of *H. caespitosum* was determined by Booth et al. (2012) but it was not related to any metabolite in particular. This is not the case of the compound isoetin 4′-*O*-β-D-glucopyranoside isolated from *P. officinarum* inflorescences by Gawrońska-Grzywacz et al. (2011) that showed a marked antiproliferative effect in colon cancer cell lines, thus supporting what Astrologova and Feklistov (2002) found on traditional uses to treat tumors with *P. officinarum* and *H. umbellatum* in Russia. However, Gawrońska-Grzywacz et al. (2011) did not include any other cell lines than these two cancer lines. In any case, the results are not considered to be outstanding in order to be further evaluated as lead anti-cancer agent when comparing to other compounds isolated from plants (e.g. celastrol, taxol).

Gastroprotective properties were found in *H. gymnocephalum* by Petrović et al. (2008) and it was related to the presence of triterpene alcohols. However, we could not find any traditional use of this species in this field of application. In contrast, references on traditional uses to treat gastric ulcers (among other related illnesses in the digestive apparatus comprised *P. officinarum*, *H. amplexicaule* (González-Tejero, 1989), *H. maculatum* (Barnaulov and Barnaulov, 2018), *H. murorum* (Hapayev and Hapayeva, 2015), *H. tandilense* (Barboza et al., 2009) and *H. umbellatum* (Kim et al., 2006)). Therefore, it would be interesting to include these species in further studies aimed to test the gastroprotective bioactivities and subsequently identify the responsible compounds.

P. officinarum decoction in wine was documented by Jäger et al. (2006) to be useful against epilepsy. In this regard, reported anti-epileptic activity of *P. officinarum* was modest (Table 14). Also, the traditional use of *H. staticifolium* as antiepileptic was also reported in old traditional Danish medicine (Adams et al., 2012) but this taxon is currently adscribed to *Tolpis staticifolia* (All.) Sch.Bip. and thus, excluded from the compilation here presented. In any case, responsible compounds were not studied. Therefore, further studies would be necessary to clarify this point.

Finally, anti-obesity and acaricidal activities were also modest (Table 14). Moreover, little evidence is provided to the antiviral and hypotensive activities found in *P. officinarum* (Tables 10 and 14, respectively).

In addition, there is a complete lack of experimental information in order to prove some of the supposed properties here compiled from popular uses of *P. officinarum* such as the emetic, laxative, haemostatic, aperient, tonic or stimulant, or to treat bone fracture, joint problems, hernia and jaundice. As the traditional use against certain illness does not mean that they have clinical effect, it would be very interesting to perform scientific research in order to verify that these plants possess the compiled properties or, on the contrary, they are simply used for tradition. In the first case, it would be also ideal to understand what chemical compounds are responsible of these proven activities.

6.4. - *Methodological considerations on the studies of bioactivities*

The revision on studies investigating *Hieracium* and *Pilosella* bioactivities demonstrated that most research was designed as *in vitro*

testing. Particularly the antimicrobial and antioxidant activities revealed higher number of studies, while the other activities such as antidiabetic, antiviral, diuretic or gastroprotective activities received less attention.

During the revision of studies on the antioxidative effects of *Hieracium* and *Pilosella* taxa it became apparent that in two cases the authors did not state what plant organs were extracted (Tepe et al., 2006; Bonomo et al., 2020) while two other studies lacked information on the extractants (Bakar et al., 2015; Borchardt et al., 2008). Both the plant organ as well as the solvents used for extraction can considerably influence the composition of the extract and hence their biological effects (e.g. Bedoya et al., 2001). However, it should be mentioned that although only one study linked the bioactivity to a single compound (Gawrońska-Grzywacz et al., 2011), most of the other studies performed HPLC analyses and evaluated the composition of the tested extracts (Milutinović et al., 2018a, b; Bakar et al., 2015; Gökbulut et al., 2017; Stanojević et al., 2008; Stanojević et al., 2009) or provided information on total polyphenolic, total flavonoid, and/or tannin content (Woo et al., 2010; Bonomo et al., 2020; Gökbulut et al., 2017; Fraisse et al., 2011; Stanojević et al., 2009). Milutinović et al. (2018b) found that high total antioxidant activities, and DPPH and hydroxyl radicals scavenging abilities were generally linked to high total phenolic contents (TPC). Exceptions from that observation were linked to higher amounts of luteolin, while several other studies linked high contents of phenolics or chlorogenic acid to high antioxidative effects (Bakar et al., 2015; Gökbulut et al., 2017; Stanojević et al., 2008, 2009; Bonomo et al., 2020). Fraisse et al. (2011) performed statistical experiments revealing a correlation between the total phenolics and the antioxidant activity ($R^2 = 0.8904$) as well as the total dihydroxycinnamic acid derivatives ($R^2 = 0.8529$). They further calculated the contribution of cichoric acid, chlorogenic acid, 1,5-, 3,5-, and 4,5-dicaffeoylquinic acids to the antioxidative effect, concluding that the dihydroxycinnamic acid derivatives are the main antioxidatives within *P. officinarum*. Bakar et al. (2015) linked the antioxidative effect to chlorogenic acid as well as flavonoids. It should be noted that in case of *P. hoppeana* subsp. *testimonialis* IC_{50} value of the root extract ($IC_{50} = 0.231$ mg/mL) was considerably lower than the corresponding value of the aerial parts ($IC_{50} = 0.864$ mg/mL) although the content of chlorogenic acid was higher in the aerial parts (1826.90 ± 8.85 μg/g plant material; roots 954.03 ± 3.52 μg/g plant material) and co-occurred with low amounts of flavonoids that were not detected in the roots. This trend was also observed in the MDA assay, in which the root extract displayed considerably lower MDA values than the aerial parts. However, this trend was not observed in case of second tested species, *H. bornmuelleri*. A similar finding was observed in case of *H. pannosum*, which root's extract had the highest content of chlorogenic acid of the tested extracts (1.25 g/100 g dry weight of plant material.) but displayed the lowest activity in the DPPH and ABTS assay. However, the root extract was most active in the ferric-reducing antioxidant power and the superoxide anion scavenging activity at the highest tested concentration (3 mg/mL). It cannot be ruled out that contents of other phenolics, i.e. caffeic acid, luteolin 7-glucoside, luteolin, and apigenin contribute to the observed effects. It should be mentioned that the contents of the phenolics were determined with a validated HPLC-DAD method that established the linearity, limit of detection (LOD), and limit of quantification (LOQ) of the method. However, in several cases the stated values of the respective analytes were below the limit of detection (S/N 3/1) (root: caffeic acid, luteolin below LOD; leaves: caffeic acid, luteolin, apigenin beneath LOD, luteolin 7-glucoside beneath LOQ; flowering heads caffeic acid beneath LOD, apigenin beneath LOQ) (Gökbulut et al., 2017).

As expected, the dichloromethane extract of the aerial flowering parts of *H. gymnocephalum* exhibited weak anti-DPPH activity ($IC_{50} = 60$ mg/mL), much lower than the polar extracts (Petrović et al., 2008). Stanojević et al. (2008) also tested a dichloromethane extract, specifically one of the aerial parts of *P. officinarum* in a DPPH assay, resulting in the finding that the IC_{50} value of the dichloromethane extract of *P. officinarum* was not within the tested concentration range ($IC_{50} >$ 0.18 mg/mL) and generally had the lowest radical scavenging activity out of the extracts. As outlined above in most cases polar compounds were responsible for the antioxidant effect that are not likely part of the apolar extract prepared in both studies. In addition, in some cases no standard deviation was provided in antioxidant assays (e.g. Koleckar et al., 2008).

Investigations on the cytoxic activity of *Hieracium* and *Pilosella* remain scarce so far. Le Coguic and Seralini (2019) observed cytotoxic effect of a non-traditional nutraceutical mixture containing *P. officinarum* but they attributed those properties to the *Taraxacum* sp. and *Fraxinus excelsior* L. content. Nevertheless, additional tests verifying this assumption were not conducted.

6.5. - *New pharmaceutical products development*

P. officinarum has been used in folk medicine for centuries, as evidenced by the sources here reviewed. It is fairly distributed in the market of medicinal products, especially to treat urinary tract problems. In fact, The European Medicines Agency recommends the oral use of *P. officinarum* to increase the amount of urine in order to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints (EMA/HMPC/680374/2013). This is very interesting in the treatment of chronic illnesses (e.g. urinary infections, prostate inflammation, etc.) where preparations made from these species might constitute a cheap alternative therapy to the conventional pharmaceutical products (Heinrich et al., 2018). In addition to the diuretic power, the proven antimicrobial and anti-inflammatory activities described could be very helpful to further develop improved phytoterapheutical products to treat or prevent these problems related to infections of the urinary tract or in conditions where the increase in diuresis could be adjuvant as well (e.g. sliming products).

Taking into consideration the anti-inflammatory, vulnerary and gastroprotective properties proven for these species it could be also promising to design new products aimed to treat gastric problems. Finally, the combination of the antimicrobial and anti-inflammatory power reported for these species makes them quite suitable for the development of new cosmetic products aimed to treat skin alterations.

All these insights seem to be the most realistic scenario in the short term in order to introduce these plants extracts, or certain compounds derived from them, in the phytoterapheutical products market for medicinal or health-promoting purposes in humans. However, clinical research involving double blind studies with standardized herbal extracts or metabolites (ideally optimized) in comparison to other pharmaceutical products would be desirable to perform.

Like for many other medicinal plants, the idea that *Hieracium*'s and *Pilosella*'s specialised metabolites could constitute a new source of molecules for the treatment of priority healthcare diseases such as cancer, viral infections, diabetes or neurological illnesses is not realistic at all in a short term. However, a more-in-depth basic research on these bioactivities (based on the reported traditional uses), and natural compounds responsible for them would clarify whether these species may offer possibilities in the treatment of these conditions. In this regard, to broad the scope of the academic research in specialised metabolites beyond phenolic acids and flavonoids present in wild taxa will be essential to certify their suitability. Ideally, to direct the phytochemical research towards certain groups of metabolites such as sesquiterpenoids and coumarines would match these goals. The sesquiterpenoids exhibit a wide range of bioactivities including anti-inflammatory activity (Lyβ et al., 1998) and cytotoxicity (Jöhrer et al., 2012). Also, sesquiterpene lactones, which fulfil the known criteria for presence of the required functional groups to exert these potential bioactivites (Zidorn et al., 1999) constitute the most interesting ones with regards to these applications (Zidorn, 2008). Given the large number of members and the few investigated taxa of *Hieracium* and *Pilosella* focusing on other compound classes than the well investigated phenolics and flavonoids, it is safe to

speculate that a number of so far not described naturally occurring sesquiterpenoids, sesquiterpene lactones, coumarines and triterpenoid alcohols (among others) can be isolated in taxa from both genera. Some of these undescribed compounds might constitute a promising reservoir for the screening of bioactivites and subsequently the possibility of new lead structures with high value for the pharmaceutical industry. Finally considered, scientific information on target specialised metabolites production and elicitation using plant *in vitro* culture systems (e.g. micropropagation, cell suspension and hairy root cultures) are completely lacking in these genera, even for *P. officinarum,* which is the most studied species. These biotechnological platforms have been proven to act as effective biofactories for the production of high-added value specialised metabolites such as phenolic compounds (Alvarado-Orea et al., 2020; Demirci et al., 2020; Karalija et al., 2020) or sesquiterpene lactones (Pourianezhad et al., 2019) and coumarines (Yousefian et al., 2021). Therefore, further investigation on phytochemical elicitation under *in vitro* culture conditions will certainly provide new insights to the revalorisation of *Hieracium* and *Pilosella* species as medicinal plants and the development of new phytoterapeutical products based on their specialised metabolites.

7. - Conclusions

The review here presented analyses the current knowledge on the ethnopharmacology, phytochemistry, and bioactivities of species belonging to *Hieracium* and *Pilosella*. Only 34 species are reported to have traditional uses. This is most probably due to the high number of range-restricted taxa, the loss of popular knowledge and the historical difficulties to distinguish the different taxa within this complex. Traditional uses having the strongest experimental support are the anti-infammatory and antimicrobial as, in our criterion, all studied extracts showed pronounced bioactivities by means of *in vitro* and, in some cases, *in vivo* models. Although diuretic activity is also experimentally tested both *in vitro* and *in vivo*, it would be beneficial to perform additional studies to finally support this traditional use. In addition, it is quite clear which metabolites are responsible to exert anti-inflammatory, antimicrobial and diuretic activities: phenolics and flavonoids. For the other bioactivities, there is no clear correlation between chemical composition and properties, or those properties are not outstanding when comparing to other plants' extracts. Therefore, the above-mentioned fields of application represent the most plausible scenario for the new marketable products development based on these species' specialised metabolites. However, as it happens to other drugs originating from plants, it would be necessary to perform clinical research including double blind studies in humans as the ultimate proof of relevant bioactivity. Partly clear evidences were observed for the antioxidant, gastroprotective, cytotoxic, antiepileptic, and antidiabetic activities as these experiments were only performed by means of *in vitro* approaches, and in some cases lacking proper experimental design (e.g. lack of positive or negative controls). Therefore, further research is highly encouraged to clarify these gaps in our knowledge. Finally considered, we found several works dealing with bioactivities of species without references on their traditional usage. On the other hand, species (e.g. *H. umbellatum*) having a quite well documented ethnopharmacological record are not tested for their bioactivities. Therefore, it would be interesting to focuss the effort of studying species with ethnopharmacological relevance in parallel to the intensification of the ethnopharmacological research efforts above mentioned. As demonstrated above, many studies investigating possible bioactivities of *Hieracium* and *Pilosella* species were restricted to the evaluation of crude extracts, thus not identifying active principles. Hence, future studies should include a bioactivity guided approach of isolation after the initial screening. Also, it would be desirable to focus on certain specialised metabolites and their bioactivities (e.g. sesquiterpenoids and sesquiterpene lactones) and the role of *in vitro* plant cell cultures in their biosynthesis and elicitation.

Author's contribution

All authors equally contributed in the research and in the manuscript preparation. Also, all authors have read and approved the final manuscript.

Declaration of competing interest

The authors hereby declare no conflict of interest.

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Abbreviations

ABTS	2,2 -azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AN	Ambiguous name
COX	Cyclooxygenase
DMSO	Dimethyl sulfoxide.
DPPH	(2,2-diphenyl-1-picryl-hydrazyl-hydrate)
ED_{50}	Median effective dose
ELISA	Enzyme-linked immunosorbent assay
GABA	Gamma-aminobutyric acid
HAses	Mammalian hyaluronidases
HIV	Human immunodeficiency viruses
IC_{50}	Half-maximal inhibitory concentration
IFN-γ	Interferon gamma
IgE	Immunoglobulin E
IL	Interleukin
IVOMD	*In vitro* organic matter digestibility
MIC	Minimum Inhibitory Concentration
MMP-9	Matrix metallopeptidase 9
NPM-9	Nona natural product mixture
NCT	Not considered taxon in World Flora Online or The Plant List
NV	Non validated name
OVA	Ovalbumin
PPI	Proton pump inhibitors
RBC	Red blood cells
SAN	Synonym of the accepted name
TMA	Trimellitic anhydride.
UR	Unresolved name
WBC	white blood cells

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