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RECEIVED 02 September 2024
ACCEPTED 07 October 2024
PUBLISHED 21 October 2024

CITATION
Mitsi C and Echeverría J (2024) The genus
Haplopappus: botany, phytochemistry,
traditional uses, and
pharmacological properties.
Front. Pharmacol. 15:1490243.
doi: 10.3389/fphar.2024.1490243

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The genus *Haplopappus*: botany, phytochemistry, traditional uses, and pharmacological properties

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Background: The genus *Haplopappus* Cass. [Asteraceae] comprises a large number of species distributed mainly in Chile and with various traditional medicinal uses.

Purpose: The present review addresses the botany, traditional uses, chemistry, biological and pharmacological activities of the genus, aiming to further potentiate the associated research and applications.

Study design and Methods: Literature data on the chemistry and bioactivity of the genus *Haplopappus* were mainly retrieved from digital databases such as SciFinder®, PubMed®, and Google Scholar®, as well as from the scientific journal publishers' platforms linked with these databases.

Results and discussion: Although the majority of the botanical taxa of the genus *Haplopappus* has been understudied, available information is promising regarding its phytochemistry and bioactivity. A total of more than 400 compounds are present in different *Haplopappus* species, mostly terpenoids and phenolic compounds. Scientific literature supports various health promoting effects of *Haplopappus* extracts and isolated compounds, principally their effect against human pathogenic bacteria and their high antioxidant capacity. The existing limitations highlighted hereby are mainly associated to the lack of modern investigation regarding a wider number of *Haplopappus* species and chemical compounds, as well as to the absence of *in vivo* bioactivity results and clinical trials.

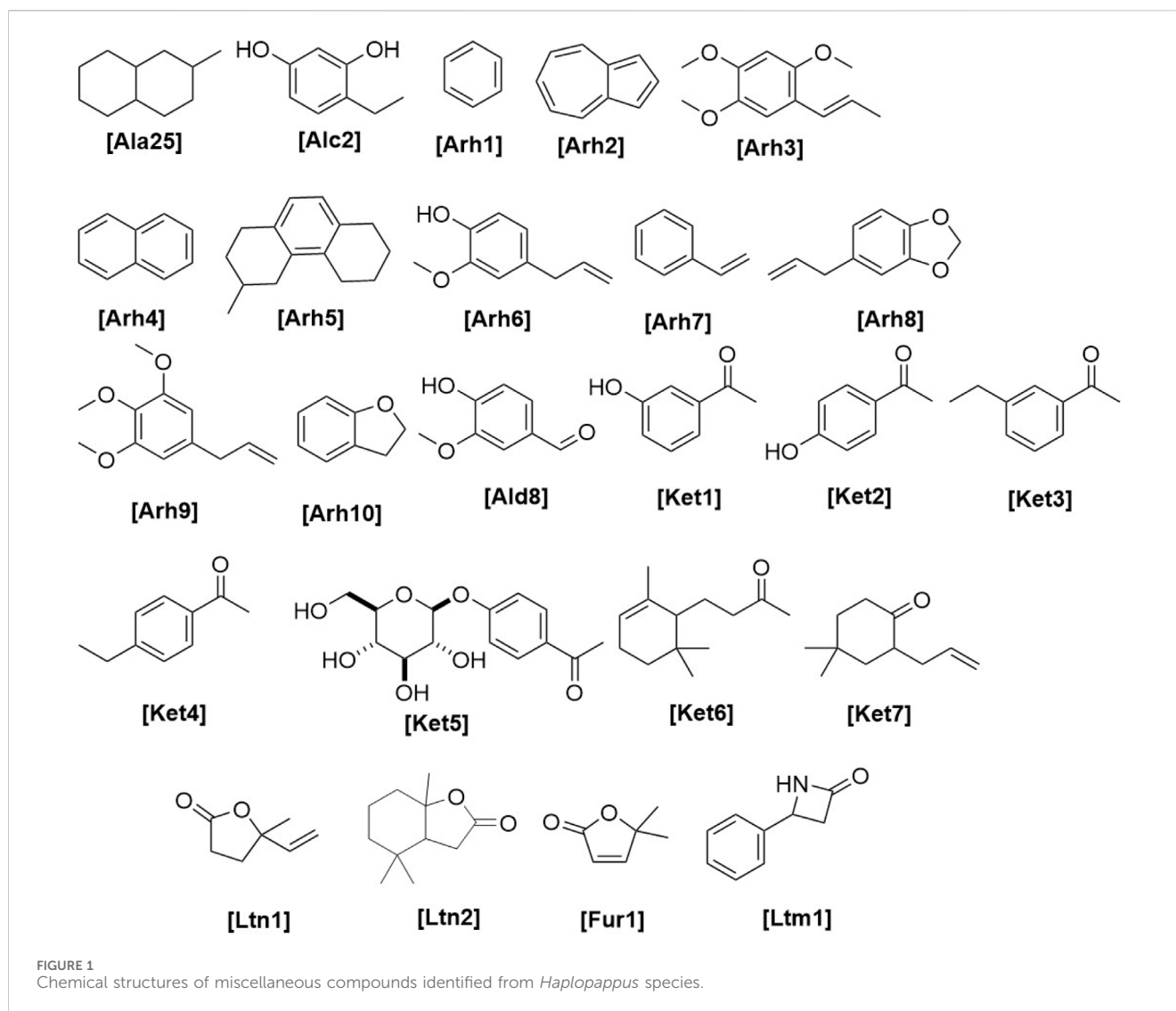
Conclusion: Scientific literature supports the ethnopharmacological, phytochemical and bioactive potential of the genus *Haplopappus*, however the aforementioned limitations need to be addressed in order to further promote and broaden both scientific research and future applications and uses.

KEYWORDS

Haplopappus genus, ethnobotany, traditional uses, phytochemistry, pharmacology

1 Introduction

Haplopappus Cass. (Asteraceae (Compositae) - Astereae - Machaerantherinae), is a strictly endemic botanical genus of southern South America, distributed in Chile, with some species also present in Argentina (Klingenberg, 2007). The vernacular name 'bailahuén' ('baylahuén' or 'vaila-huen') has been mainly attributed to the species *Haplopappus baylahuen* Remy, although the other species of the genus are commonly referred to using the same name (Vogel et al., 2007).



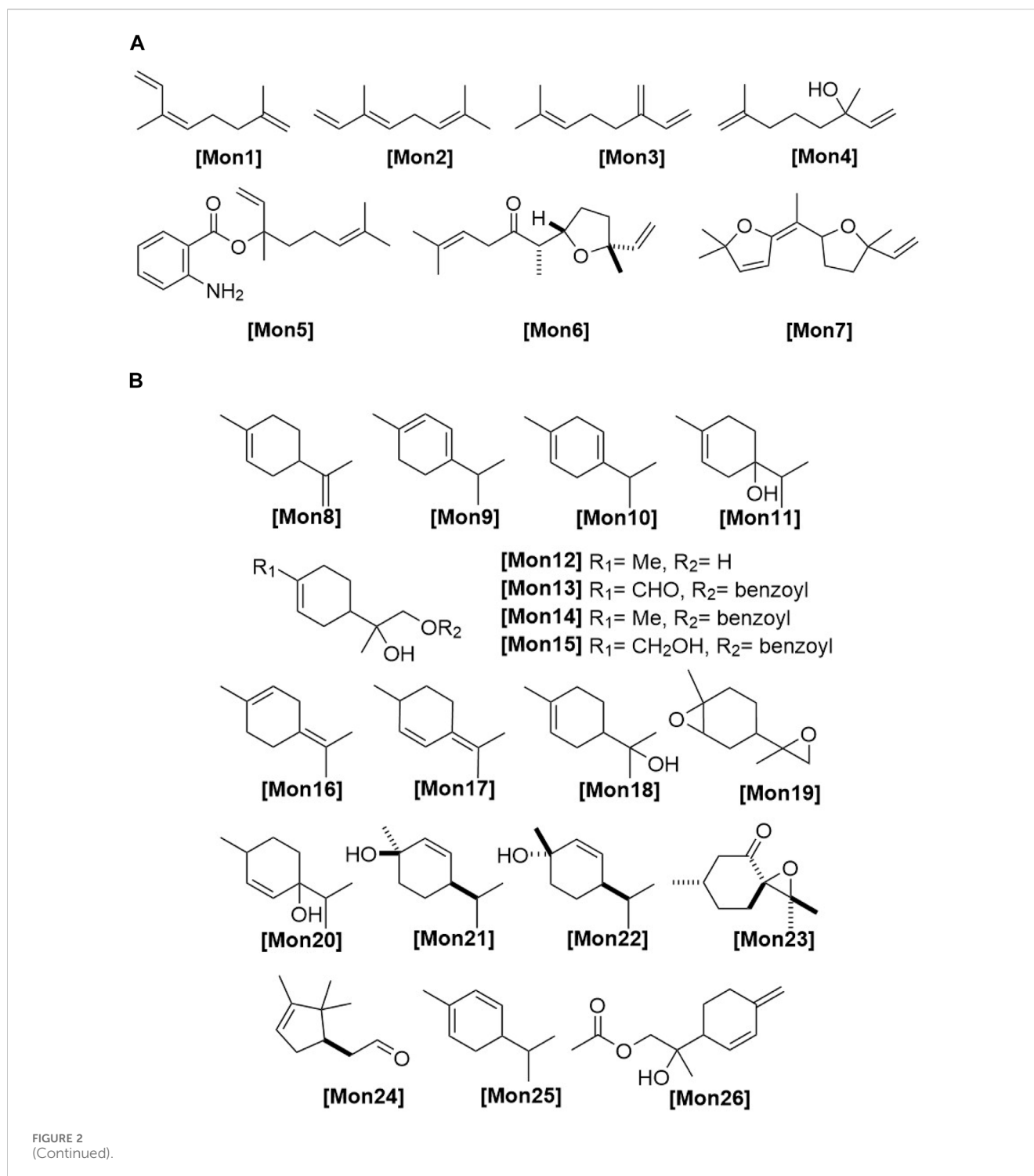
The different species of the genus *Haplopappus*, although used without differentiation in terms of botanical taxa, are of high ethnopharmacological importance and form part of the longstanding traditional medicines of the Andean peoples. In Chile, where the genus is mainly distributed, its species have been widely used in all territory, from the Aymara communities in the north to Mapuche communities in the south, and in big cities by different social groups (Hoffmann et al., 1992). *Bailahuén* is used at the prevention and/or treatment of various human and animal pathologies, mainly -but not exclusively- associated to gastrointestinal ailments and wound healing (Muñoz et al., 1981; de Mösbach, 1992; Hoffmann et al., 1992). Alongside its traditional use, *H. baylahuén* is also included in the German Homeopathic Pharmacopeia as a herbal medicine against fatigue and low blood pressure, although its use is considered limited (Arzneibuch, 2006; Vogel et al., 2007).

Regarding its commercialization, it is reported that its production in Chile is exclusively based on the collection of plant material in the wild, which, in most cases, is realized by non-trained individuals (Vogel et al., 2007). Furthermore, in the same study it is

highlighted that the 80% of *bailahuén* commercial samples correspond to *Haplopappus multifolius*, probably due to the fact that this species is distributed in the Metropolitan Region of Santiago, where the companies that commercialize the plant material at a national and international level are also located. The over-exploitation of *H. multifolius*, along with inadequate collection practices, have led to the species being recently included in The IUCN Red List of Threatened Species as Near Threatened (Plummer, 2022).

In this context, despite its high botanical diversity and the rich ethnopharmacological background of the genus *Haplopappus*, both scientific investigation and commercial use is often limited to a few botanical taxa, while in many cases the traditional knowledge associated with the genus is not taken into consideration, thus hindering unravelling the full phytochemical and bioactive potential of the genus.

Thus, the present article aims to present a comprehensive review of the current state of knowledge regarding the botany, traditional uses, chemistry, biological and pharmacological activities of the genus *Haplopappus* in an attempt to underline its phytochemical



uniqueness, elucidate its bioactive potential, and highlight future research opportunities.

2 Methods

Literature data on the chemistry and bioactivity of the genus *Haplopappus* were mainly retrieved from digital databases such as SciFinder[®], PubMed[®], and Google Scholar[®], as well as from the

scientific journal publishers' platforms linked with these databases. The search strategy included the scientific name of the genus, excluding the species presently classified in other genera, i.e., *Ericameria* Nutt., *Grindelia* Willd., *Gundlachia* A.Gray, *Isocoma* Nutt., *Notopappus* L. Klingberg (Klingenberg, 2007; POWO, 2024). All publications in peer-reviewed journals until May 2024 were considered. The chemical compounds present in the raw materials were classified according to their pathway and superclass (Supplementary Table S1; Figures 1–11) using the NPClassifier tool (Kim et al., 2021).

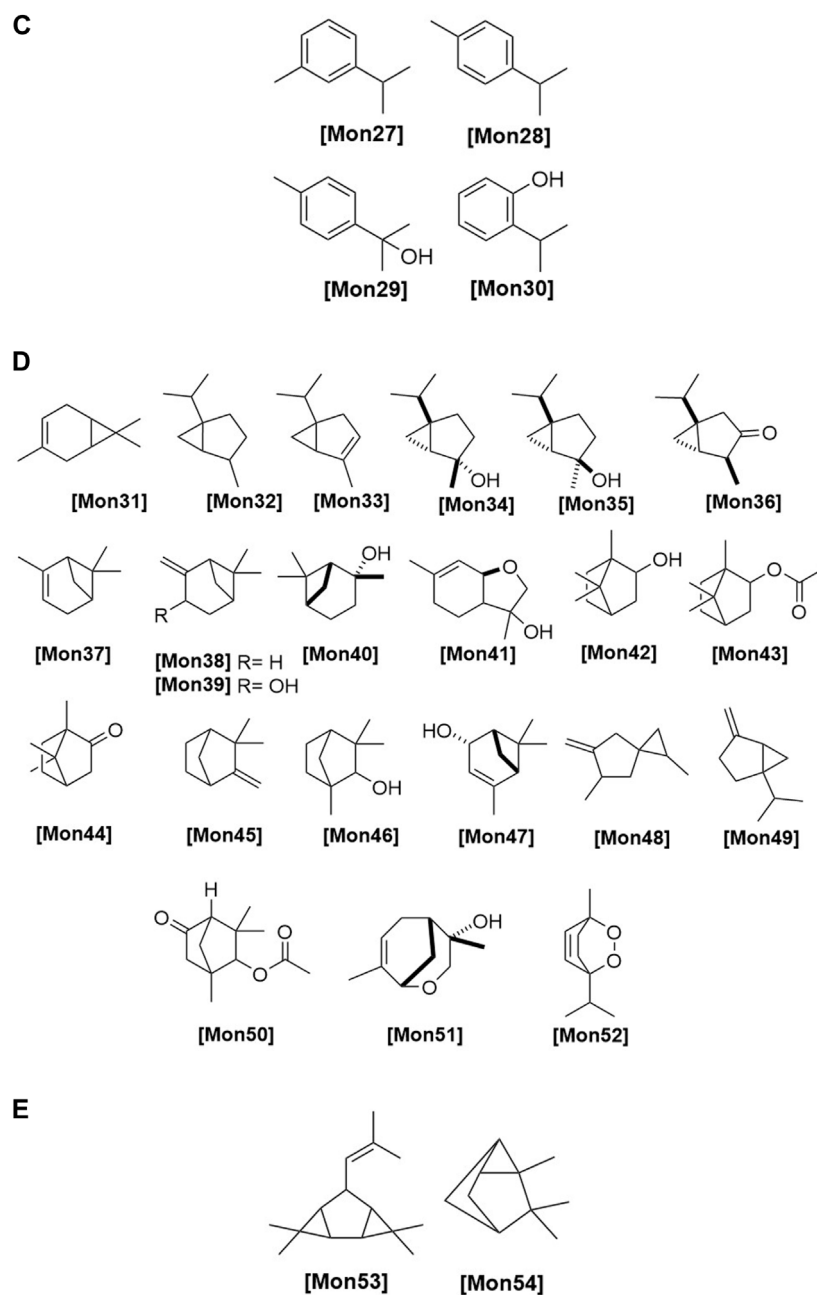


FIGURE 2

(Continued). (A) Chemical structures of acyclic monoterpenes identified from *Haplopappus* species. (B) Chemical structures of monocyclic monoterpenes identified from *Haplopappus* species. (C) Chemical structures of aromatic monocyclic monoterpenes identified from *Haplopappus* species. (D) Chemical structures of bicyclic monoterpenes identified from *Haplopappus* species. (E) Chemical structures of tricyclic monoterpenes identified from *Haplopappus* species.

3 Botany and distribution

The genus *Haplopappus* Cass. (Asteraceae - Astereae - Machaerantherinae) is a strictly endemic genus of South America and its species are mainly distributed in Chile and, to a lesser extent, Argentina (Klingenberg, 2007; Rodriguez et al., 2018; Zuloaga et al., 2019; García et al., 2024).

According to the latest taxonomic studies of the genus and after the separation of numerous, mainly North American, species that formed the genus *Notopappus* L. Klingenberg, the genus

Haplopappus consists of 70 specific and intraspecific taxa (Table 1) and is subdivided into three subgenera (*Haplopappus* subgen. *Haplopappus*, *H.* subgen. *Grindeloidae* Klingenberg, and *H.* subgen. *Baylahuen* Klingenberg) and five sections: *Haplopappus* sect. *Haplopappus*, *H.* sect. *Gymnocomma* Nuttall, *H.* sect. *Grindeloidae* Klingenberg, *H.* sect. *Chromochaeta* Candolle, and *H.* sect. *Leiachaenium* Candolle (Klingenberg, 2007; García et al., 2018; García et al., 2024). *Haplopappus* taxonomy is mainly based on morphological traits, due to the limited phylogenetic data available up to date (García et al., 2024). In general, *Haplopappus* species are

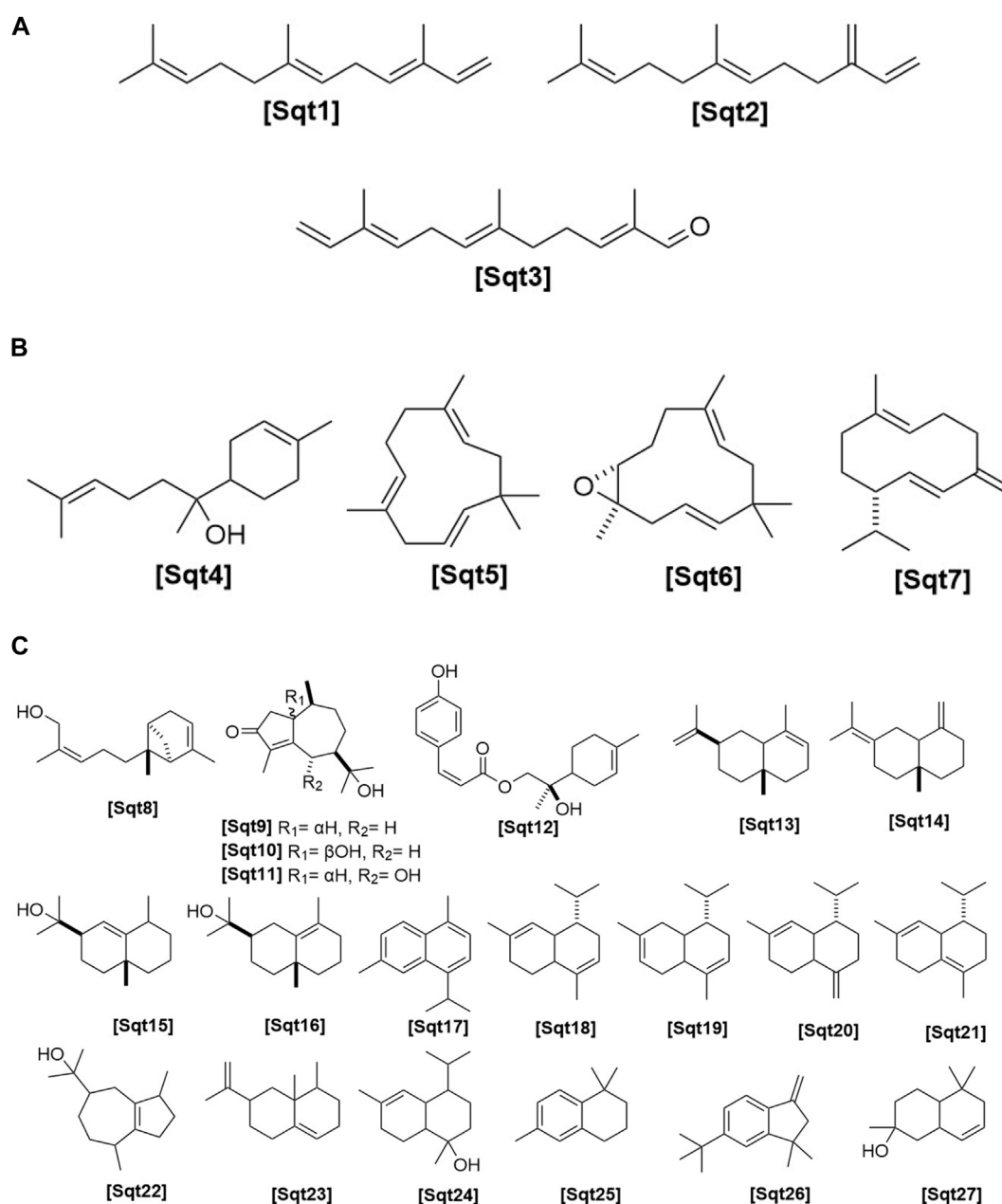


FIGURE 3
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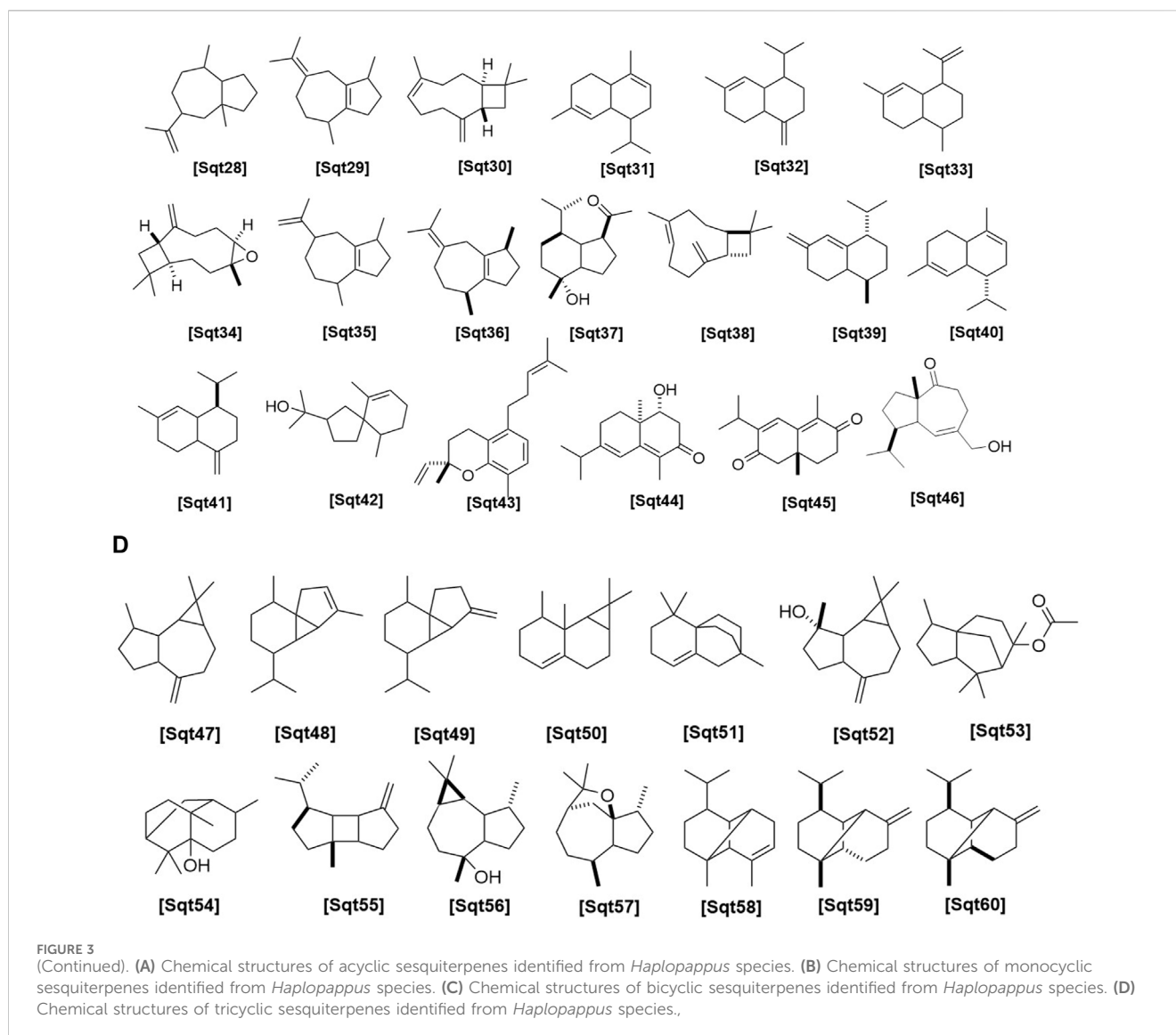
shrubs or subshrubs, with aerial parts that bear glandular trichomes, usually yellow florets, and numerous pappus bristles (Klingenberg, 2007; García et al., 2024).

4 Phytochemistry

Available scientific literature provides relevant information on the phytochemistry of the genus *Haplopappus*. However, it must be mentioned that this information refers to only 28 species and subspecies of a total of 70 taxa (Table 1), thus highlighting the largely understudied potential of the genus *Haplopappus* and stressing the need to further investigate its phytochemistry.

Moreover, of these 28 taxa for which scientific evidence is available, for the 24 there are less than 35 compounds reported per taxa, whereas the remaining four species are associated to a higher -yet still rather diverse-number of reported compounds, i.e., *H. foliosus* ($n = 146$), *H. velutinus* ($n = 59$), *H. chrysanthemifolius* ($n = 52$), *H. bustillosianus* ($n = 40$).

Regarding the type of metabolites reported in *Haplopappus* species, more than 400 different molecules have been detected in various plant parts of the studied taxa. However, the number of reported compounds per chemical group is highly diverse, to an extent that it raises the question of whether this variability can be solely attributed to differences at a plant metabolic level or it can also be associated with a focus of scientific research towards certain groups of



metabolites, e.g., terpenoids and phenolics. Indeed, products of the terpenoid metabolic pathway are by far the most abundant group of molecules reported in the genus *Haplopappus*, including more than 200 compounds, i.e. 54 monoterpenoids (abbreviated as **Mon** in compound codification used in the present review), 60 sesquiterpenoids (**Sqt**), 107 diterpenoids (**Dit**), five triterpenoids (**Tri**), one meroterpenoid (**Mer**) and two steroids (**Str**). The second most abundant group of reported compounds includes flavonoids (**Flv**; flavonols, $n = 46$; flavones, $n = 20$; flavanones, $n = 8$; flavanonols, $n = 11$) and other products of the metabolic pathway of shikimic acid, i.e., coumarins (**Cum**, $n = 16$), benzoic (**Ben**, $n = 3$) and cinnamic (**Cin**, $n = 12$) acid derivatives. Other compounds reported in the genus *Haplopappus* include alkanes (**Ala**, $n = 29$), alkenes (**Ale**, $n = 4$), alkynes (**Aly**, $n = 1$), alcohols (**Alc**, $n = 5$), ethers (**Eth**, $n = 1$), aromatic hydrocarbons and derivatives (**Arh**, $n = 10$), aldehydes (**Ald**, $n = 8$), ketones (**Ket**, $n = 7$), esters (**Est**, $n = 8$), furanones (**Fur**, $n = 1$), lactones (**Ltn**, $n = 2$) and lactams (**Ltm**, $n = 1$).

The aforementioned compounds as classified per chemical group are detailed in Figures 1–11 and Tables 2–4, and

Supplementary Table S1, while their distribution among the studied *Haplopappus* taxa is presented as follows.

4.1 *H. angustifolius* (DC.) Reiche

Information on the chemical composition of *H. angustifolius* is limited to reports of the presence of hentriacontane (**Ala22**), hexacosanol (**Alc1**), the diterpenes haplopappic acid (**Dit96**) and its methylester (**Dit97**) and the triterpenes friedelin (**Tri1**) and *epi*-friedelinol (**Tri3**) in the aerial parts of the plant (Silva and Sammes, 1973).

4.2 *H. anthylloides* Meyen & Walp

The ketone 4-hydroxyacetophenone (**Ket2**) is the only compound identified in the aerial parts of *H. anthylloides* (Zdero et al., 1990).

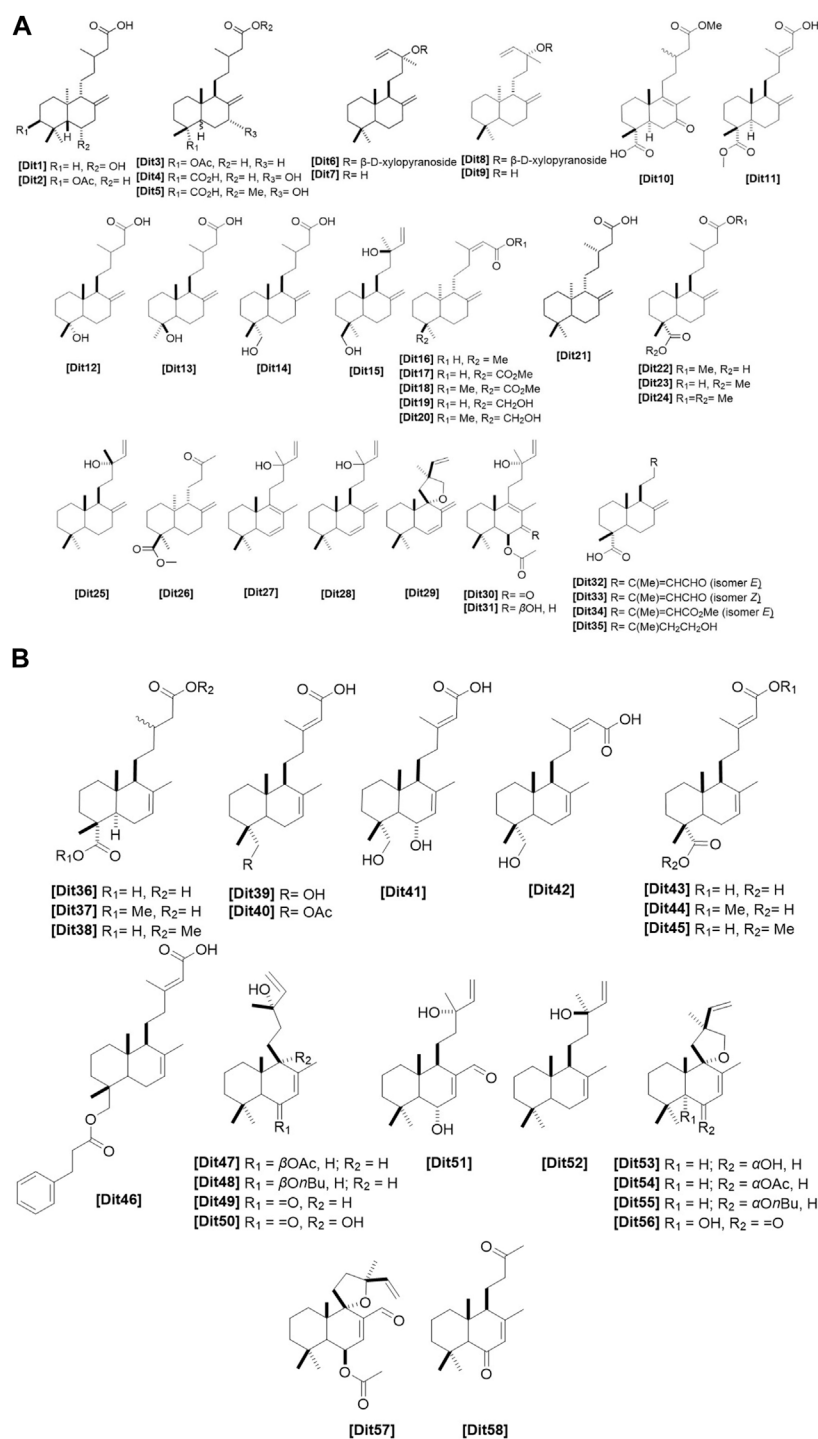
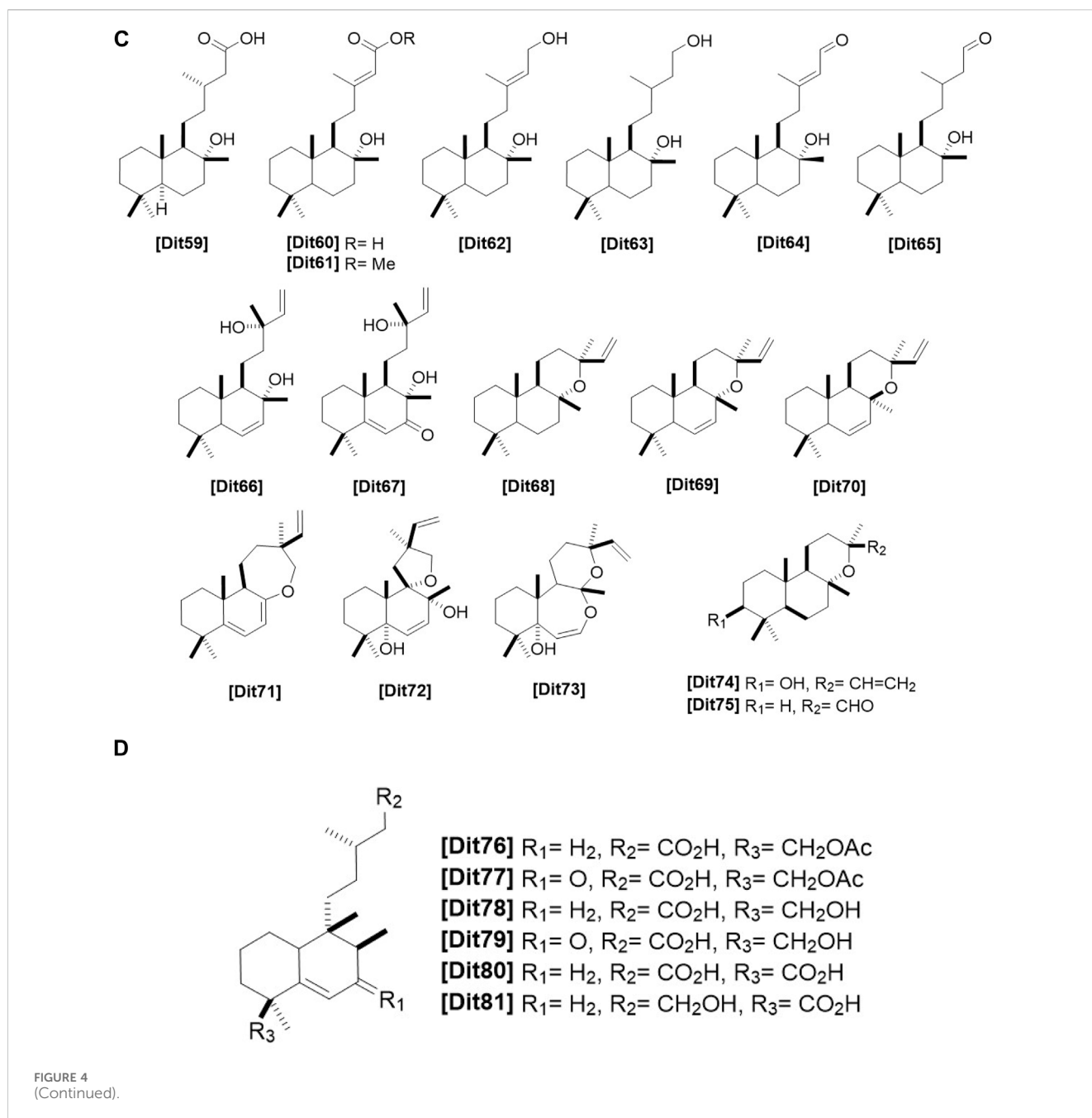


FIGURE 4
(Continued).

4.3 *H. arbutoides* Remy

The majority of the compounds identified in the aerial parts and/or resin of *H. arbutoides* belong to the diterpenoids group, i.e. 15-oxo-labda-8(17),14*E*-diene-18-oic acid (Dit32), 15-oxo-labda-8(17),14*Z*-diene-18-oic acid (Dit33), labda-8(17),13*E*-dien-15,18-dioic acid 15-methyl ester (Dit34), 15-hydroxylabd-8(17)-en-18-oic

acid (Dit35), labd-13(*E*)-ene-8 α ,15-diol (Dit62), 13*R*-labdane-8,15-diol (Dit63), 8 α -hydroxy-*ent*-labd-13(14)*Z*-en-15-al (Dit64), 8 α -hydroxylabdan-15-al (Dit65), *epi*-manoyl oxide (Dit68), 8,13-epoxy-14-labdeb-3-ol (Dit74), 8,13-epoxy-labdan-15-al (Dit75), 15-oxocleroda-3,13*E*-dien-18-oic acid (Dit91), and 15-oxocleroda-3,13*Z*-dien-18-oic acid (Dit92) (Zdero et al., 1991a; Rossomando et al., 1995). Additionally, the aerial parts are reported to contain 4-



hydroxyacetophenone (**Ket2**), the sesquiterpene 1 β -hydroxy- β -cyperone (**Sqt44**) and the flavonols santin (**Flv41**) and penduletin (**Flv45**) (Zdero et al., 1991a; Rossomando et al., 1995).

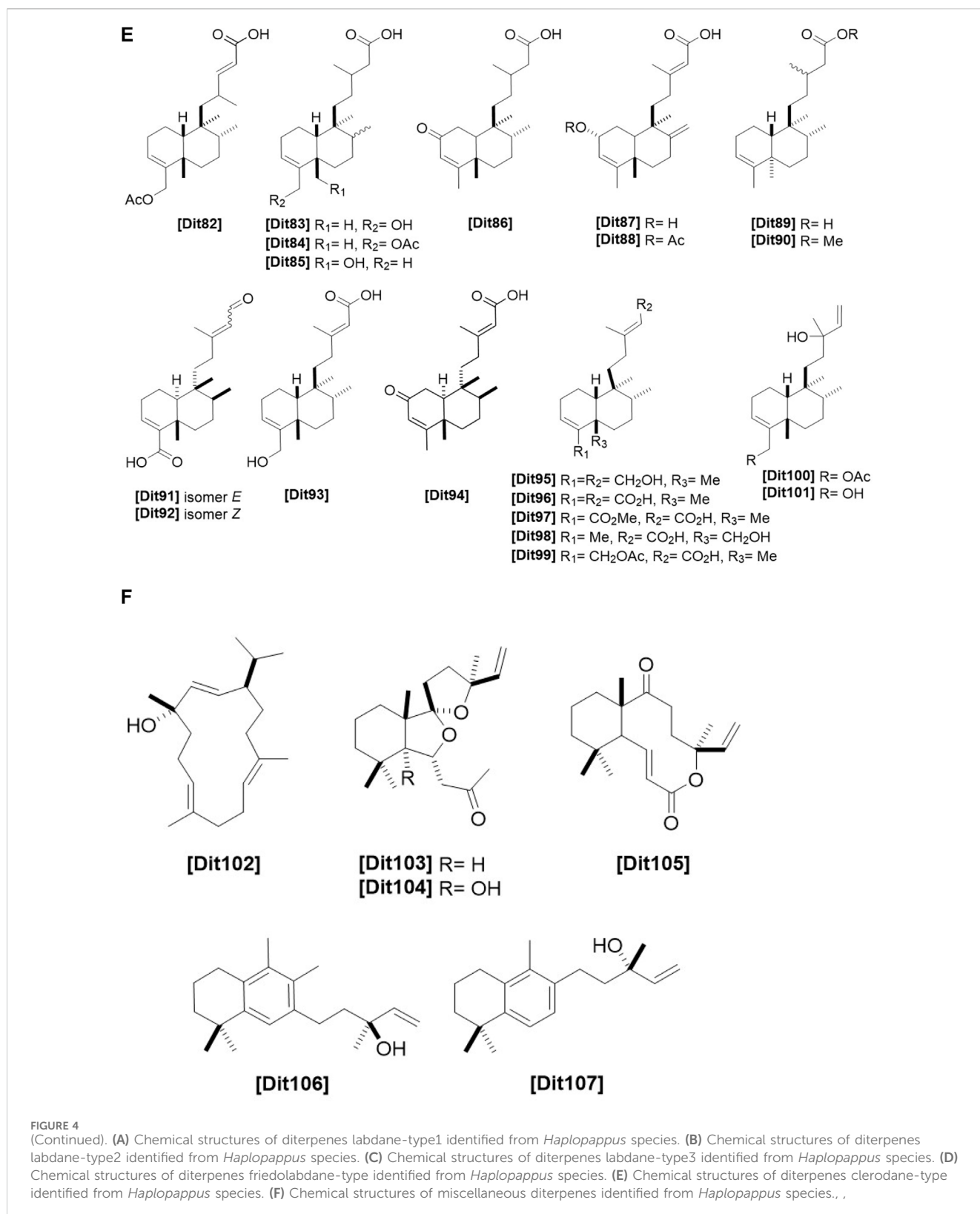
4.4 *H. baylahuen* Remy

The essential oil of the leaves of *H. baylahuen* is reported to contain eicosane (**Ala11**), benzene (**Arh1**), azulene (**Arh2**), naphthalene (**Arh4**), and the sesquiterpenes bergamotol (**Sqt8**) and α -cadinol (**Sqt24**) (Becerra et al., 2010). Phenolic compounds detected in this species include quercetin (**Flv1**), quercetin 3-methyl ether (**Flv2**), rhamnetin (**Flv17**), isorhamnetin (**Flv18**), kaempferol (**Flv21**), rhamnocitrin (**Flv25**), velutin (**Flv57**), sakuranetin (**Flv67**),

persicogenin (**Flv69**), sternbin (**Flv70**), 7,4'-dimethylaromadendrin (**Flv75**), 7-O-methylaromadendrin (**Flv76**), 7,3'-di-O-methyltaxifolin (**Flv81**), dihydromyricetin (**Flv82**), prenyletin (**Cum3**), and 3,5-dicaffeoylquinic acid (**Cin12**) (Schwenker et al., 1967; Hörhammer et al., 1973; Nuñez-Alarcon et al., 1993; Vera et al., 2001; Schmeda-Hirschmann et al., 2015).

4.5 *H. bezanillanus* (Remy) Reiche

The compounds detected in the aerial parts of *H. bezanillanus* are the diterpenoid labd-13(E)-ene-8 α ,15-diol (**Dit62**), the steroid β -sitosterol (**Str2**) and the flavonol jaceidin 7-methyl ether (**Flv44**) (Maldonado et al., 1993).



4.6 *H. bustillosianus* Remy

The aerial parts of *H. bustillosianus* contain the alkenes C₁₁H₂₄ - C₁₄H₃₀ (Ala2 - Ala5), C₁₆H₃₄ - C₃₃H₆₈ (Ala7 - Ala24), along with 3-hydroxyacetophenone (Ket1) and

the flavonoids santin (Flv41) and 3,6-dimethoxyapigenin (Flv48) (Urzúa et al., 2007a). Their phenolic profile includes α-linalool (Mon4), α-pinene (Mon37), β-pinene (Mon38), α-bisabolol (Sqt4), humulene (Sqt5), α-cadinene (Sqt18), γ-cadinene (Sqt20), δ-cadinene (Sqt21), (-)-isocaryophyllene (Sqt30), α-

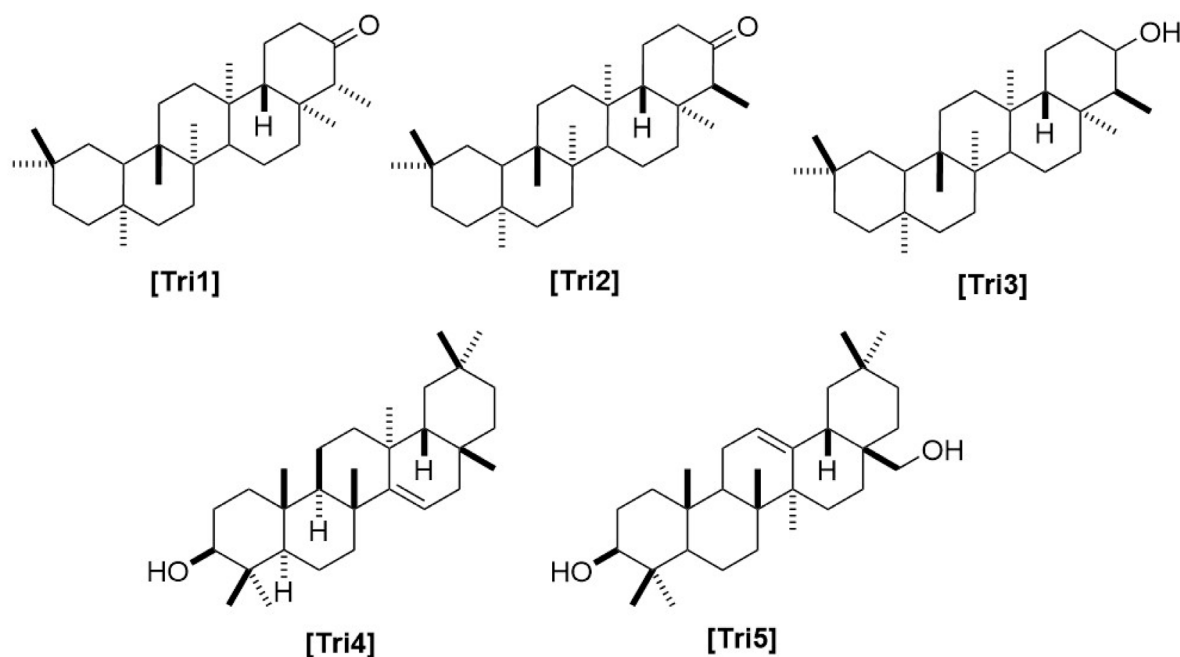


FIGURE 5
Chemical structures of triterpenes and triterpenoids identified from *Haplopappus* species.

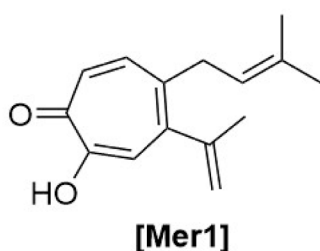


FIGURE 6
Chemical structures of meroterpenes identified from *Haplopappus* species.

cubebene (Sqt48), β -cubebene (Sqt49), α -copaene (Sqt58), populifolic acid (Dit89) and its methyl ester (Dit90), and thunbergol (Dit102) (Urzúa et al., 2007a).

4.7 *H. chrysanthemifolius* (Less.) DC

The phytochemistry of *H. chrysanthemifolius* has been thoroughly investigated and various chemical groups of compounds have been identified in this species. Among them, in the flower heads there are present the alkanes $C_{10}H_{22}$ – $C_{19}H_{40}$ (Ala1 – Ala10), $C_{21}H_{44}$ – $C_{33}H_{68}$ (Ala12 – Ala24), 2-methyldecalin (Ala25), 2,4,6-trimethyloctane (Ala26), 2,6-dimethylundecane (Ala27), 4,6-dimethylundecane (Ala28), and 2,10-dimethylundecane Ala29) (Urzúa et al., 2007a). Furthermore, the terpenoid profile of the species includes β -myrcene (Mon3), limonene (Mon8), α -pinene (Mon37), β -pinene (Mon38), humulene (Sqt5), δ -cadinene (Sqt21), (–)-isocaryophyllene (Sqt30),

β -bulgarene (Sqt31), γ -bulgarene (Sqt32), (–)-amorpha-4,11-diene (Sqt33), α -cubebene (Sqt48), β -cubebene (Sqt49), (–)-calarene (Sqt50), 1,3,4,5,6,7-hexahydro-2,5,5-trimethyl-2H-2,4a-ethanonaphthalene (Sqt51), α -copaene (Sqt58), 6 α -hydroxy-*ent*-labd-8(17)-en-15-oic acid (Dit1), 3 β -acetoxy-*ent*-labd-8(17)-en-15-oic acid (Dit2), and 18 α -acetoxy-*ent*-labd-8(17)-en-15-oic acid (Dit3) (Faini et al., 1999; Urzua et al., 2007b). Regarding the phenolic compounds of *H. chrysanthemifolius*, it is reported the presence of quercetin (Flv1), tamarixetin (Flv3), ayanin (Flv7), myricetin 3,7,4'-trimethyl ether (Flv36), luteolin (Flv53), and diosmetin (Flv58) (Faini et al., 1999; Urzua et al., 2007b; Urzúa et al., 2012).

4.8 *H. coquimbensis* (Hook. & Arn.) Klingenberg

The aerial parts of *H. coquimbensis* (syn. *H. hirtellus* Phil. (Klingenberg, 2007)) contain the terpenoids 7,13-labdadien-15,18-dioic acid 15-methyl ester (Dit44) and *epi*-friedelin (Tri2), as well as stigmasterol (Str1) (Maldonado et al., 1993). Regarding its flavonoid profile, the following compounds were detected in its aerial parts: kaempferol 7,4'-dimethyl ether (Flv27), kaempferol 3,7,4'-trimethyl ether (Flv29), pachypodol (Flv46), sakuranetin 4'-methyl ether (Flv68), eriodictyol 7,3'-dimethyl ether (Flv72), 7,4'-dimethylaromadendrin (Flv75), and 7,3'-di-*O*-methyltaxifolin (Flv81) (Maldonado et al., 1993).

4.9 *H. deserticola* Phil

In the aerial parts of *H. deserticola* there were detected the diterpenoids methyl-*ent*-4-*epi*-agath-18-oate (Dit17), dimethyl-*ent*-

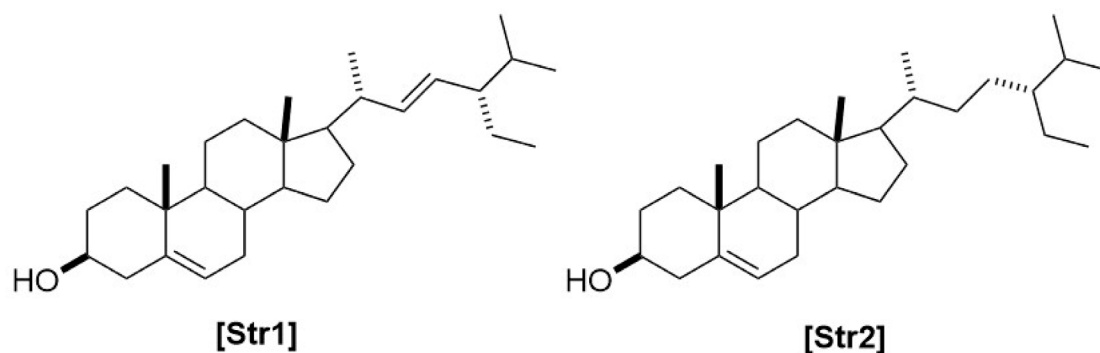


FIGURE 7
Chemical structures of steroids identified from *Haplopappus* species.

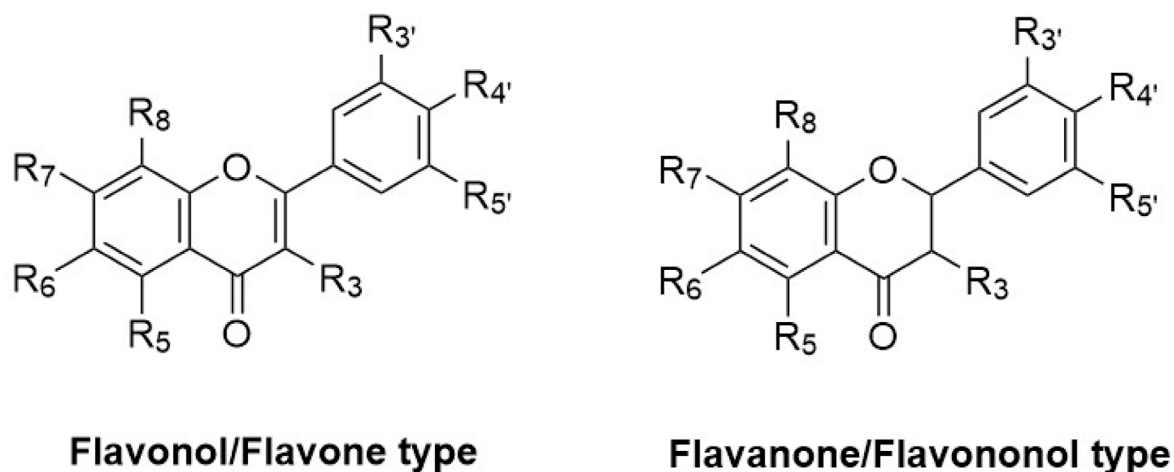


FIGURE 8
Chemical structures and substitution patterns of flavonoids identified from *Haplopappus* species.

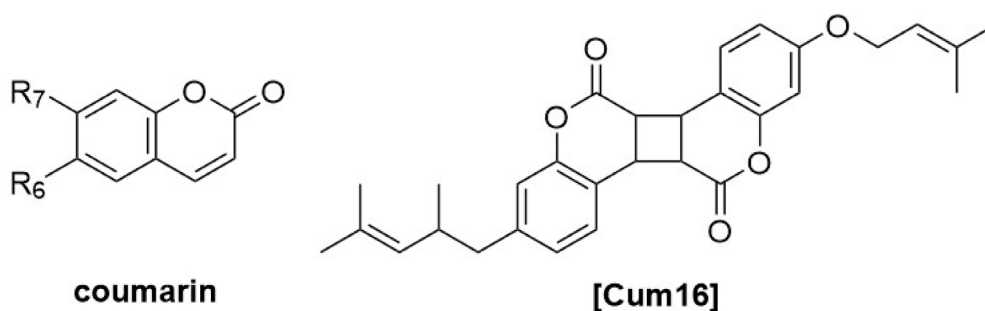


FIGURE 9
Chemical structures and substitution patterns of coumarins identified from *Haplopappus* species.

4-*epi*-agathoate (**Dit18**), copaiiferolic acid (**Dit19**), copaiiferolic acid 15-methyl ester (**Dit20**), methyl haplodesertoate (**Dit26**), 8 α -hydroxyanticopalic acid (**Dit60**), 8 α -hydroxyanticopalic acid methyl ester (**Dit61**), *ent*-19-hydroxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (**Dit98**), and 18-acetoxy-*cis*-cleroda-3,13(*E*)-dien-15-oic

acid (**Dit99**), along with the sesquiterpenoid germacrene D (**Sqt7**) (Zdero et al., 1990; Urzúa Moll et al., 1997; Tojo et al., 1999).

Regarding its phenolic composition, the aerial parts of this species are reported to contain the flavonoids quercetin (**Flv1**), quercetin 3-methyl ether (**Flv2**), isokaempferide (**Flv23**), 3,8-

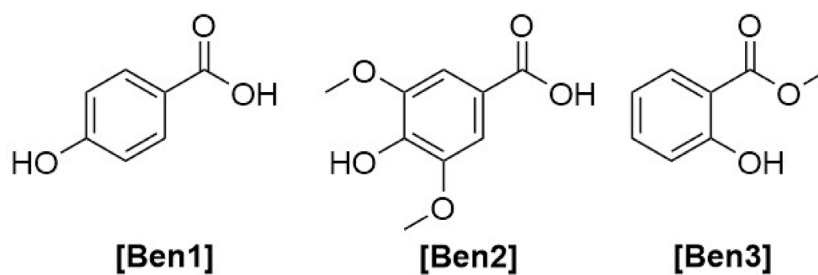


FIGURE 10
Chemical structures of benzoic acid derivatives identified from *Haplopappus* species.

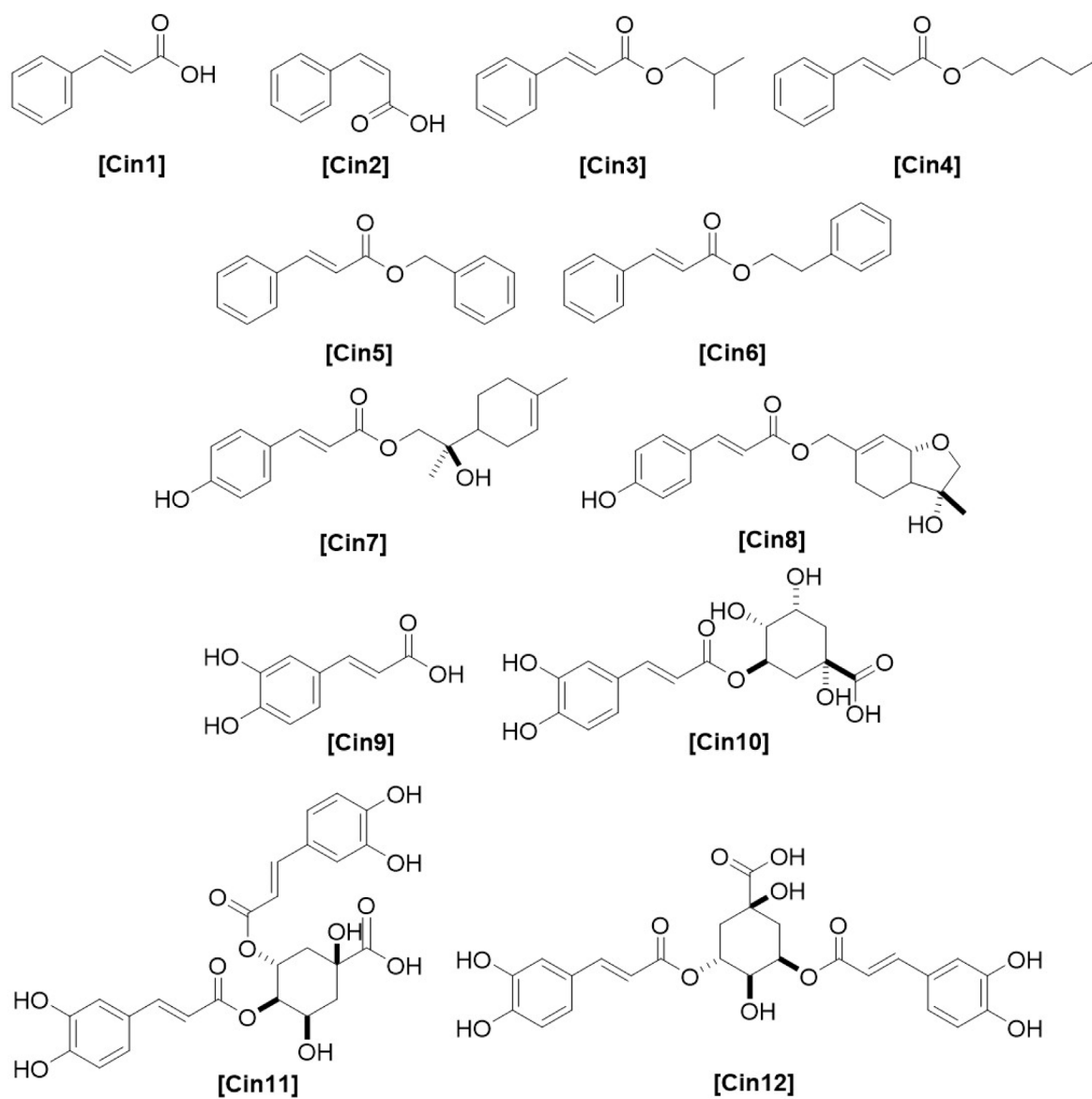


FIGURE 11
Chemical structures of cinnamic acid derivatives identified from *Haplopappus* species.

TABLE 1 Scientific names and distribution of reported *Haplopappus* species (Klingenberg, 2007; Garcia et al., 2018; García et al., 2024).

| No. | <i>Haplopappus</i> species | Synonyms | Distribution ^a |
|-----|---|--|---|
| 1 | <i>H. angustifolius</i> (DC.) Reiche subsp. <i>angustifolius</i> | <i>Aster atenes</i> Kuntze, <i>Aster sternbergii</i> Kuntze, <i>H. durus</i> Reiche, <i>Pyrocoma angustifolia</i> DC., <i>Pyrocoma rigida</i> Phil | Chile (Atacama, Coquimbo) |
| 2 | <i>H. angustifolius</i> (DC.) Reiche subsp. <i>saxatilis</i> (Remy) Klingenb | <i>Aster saxatilis</i> (Remy) Kuntze, <i>Haplodiscus sphacelatus</i> Phil., <i>H. saxatilis</i> (Remy) Reiche, <i>H. sphacelatus</i> (Phil.) Reiche, <i>Pyrocoma saxatilis</i> Remy | Chile (Coquimbo, Metropolitan of Santiago, Maule) |
| 3 | <i>H. anthylloides</i> Meyen & Walp | <i>Aster anthylloides</i> (Meyen & Walp.) Kuntze, <i>Aster radicans</i> (Remy) Kuntze, <i>H. radicans</i> Remy | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) Argentina (Mendoza) |
| 4 | <i>H. arbutoides</i> Remy | <i>Aster arbutoides</i> (Remy) Kuntze, <i>H. obovatus</i> Phil., <i>H. baccharidifolius</i> Phil., <i>H. zanartui</i> (Phil.) Reiche | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Ñuble, Biobío, Araucanía) |
| 5 | <i>H. baylahuen</i> Remy subsp. <i>baylahuen</i> | <i>Aster baylahuen</i> (Remy) Kuntze, <i>H. domeykoi</i> Phil., <i>H. lastarrianus</i> Remy, <i>H. medicinalis</i> Phil | Chile (Atacama, Coquimbo) Argentina (San Juan) |
| 6 | <i>H. baylahuen</i> Remy subsp. <i>fluehmannii</i> (Phil.) Klingenb | <i>H. fluehmannii</i> Phil | Chile (Atacama) |
| 7 | <i>H. bezanillanus</i> (Remy) Reiche | <i>Aster bezanillanus</i> (Remy) Kuntze, <i>Pyrocoma bezanillana</i> Remy | Chile (Coquimbo) |
| 8 | <i>H. boelckeii</i> Tortosa & A. Bartoli | - | Argentina (Mendoza) |
| 9 | <i>H. bustillosianus</i> Remy | <i>Aster bustillosianus</i> (Remy) Kuntze, <i>Aster patagoniensis</i> Kuntze, <i>H. australis</i> Phil., <i>H. glutinosus</i> f. <i>patagonicus</i> (Phil.) Cabrera, <i>H. patagonicus</i> Phil., <i>H. subandinus</i> Phil | Chile (Maule, Ñuble, Biobío, Araucanía, Los Lagos) Argentina |
| 10 | <i>H. cerberoanus</i> (Remy) Reiche subsp. <i>cerberoanus</i> | <i>Aster cerberoanus</i> (Remy) Kuntze, <i>Pyrocoma cerberoana</i> Remy | Chile (Atacama, Coquimbo) Peru |
| 11 | <i>H. cerberoanus</i> (Remy) Reiche subsp. <i>elquianus</i> Klingenb | - | Chile (Coquimbo) |
| 12 | <i>H. chrysanthemifolius</i> (Less.) DC. | <i>Andromachia alternifolia</i> Kuntze, <i>Diplopappus chrysanthemifolius</i> Less., <i>Grindelia glutinosa</i> Bertero, <i>H. berteroi</i> DC., <i>H. leucanthemifolius</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Ñuble, Biobío, Metropolitan of Santiago) |
| 13 | <i>H. coquimbensis</i> (Hook. & Arn.) Klingenb | <i>Aster hirtellus</i> (Phil.) Kuntze, <i>Diplopappus coquimbensis</i> Hook. & Arn., <i>Haplodiscus elatus</i> Phil., <i>H. acanthodon</i> Phil. Reiche, <i>H. elatus</i> (Phil.) Reiche, <i>H. hirtellus</i> Phil., (Phil.) <i>H. hirtellus</i> Phil. var. <i>hirsutus</i> , <i>H. limarensis</i> Phil., <i>H. vidalii</i> Phil | Chile (Atacama, Coquimbo, Valparaíso, Libertador Bernardo O'Higgins) |
| 14 | <i>H. colliguayensis</i> M.A.Villalobos, V.Morales & Nic.García | - | Chile (Valparaíso) |
| 15 | <i>H. decurrens</i> Remy | <i>Aster remyanus</i> Kuntze | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Metropolitan of Santiago) |
| 16 | <i>H. deserticola</i> Phil | <i>H. involucratus</i> Phil., <i>H. rengifoanus</i> Phil | Chile (Antofagasta, Atacama, Coquimbo) |
| 17 | <i>H. diplopappus</i> Remy subsp. <i>diplopappus</i> | <i>Aster diplopappus</i> (Remy) Kuntze, <i>Diplopappus spinulosus</i> Hook. & Arn., <i>H. heterophyus</i> Phil., <i>H. pallidus</i> Phil <i>H. peteroanus</i> Phil., <i>H. reticulatus</i> Phil | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |
| 18 | <i>H. diplopappus</i> Remy subsp. <i>villosus</i> (Phil.) L. Klingenberg | <i>Aster villiger</i> Kuntze, <i>Diplopappus spinulosus</i> Hook. & Arn., <i>H. diplopappus</i> Remy var. <i>struthionum</i> (Speg.) Cabrera, <i>H. villosus</i> Phil | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) Argentina (Chubut, Mendoza, Santa Cruz) |
| 19 | <i>H. donianus</i> (Hook. & Arn.) Sch.Bip. ex Reiche | <i>Diplopappus donianus</i> Hook. & Arn., <i>Haplodiscus exserens</i> Phil., <i>Haplodiscus tenuifolius</i> Phil., <i>H. canescens</i> var. <i>exserens</i> (Phil.) Reiche | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Biobío) |
| 20 | <i>H. foliosus</i> (Hook. & Arn.) Hook. & Arn. subsp. <i>foliosus</i> | <i>Aster foliosus</i> (DC.) Kuntze, <i>Aster polyphyllus</i> (Phil.) Kuntze, <i>Diplopappus foliosus</i> Hook. & Arn., <i>Haplodiscus densifolius</i> Phil., <i>Haplodiscus polyphyllus</i> Phil., <i>H. foliosus</i> DC., <i>H. phyllophorus</i> Reiche | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |
| 21 | <i>H. foliosus</i> (Hook. & Arn.) Hook. & Arn. subsp. <i>meyenii</i> (Walp.) L. Klingenberg | <i>Aster meyenii</i> (Walp.) Kuntze, <i>H. meyenii</i> Walp | Chile (Coquimbo) |

(Continued on following page)

TABLE 1 (Continued) Scientific names and distribution of reported *Haplopappus* species (Klingenberg, 2007; García et al., 2018; García et al., 2024).

| No. | <i>Haplopappus</i> species | Synonyms | Distribution ^a |
|-----|---|--|---|
| 22 | <i>H. glabratus</i> Phil | <i>Aster glabratus</i> (Phil.) Kuntze, <i>H. arbutoides</i> Remy var. <i>glabratus</i> (Phil.) Reiche | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) Argentina (Chubut, Neuquén, Río Negro, Santa Cruz) |
| 23 | <i>H. glutinosus</i> Cass | <i>Aster senebierifolius</i> Kuntze, <i>Diplopappus coronopifolius</i> Less., <i>H. coronopifolius</i> DC. | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Biobío, Araucanía, Los Ríos, Los Lagos, Aisén) Argentina |
| 24 | <i>H. grindelioides</i> (Less.) DC. | <i>Aster grindelioides</i> (Less.) Kuntze, <i>Aster marginalis</i> (Phil.) Kuntze, <i>Aster reversus</i> Kuntze, <i>Diplopappus grindelioides</i> Less., <i>H. corniculatus</i> Phil., <i>H. heterocomus</i> Phil., <i>H. marginalis</i> Phil., <i>H. reflexus</i> Phil | Chile (Libertador Bernardo O'Higgins, Maule, Ñuble, Biobío, Araucanía, Magallanes, Metropolitan of Santiago) Argentina (Chubut, Mendoza, Neuquén, Río Negro, Santa Cruz) |
| 25 | <i>H. humilis</i> (Phil.) Reiche | <i>Haplodiscus humilis</i> Phil | Chile (Libertador Bernardo O'Higgins, Maule, Ñuble, Biobío, Metropolitan of Santiago) |
| 26 | <i>H. integerrimus</i> (Hook. & Arn.) H.M. Hall | <i>Diplopappus integerrimus</i> Hook. & Arn., <i>Grindelia acerosa</i> Bertero, <i>H. acerosus</i> Phil., <i>H. pulchellus</i> var. <i>elongatus</i> Remy, <i>Steriphe acerosa</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Biobío, Metropolitan of Santiago) |
| 27 | <i>H. kingii</i> (Phil.) Reiche | <i>Haplodiscus kingii</i> Phil | Chile (Atacama) |
| 28 | <i>H. linifolius</i> (Phil.) Reiche | <i>Aster linodes</i> (Phil.) Kuntze, <i>Pyrrocoma linifolia</i> Phil | Chile (Atacama, Coquimbo) |
| 29 | <i>H. litoralis</i> Phil | - | Chile (Coquimbo, Valparaíso) |
| 30 | <i>H. macrocephalus</i> (Poepp. Ex Less.) DC. | <i>Aster macrocephalus</i> (Poepp. ex Less.) Kuntze, <i>Aster spinuliger</i> Kuntze, <i>Diplopappus macrocephalus</i> Poepp. ex Less., <i>H. caespitosus</i> Nutt., <i>H. scaposus</i> Remy, <i>H. serrulatus</i> Reiche, <i>H. spinulosus</i> Phil | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Ñuble Biobío, Araucanía, Metropolitan of Santiago) |
| 31 | <i>H. maulinus</i> Klingeb | - | Chile (Maule, Biobío) |
| 32 | <i>H. mendocinus</i> Tortosa & A. Bartoli | - | Argentina (La Pampa, Mendoza) |
| 33 | <i>H. mieresii</i> P. Medina & Nic. García | - | Chile (Coquimbo) |
| 34 | <i>H. mucronatus</i> (Hook. & Arn.) Hook | <i>Aplopappus macraenus</i> Gray, <i>Aster ilicifolius</i> (Remy) Kuntze, <i>Aster macraenus</i> (Remy) Kuntze, <i>Baccharis hookeriana</i> DC., <i>Baccharis mucronata</i> Hook. & Arn., <i>Diplopappus mucronatus</i> Hook. & Arn., <i>H. axilliflorus</i> Phil., <i>H. fonckii</i> Phil., <i>H. hookerianus</i> DC., <i>H. ilicifolius</i> Remy, <i>H. ilicifolius</i> var. <i>platylepis</i> (Phil.) Reiche, <i>H. platylepis</i> Phil., <i>H. macraenus</i> (Remy) Reiche, <i>Pyrrocoma macraena</i> Remy | Chile (Atacama, Coquimbo, Valparaíso) |
| 35 | <i>H. multifolius</i> Reiche subsp. <i>baccharidiformis</i> Klingeb | - | Chile (Metropolitan of Santiago) |
| 36 | <i>H. multifolius</i> Reiche subsp. <i>multifolius</i> | <i>Aster multifolius</i> (Reiche) Kuntze, <i>Diplopappus foliolosus</i> Hook. & Arn., <i>Diplopappus ilicifolius</i> Hook. & Arn., <i>H. rotundifolius</i> H.M. Hall, <i>Pyrrocoma foliosa</i> Phil | Chile (Coquimbo, Valparaíso, Metropolitan of Santiago) |
| 37 | <i>H. multifolius</i> Reiche subsp. <i>ovalifolius</i> Klingeb | - | Chile (Valparaíso, Metropolitan of Santiago) |
| 38 | <i>H. nahuelbutae</i> Klingeb | - | Chile (Biobío, Araucanía) |
| 39 | <i>H. ochagavianus</i> Phil | <i>Aster ochagaviensis</i> Kuntze, <i>H. reicheanus</i> H.M. Hall, <i>H. tiltiensis</i> Phil., <i>H. vernicosus</i> Reiche | Chile (Coquimbo, Valparaíso, Metropolitan of Santiago) |
| 40 | <i>H. paucidentatus</i> Phil | <i>Aster glutinosus</i> (Less.) Kuntze, <i>Aster oligodontus</i> Kuntze, <i>Diplopappus glutinosus</i> Less., <i>H. glutinosus</i> (Less.) DC., <i>H. glutinosus</i> f. <i>spathulata</i> Cabrera., <i>H. prostratus</i> Phil | Chile (Maule, Ñuble Biobío, Araucanía, Los Lagos) |
| 41 | <i>H. parvifolius</i> (DC.) Gay | <i>Aster parvifolius</i> (DC.) Kuntze, <i>Pyrrocoma parvifolia</i> DC. | Chile (Atacama, Coquimbo) |
| 42 | <i>H. pulchellus</i> DC. | <i>Aster valparaisanus</i> Kuntze | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |

(Continued on following page)

TABLE 1 (Continued) Scientific names and distribution of reported *Haplopappus* species (Klingenberg, 2007; García et al., 2018; García et al., 2024).

| No. | <i>Haplopappus</i> species | Synonyms | Distribution ^a |
|-----|---|---|---|
| 43 | <i>H. philippii</i> (Kuntze) H.M. Hall | <i>Aster philippii</i> Kuntze, <i>H. breviradiatus</i> Reiche, <i>H. paniculatus</i> Phil | Chile (Atacama, Coquimbo, Valparaíso) |
| 44 | <i>H. pinea</i> (Phil.) Reiche | <i>Aster pineus</i> (Phil.) Kuntze, <i>Pyrracoma pinea</i> Phil | Chile (Coquimbo, Valparaíso) |
| 45 | <i>H. pinnatifidus</i> Nutt | <i>Aster andinus</i> Kuntze, <i>Aster setiger</i> (Phil.) Kuntze, <i>Diplopappus setiger</i> Hook. & Arn., <i>H. setigerus</i> (Phil.) Meigen, <i>Pyrracoma nuttalli</i> Remy, <i>Pyrracoma setigera</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |
| 46 | <i>H. poeppigianus</i> (Hook. & Arn.) A. Gray | <i>Aster griseus</i> Kuntze, <i>Diplopappus poeppigianus</i> Hook. & Arn., <i>Grindelia canescens</i> Bertero, <i>Haplodiscus polycladus</i> Phil., <i>H. argenteus</i> Steud., <i>H. canescens</i> (Phil.) Reiche, <i>Pyrracoma canescens</i> Phil | Chile (Valparaíso, Libertador Bernardo O'Higgins, Metropolitan of Santiago) |
| 47 | <i>H. punctatus</i> (Willd.) Hall | <i>Aster adalbertii</i> Kuntze, <i>Aster pedunculatus</i> (Remy) Kuntze, <i>Conyza punctata</i> Willd., <i>Diplopappus chamissonis</i> Less., <i>H. chamissonis</i> (Less.) DC., <i>H. corymbosus</i> (Phil.) Reiche, <i>H. pedunculatus</i> Remy, <i>H. rosmarinifolius</i> Reiche, <i>Steriphe corymbosa</i> Phil | Chile (Maule, Biobío) |
| 48 | <i>H. pusillus</i> Klingenb | <i>Aster cuneifolius</i> (Nutt.) Kuntze, <i>Diplopappus bellidifolius</i> Hook. & Arn., <i>H. cuneifolius</i> Nutt., <i>H. nanus</i> Phil | Chile (Coquimbo, Valparaíso, Metropolitan of Santiago) |
| 49 | <i>H. racemiger</i> Klingenb | - | Chile (Atacama, Coquimbo) |
| 50 | <i>H. reicheanus</i> H.M. Hall | - | Chile (Coquimbo, Valparaíso, Metropolitan of Santiago) |
| 51 | <i>H. remyanus</i> Wedd | <i>Aster remyanus</i> (Wedd.) Kuntze, <i>Haplodiscus latifolius</i> Phil., <i>Haplodiscus vernicosus</i> Phil., <i>Haplodiscus vernicosus</i> var. <i>geissei</i> Phil., <i>H. latifolius</i> (Phil.) Reiche, <i>H. prinophyllus</i> Phil., <i>Pyrracoma ilicifolia</i> Remy | Chile (Atacama, Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Metropolitan of Santiago) |
| 52 | <i>H. rengifoanus</i> Remy | <i>Aster rengifoanus</i> Kuntze, <i>Haplodiscus pachyphyllus</i> Phil., <i>Pyrracoma densifolia</i> Phil | Chile (Antofagasta, Atacama, Coquimbo, Libertador Bernardo O'Higgins) |
| 53 | <i>H. retinervius</i> (Kuntze) Klingenb | <i>Aster retinervius</i> Kuntze, <i>Haplodiscus ischnos</i> Phil., <i>Haplodiscus landbecki</i> Phil., <i>Pyrracoma reticulata</i> Phil., <i>H. ischnos</i> (Phil.) Reiche, <i>H. reticulatus</i> (Phil.) Reiche | Chile (Coquimbo, Valparaíso) |
| 54 | <i>H. rigidus</i> Phil | <i>Aster atacamensis</i> Kuntze | Chile (Antofagasta, Atacama, Coquimbo) Argentina (Catamarca, Salta) Bolivia (Potosí) |
| 55 | <i>H. rosulatus</i> H.M. Hall | - | Chile (Antofagasta, Atacama, Coquimbo) |
| 56 | <i>H. schumannii</i> (Kuntze) G.K. Br. & W.D. Clark | <i>Aster schumannii</i> Kuntze, <i>H. armerioides</i> Phil., <i>H. poeppigianus</i> (Hook. & Arn.) A. Gray var. <i>radiatus</i> A. Gray, <i>H. sericeus</i> Phil., <i>Steriphe navarroi</i> Phil | Chile (Valparaíso, Metropolitan of Santiago) |
| 57 | <i>H. scrobiculatus</i> (Nees) DC. | <i>Aster cuneifolius</i> (Nutt.) Kuntze, <i>Aster densifolius</i> (Remy) Kuntze, <i>Diplopappus cuneatus</i> Hook. & Arn., <i>Diplopappus scrobiculatus</i> Nees, <i>H. densifolius</i> Remy, <i>Perezia spathulata</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Ñuble, Biobío, Araucanía, Metropolitan of Santiago) Argentina (Mendoza, San Juan) |
| 58 | <i>H. setulosus</i> Klingenb | - | Chile (Maule, Ñuble) |
| 59 | <i>H. stelliger</i> Remy | <i>Aster denticulatus</i> (Phil.) Kuntze, <i>Aster stelliger</i> (Remy) Kuntze, <i>H. denticulatus</i> (Phil.) Reiche, <i>Pyrracoma denticulata</i> Phil | Chile (Coquimbo) |
| 60 | <i>H. stolpii</i> Phil | - | Chile (Maule, Ñuble, Biobío, Araucanía, Metropolitan of Santiago) |
| 61 | <i>H. taeda</i> Reiche | <i>Haplodiscus peteroanus</i> Phil., <i>Haplodiscus graveolens</i> Phil., <i>H. graveolens</i> (Phil.) Reiche | Chile (Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |
| 62 | <i>H. teillieri</i> A.Cádiz-Véliz, V.Morales & Nic.García | - | Chile (Coquimbo, Valparaíso) |
| 63 | <i>H. uncinatus</i> Phil | - | |

(Continued on following page)

TABLE 1 (Continued) Scientific names and distribution of reported *Haplopappus* species (Klingenberg, 2007; García et al., 2018; García et al., 2024).

| No. | <i>Haplopappus</i> species | Synonyms | Distribution ^a |
|-----|---|---|---|
| | | <i>Aster uncinatus</i> (Phil.) Kuntze, <i>Diplopappus canescens</i> Hook. & Arn., <i>H. candolei</i> Phil., <i>H. uncinatus</i> Phil. var. <i>candolei</i> (Phil.) Reiche | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) |
| 64 | <i>H. undulatus</i> Klingenb | - | Chile (Coquimbo, Valparaíso, Metropolitan of Santiago) |
| 65 | <i>H. valparadiasiacus</i> Klingenb | <i>Diplopappus inuloides</i> Hook. & Arn., <i>H. berteroi</i> var. <i>lanceolatus</i> DC., <i>H. formosus</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Metropolitan of Santiago) |
| 66 | <i>H. velutinus</i> Remy subsp. <i>illinitus</i> (Phil.) Klingenb | <i>H. glutinosus</i> var. <i>illinitus</i> (Phil.) Reiche, <i>H. illinitus</i> Phil | Chile (Libertador Bernardo O'Higgins, Maule) |
| 67 | <i>H. velutinus</i> Remy subsp. <i>longipes</i> (Phil.) Klingenb | <i>Aster longipes</i> (Phil.) Kuntze, <i>Pyrrocoma longipes</i> Phil | Chile (Libertador Bernardo O'Higgins, Maule) |
| 68 | <i>H. velutinus</i> Remy subsp. <i>velutinus</i> | <i>Aster gayanus</i> Kuntze, <i>Aster scopiformis</i> Kuntze, <i>Diplopappus glutinosus</i> Hook. & Arn., <i>Haplodiscus fallax</i> Phil., <i>Haplodiscus longiscapus</i> Phil., <i>H. fallax</i> (Phil.) Reiche, <i>H. stenophyllus</i> Phil., <i>H. virgatus</i> Phil., <i>Pyrrocoma scaposa</i> Phil | Chile (Coquimbo, Valparaíso, Libertador Bernardo O'Higgins, Maule, Metropolitan of Santiago) Argentina (Mendoza) |
| 69 | <i>H. vicuniensis</i> Klingenb | - | Chile (Coquimbo) |
| 70 | <i>H. villanuevae</i> Phil | - | Chile (Antofagasta, Atacama) |

^a(Rodríguez et al., 2018; Zuloaga et al., 2019; POWO, 2024).

dimethylherbacetin (**Flv37**), 3,8,4'-trimethylherbacetin (**Flv38**), and 5,7,4'-trihydroxy-3,8,3'-trimethoxyflavone (**Flv39**); the coumarins 7-*O*-prenylscooletin (**Cum10**), 7-*O*-geranylscopoletin (**Cum11**), *O*-prenylumbelliferone (**Cum15**) and the dimeric umbelliferone 3,3-dimethylallyl ether (**Cum16**), as well as the cinnamic acid derivatives chlorogenic acid (**Cin10**), 3,4-dicaffeoylquinic acid (**Cin11**), and 3,5-dicaffeoylquinic acid (**Cin12**) (Zdero et al., 1990; Tojo et al., 1999; Schmeda-Hirschmann et al., 2015).

4.10 *H. diplopappus* Remy

The resinous exudate of *H. diplopappus* is reported to contain the diterpenoid *ent*-manool (**Dit9**) and its 13-*O*- β -xylopyranoside (**Dit8**) (Urzúa et al., 1995a).



4.11 *H. foliosus* (Hook. & Arn.) Hook. & Arn

H. foliosus is the species for which the greatest number of compounds has been reported. Among them, there are the alkanes C₁₂H₂₆ (**Ala3**), C₁₄H₃₀ (**Ala5**), C₁₆H₃₄ (**Ala7**), C₁₈H₃₈ (**Ala9**), and C₂₃H₄₈ - C₃₃H₆₈ (**Ala14** - **Ala24**) (Silva and Sammes, 1973; Urzúa et al., 2000; Urzúa, 2004). Furthermore, the aerial parts of this species contain 11-tricosene (**Ale1**), hexacosanol (**Alc1**), ethylresorcinol (**Alc2**), diisopropyl ether (**Eth1**), α -asarone (**Arh3**), 1,2,3,4,5,6,7,8-octahydro-1-methylphenantrene (**Arh5**), eugenol (**Arh6**), styrene (**Arh7**), safrol (**Arh8**), elemicin (**Arh9**), dihydrobenzofuran (**Arh10**), benzaldehyde (**Ald1**), 2,3-dichloro-2-methylpropanal (**Ald2**), *trans*-2-hexenal (**Ald3**), nonanal (**Ald4**), decanal (**Ald5**), 3-ethylbenzaldehyde (**Ald6**), 4-vinylbenzaldehyde (**Ald7**), 3-hydroxyacetophenone (**Ket1**), 3-ethylacetophenone (**Ket3**), 4-ethylacetophenone (**Ket4**), dihydro- α -ionone (**Ket6**), 4,4-dimethyl-2-allylcyclohexanone (**Ket7**), (*Z*)-3-hexenyl acetate

(**Est8**), tetrahydroactinidiolide (**Ltn2**), 4-phenyl-2-azetidione (**Ltm1**), and stigmaterol (**Str1**) (Silva and Sammes, 1973; Urzúa et al., 2000; 2010; Urzúa, 2004; Villagra et al., 2021).

The terpenoid fraction of *H. foliosus* has been thoroughly studied and more than 70 compounds have been reported. Among them, there are the monoterpenoids *cis*- α -ocimene (**Mon1**), β -ocimene (**Mon2**), β -myrcene (**Mon3**), limonene (**Mon8**), α -terpinene (**Mon9**), γ -terpinene (**Mon10**), terpinen-4-ol (**Mon11**), terpinolene (**Mon16**), isoterpinolene (**Mon17**), α -terpineol (**Mon18**), *p*-menth-2-en-4-ol (**Mon19**), *trans*-*p*-menth-2-en-1-ol (**Mon21**), *cis*-*p*-menth-2-en-1-ol (**Mon22**), α -phellandrene (**Mon25**), *m*-cymene (**Mon27**), *p*-cymene (**Mon28**), *p*-cymen-8-ol (**Mon29**), *o*-cumenol (**Mon30**), 3-carene (**Mon31**), thujane (**Mon32**), α -thujene (**Mon33**), *cis*-(+/-)-4-thujanol (**Mon34**), 4-thujanol (**Mon35**), α -thujone (**Mon36**), α -pinene (**Mon37**), β -pinene (**Mon38**), pinocarveol (**Mon39**), borneol (**Mon42**), bornyl acetate (**Mon43**), camphor (**Mon44**), camphene (**Mon45**), fenchol (**Mon46**), 1,5-dimethyl-6-methylenespiro[2.4]heptane (**Mon48**), sabinene (**Mon49**), 5-(acetyloxy)-4,6,6-trimethyl-endobicyclo[2.2.1]heptan-2-one (**Mon50**), ascaridole (**Mon52**), and tricyclene (**Mon54**) (Urzúa et al., 2000; 2010; Urzúa, 2004; Villagra et al., 2021). The equally diverse sesquiterpenoid fraction includes germacrene D (**Sqt7**), (1 α ,7 β ,10 β)-11-hydroxy-4-guaien-3-one (**Sqt9**), (1 β ,7 β ,10 β)-1,11-dihydroxy-4-guaien-3-one (**Sqt10**), (1 α ,6 α ,7 β ,10 β)-6,11-dihydroxy-4-guaien-3-one (**Sqt11**), α -selinene (**Sqt13**), γ -selinene (**Sqt14**), 5-eudesmen-11-ol (**Sqt15**), γ -eudesmol (**Sqt16**), cadalene (**Sqt17**), α -cadinene (**Sqt18**), β -cadinene (**Sqt19**), γ -cadinene (**Sqt20**), δ -cadinene (**Sqt21**), guaiol (**Sqt22**), 1(10),11-eremophiladiene (**Sqt23**), α -cadinol (**Sqt24**), ionene (**Sqt25**), 6-(1,1-dimethylethyl)-2,3-dihydro-1,1-dimethyl-3-methylene-1*H*-indene (**Sqt26**), δ -ambrinol (**Sqt27**), decahydro-3 α ,8-dimethyl-5-(1-methylethenyl)azulene (**Sqt28**), 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethylidene)azulene (**Sqt29**), β -guaiene

TABLE 2 Substitution pattern of flavonols and flavones reported in species of the genus *Haplopappus*.

| No. | Compound | R ₃ | R ₅ | R ₆ | R ₇ | R ₈ | R _{3'} | R _{4'} | R _{5'} |
|-----------|--|----------------|----------------|----------------|----------------|---|-----------------|-----------------|-----------------|
| Flavonols | | | | | | | | | |
| Flv1 | quercetin | OH | OH | H | OH | H | OH | OH | H |
| Flv2 | quercetin 3-methyl ether | OMe | OH | H | OH | H | OH | OH | H |
| Flv3 | tamarixetin (quercetin 4'-methyl ether) | OH | OH | H | OH | H | OH | OMe | H |
| Flv4 | rhamnazin (quercetin 7,3'-dimethyl ether) | OH | OH | H | OMe | H | OMe | OH | H |
| Flv5 | quercetin 3,3'-dimethyl ether | OMe | OH | H | OH | H | OMe | OH | H |
| Flv6 | quercetin 3,7-dimethyl ether | OMe | OH | H | OMe | H | OH | OH | H |
| Flv7 | ayanin | OMe | OH | H | OMe | H | OH | OMe | H |
| Flv8 | retusin (5-hydroxy-3,7,3',4'-tetramethoxyflavone) | OMe | OH | H | OMe | H | OMe | OMe | H |
| Flv9 | 3-O-acetyl-7-methylquercetin | OAc | OH | H | OMe | H | OH | OH | H |
| Flv10 | isoquercitrin (quercetin-3-β-D-glucoside) | O-Glu | OH | H | OH | H | OH | OH | H |
| Flv11 | hyperoside (quercetin-3-β-D-galactoside) | O-Gal | OH | H | OH | H | OH | OH | H |
| Flv12 | quercetagenin 3-methyl ether | OMe | OH | OH | OH | H | OH | OH | H |
| Flv13 | quercetagenin 3,7-dimethyl ether | OMe | OH | OH | OMe | H | OH | OH | H |
| Flv14 | centaureidin | OMe | OH | OMe | OH | H | OH | OMe | H |
| Flv15 | betuletol (3,5,7-trihydroxy-6,4'-dimethoxyflavone) | OH | OH | OMe | OH | H | H | OMe | H |
| Flv16 | eupatolitin | OH | OH | OMe | OMe | H | OH | OH | H |
| Flv17 | rhamnetin | OH | OH | H | OMe | H | OH | OH | H |
| Flv18 | isorhamnetin | OH | OH | H | OH | H | OMe | OH | H |
| Flv19 | isorhamnetin-3-β-D-glucoside | O-Glu | OH | H | OH | H | OMe | OH | H |
| Flv20 | isorhamnetin-3-β-D-galactoside | O-Gal | OH | H | OH | H | OMe | OH | H |
| Flv21 | kaempferol | OH | OH | H | OH | H | H | OH | H |
| Flv22 | astragalin (kaempferol 3-β-D-glucoside) | O-Glu | OH | H | OH | H | H | OH | H |
| Flv23 | isokaempferide (kaempferol 3-methyl ether) | OMe | OH | H | OH | H | H | OH | H |
| Flv24 | kaempferol 3-methyl ether 7-β-D-glucoside | OMe | OH | H | O-Glu | H | H | OH | H |
| Flv25 | rhamnocitrin (kaempferol 7-methyl ether) | OH | OH | H | OMe | H | H | OH | H |
| Flv26 | ermanin (kaempferol 3,4'-dimethyl ether) | OMe | OH | H | OH | H | H | OMe | H |
| Flv27 | kaempferol 7,4'-dimethyl ether | OH | OH | H | OMe | H | H | OMe | H |
| Flv28 | kumatakenin (kaempferol 3,7-dimethyl ether) | OMe | OH | H | OMe | H | H | OH | H |
| Flv29 | kaempferol 3,7,4'-trimethyl ether | OMe | OH | H | OMe | H | H | OMe | H |
| Flv30 | 3-O-acetyl-7,4'-dimethylkaempferol | OAc | OH | H | OMe | H | H | OMe | H |
| Flv31 | haplopappin | OMe | OH | H | OH |  | H | OMe | H |
| Flv32 | haplopappin A | OH | OH | H | OMe |  | H | OMe | H |
| Flv33 | myricetin | OH | OH | H | OH | H | OH | OH | OH |
| Flv34 | myricetin 3',4'-dimethyl ether | OH | OH | H | OH | H | OMe | OMe | OH |
| Flv35 | myricetin 3,3',4'-trimethyl ether | OMe | OH | H | OH | H | OMe | OMe | OH |

(Continued on following page)

TABLE 2 (Continued) Substitution pattern of flavonols and flavones reported in species of the genus *Haplopappus*.

| No. | Compound | R ₃ | R ₅ | R ₆ | R ₇ | R ₈ | R _{3'} | R _{4'} | R _{5'} |
|----------|---|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|
| Flv36 | myricetin 3,7,4'-trimethyl ether | OMe | OH | H | OMe | H | OH | OMe | OH |
| Flv37 | 3,8-dimethylherbacetin (5,7,4'-trihydroxy-3,8-dimethoxyflavone) | OMe | OH | H | OH | OMe | H | OH | H |
| Flv38 | 3,8,4'-trimethylherbacetin (5,7-dihydroxy-3,8,4'-trimethoxyflavone) | OMe | OH | H | OH | OMe | H | OMe | H |
| Flv39 | 5,7,4'-trihydroxy-3,8,3'-trimethoxyflavone | OMe | OH | H | OH | OMe | OMe | OH | H |
| Flv40 | 3,5-dihydroxy-3',4',6,7-tetramethoxyflavone | OH | OH | OMe | OMe | H | OMe | OMe | H |
| Flv41 | santin | OMe | OH | OMe | OH | H | H | OMe | H |
| Flv42 | eupatorin | H | OH | OMe | OMe | H | OH | OMe | H |
| Flv43 | jaceidin | OMe | OH | OMe | OH | H | OMe | OH | H |
| Flv44 | jaceidin 7-methyl ether | OMe | OH | OMe | OMe | H | OMe | OH | H |
| Flv45 | penduletin | OMe | OH | OMe | OMe | H | H | OH | H |
| Flv46 | pachypodol | OMe | OH | H | OMe | H | OMe | OH | H |
| Flavones | | | | | | | | | |
| Flv47 | apigenin | H | OH | H | OH | H | H | OH | H |
| Flv48 | 3,6-dimethoxyapigenin | OMe | OH | OMe | OH | H | H | OH | H |
| Flv49 | vicenin-2 | H | OH | C-Glu | OH | C-Glu | H | OH | H |
| Flv50 | vitexin | H | OH | H | OH | C-Glu | H | OH | H |
| Flv51 | isovitexin | H | OH | C-Glu | OH | H | H | OH | H |
| Flv52 | isoschaftoside | H | OH | C-Ara | OH | C-Glu | H | OH | H |
| Flv53 | luteolin | H | OH | H | OH | H | OH | OH | H |
| Flv54 | luteolin 5-glucoside | H | O-Glu | H | OH | H | OH | OH | H |
| Flv55 | luteolin 7-glucoside | H | OH | H | O-Glu | H | OH | OH | H |
| Flv56 | chrysoeriol | H | OH | H | OH | H | OMe | OH | H |
| Flv57 | velutin (luteolin 7, 3'-dimethyl ether) | H | OH | H | OMe | H | OMe | OH | H |
| Flv58 | diosmetin | H | OH | H | OH | H | OH | OMe | H |
| Flv59 | eupafolin (6-methoxyluteolin) | H | OH | OMe | OH | H | OH | OH | H |
| Flv60 | 6-methoxyluteolin 4'-methyl ether | H | OH | OMe | OH | H | OH | OMe | H |
| Flv61 | cirsiliol (6-methoxyluteolin 7-methyl ether) | H | OH | OMe | OMe | H | OH | OH | H |
| Flv62 | hispidulin (scutellarein 6-methyl ether) | H | OH | OMe | OH | H | H | OH | H |
| Flv63 | pectolinarigenin | H | OH | OMe | OH | H | H | OMe | H |
| Flv64 | scutellarein 6-β-D-glucoside | H | OH | O-Glu | OH | H | H | OH | H |
| Flv65 | 3',4'-dihydroxyflavone 5-glucoside | H | O-Glu | H | H | H | OH | OH | H |
| Flv66 | verbenacoside | H | O-Glu | H | H | H | H | OH | H |

(Sqt36), (-)-caryophyllene (Sqt38), *epi*-bicyclosquiphellandrene (Sqt39), α -muurolene (Sqt40), γ -muurolene (Sqt41), agarospirol (Sqt42), aromadendrene (Sqt47), α -cubebene (Sqt48), β -cubebene (Sqt49), spathulenol (Sqt52), β -bourbonene (Sqt55), α -copaene (Sqt58), β -copaene (Sqt59), and β -ylangene (Sqt60) (Labbé et al., 1998; Urzúa et al., 2000; 2010; Urzúa, 2004; Villagra et al., 2021). Much less diverse are the reported di- and triterpenoid profiles of the species, which include 2 α -hydroxy-*cis*-clero-3,13(Z),8(17)-trien-15-oic acid (Dit87), 2 α -acetoxy-*cis*-clero-3,13(Z),8(17)-trien-15-oic

acid (Dit88), haplopappic acid (Dit96), friedelin (Tri1), and *epi*-friedelinol (Tri3) (Silva and Sammes, 1973; Urzúa et al., 2003).

The flavonoid profile of *H. foliosus* has also been thoroughly investigated and reported to include quercetin 3-methyl ether (Flv2), rhamnazin (Flv4), isoquercitrin (Flv10), hyperoside (Flv11), beturetol (Flv15), eupatolin (Flv16), isorhamnetin (Flv18), isorhamnetin 3- β -D-glucoside (Flv19), kaempferol (Flv21), astragalol (Flv22), isokaempferide (Flv23), kaempferol 3-methyl ether 7- β -D-glucoside (Flv24), ermanin (Flv26),

TABLE 3 Substitution pattern of flavanones and flavanonols reported in species of the genus *Haplopappus*.

| No. | Compound | R ₃ | R ₅ | R ₆ | R ₇ | R ₈ | R _{3'} | R _{4'} | R _{5'} |
|-------------|---|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|
| Flavanones | | | | | | | | | |
| Flv67 | sakuranetin (5,4'-dihydroxy-7-methoxyflavone) | H | OH | H | OMe | H | H | OH | H |
| Flv68 | sakuranetin 4'-methyl ether | H | OH | H | OMe | H | H | OMe | H |
| Flv69 | persicogenin | H | OH | H | OMe | H | OH | OMe | H |
| Flv70 | sternbin | H | OH | H | OMe | H | OH | OH | H |
| Flv71 | eriodictyol | H | OH | H | OH | H | OH | OH | H |
| Flv72 | eriodictyol 7,3'-dimethyl ether | H | OH | H | OMe | H | OMe | OH | H |
| Flv73 | eriodictyol 7,3',4'-trimethyl ether | H | OH | H | OMe | H | OMe | OMe | H |
| Flv74 | pinostrobin | H | OH | H | OMe | H | H | H | H |
| Flavanonols | | | | | | | | | |
| Flv75 | 7,4'-dimethylaromadendrin | OH | OH | H | OMe | H | H | OMe | H |
| Flv76 | 7-O-methylaromadendrin | OH | OH | H | OMe | H | H | OH | H |
| Flv77 | 3-O-acetyl-7-O-aromadendrin | OAc | OH | H | OMe | H | H | OH | H |
| Flv78 | padmatin | OH | OH | H | OMe | H | OH | OH | H |
| Flv79 | 3-O-acetylpadmatin | OAc | OH | H | OMe | H | OH | OH | H |
| Flv80 | blumeatin B | OH | OH | H | OMe | H | OH | OMe | H |
| Flv81 | 7,3'-di-O-methyltaxifolin | OH | OH | H | OMe | H | OMe | OH | H |
| Flv82 | dihydromyricetin | OH | OH | H | OH | H | OH | OH | OH |
| Flv83 | alpinone 3-acetate | OAc | OH | H | OMe | H | H | H | H |

kumatakenin (Flv28), haplopappin (Flv31), and haplopappin A (Flv32) (Ulubelen et al., 1982; Tschesche et al., 1985; Urzúa, 2004).

Furthermore, the following coumarins were detected in *H. foliosus*: esuletin (Cum1), prenyletin (Cum3), scopoletin (Cum9), and scoparone (Cum12) (Ulubelen et al., 1982; Urzúa, 2004), along with the benzoic and cinnamic acid derivatives methyl salicylate (Ben3), *trans*-cinnamic acid (Cin1), *cis*-cinnamic acid (Cin2), isobutyl-(*E*)-cinnamate (Cin3), pentyl-(*E*)-cinnamate (Cin4), benzyl-(*E*)-cinnamate (Cin5), and 2-phenylethyl-(*E*)-cinnamate (Cin6) (Urzúa et al., 2000; Urzúa, 2004; Villagra et al., 2021).

4.12 *H. glutinosus* Cass

The aerial parts of *H. glutinosus* are reported to contain 4-hydroxyacetophenone (Ket2), β -farnesene (Sqt2), germacrene D (Sqt7), 6,18-dihydroxy-*ent*-labd-7,13*E*-dien-15-oic acid (Dit41), 4-hydroxybenzoic acid (Ben1), syringic acid (Ben2), *trans*-cinnamic acid (Cin1), caffeic acid (Cin9), and chlorogenic acid (Cin10) (Jakupovic et al., 1986; Marambio and Silva, 1996). Furthermore, the flavonoid profile of the species includes isokaempferide (Flv23), ermanin (Flv26), santin (Flv41), jaceidin (Flv43), apigenin (Flv47), 3,6-dimethoxyapigenin (Flv48), luteolin 5- (Flv54) and 7- (Flv55) glucosides, hispidulin (Flv62), pectolinarigenin (Flv63), 3',4'-dihydroxyflavone 5-glucoside (Flv65), and verbenacoside (Flv66) (Marambio and Silva, 1996; Valant-Vetschera and Wollenweber, 2007).

4.13 *H. integerrimus* (Hook. & Arn.) H.M. Hall

Scientific literature only contains information on the flavonoid profile of the leaves of *H. integerrimus* var. *punctatus* (Willd.) G.K.Br. & W.D.Clark, according to which the following compounds were detected: quercetin (Flv1), quercetin 3-methyl ether (Flv2), rhamnazin (Flv4), quercetin 3,3'-dimethyl ether (Flv5), quercetin 3,7-dimethyl ether (Flv6), isoquercitrin (Flv10), isorhamnetin (Flv18), myricetin 3',4'dimethyl ether (Flv34), and myricetin 3,3',4'-trimethyl ether (Flv35) (Ayanoglu et al., 1981).

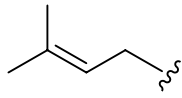
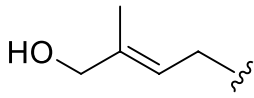
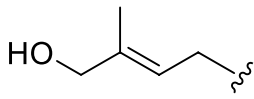
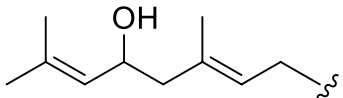
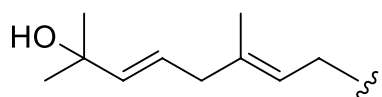
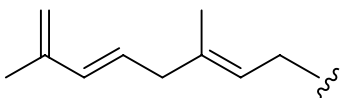
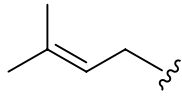
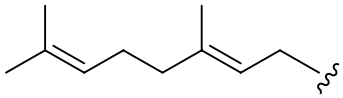
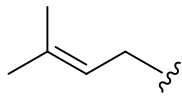
4.14 *H. litoralis* Phil

The resin of *H. litoralis* is reported to contain the diterpenoids 18 α -acetoxylabd-8(17)-en-15-oic acid (Dit3), 18-hydroxylabd-8(17)-en-15-oic acid (Dit14), (+)-copalic acid (Dit16), and (-)-eperuic acid (Dit21) (Urzúa et al., 2004b). Moreover, the flavonols ayanin (Flv7) and retusin (Flv8) were identified in the resinous exudate of this species (Urzúa et al., 2012).

4.15 *H. multifolius* Reiche

The terpenoids 2,9-epoxy-*p*-menth-6-en-8-ol (Mon51), 9-*cis*-*p*-coumaroyloxy- α -terpineol (Sqt12), 18-hydroxylabda-7,13(*E*)-dien-15-oic acid (Dit39), and 18-hydroxylabda-7,13(*Z*)-dien-15-

TABLE 4 Substitution pattern of coumarins reported in species of the genus *Haplopappus*.

| No. | Compound | R ₆ | R ₇ |
|-------|---|----------------|---|
| Cum1 | esculetin | OH | H |
| Cum2 | esculin | Glu | H |
| Cum3 | prenyletin | OH |  |
| Cum4 | haplopinol | OH |  |
| Cum5 | 6-deoxyhaplopinol | H |  |
| Cum6 | 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin | OH |  |
| Cum7 | 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin | OH |  |
| Cum8 | 6-hydroxy-7-[(E,E)-3',7'-dimethyl-2',4',7'-octatrienyloxy] coumarin | OH |  |
| Cum9 | scopoletin | OMe | H |
| Cum10 | 7-O-prenylscopoletin | OMe |  |
| Cum11 | 7-O-geranylscopoletin | OMe |  |
| Cum12 | scoparone | OMe | Me |
| Cum13 | hernianin | H | Me |
| Cum14 | umbelliferone | H | H |
| Cum15 | O-prenylumbelliferone | H |  |

oic acid (**Dit42**) are present in the aerial parts of *H. multifolius* (Maatooq et al., 2002). However, the phenolic composition of this species has been more thoroughly investigated and the following compounds have been identified: quercetin (**Flv1**), quercetin 3-methyl ether (**Flv2**), isorhamnetin (**Flv18**), persicogenin (**Flv69**), sternbin (**Flv70**), 3-*O*-acetylpadmatin (**Flv79**), blumeatin B (**Flv80**), esculetin (**Cum1**), esculin (**Cum2**), prenyletin (**Cum3**), haplopinol (**Cum4**), 6-deoxyhaplopinol (**Cum5**), 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin (**Cum6**), 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin (**Cum7**), 6-hydroxy-7-[(*E,E*)-3',7'-dimethyl-2',4',7'-octatrienyloxy] coumarin (**Cum8**), hernianin (**Cum13**), umbelliferone (**Cum14**), *O*-prenylumbelliferone (**Cum15**), and 3,5-dicaffeoylquinic acid

(**Cin12**) (Chiang et al., 1982; Nuñez-Alarcón and Quiñones, 1995; Urzúa et al., 1995b; Maatooq et al., 2002; Torres et al., 2004; 2006; 2013; Schmeda-Hirschmann et al., 2015).

4.16 *H. parvifolius* (DC.) Gay

The group of compounds identified in the aerial parts of *H. parvifolius* includes mainly diterpenoids, as well as the sesquiterpenoids 2,8-dimethyl-2'-vinyl-5-[4-methyl-pent-3-enyl]-chromane (**Sqt43**) and aphanamol I (**Sqt46**) (Zdero et al., 1991b). The diterpenoids detected in this species are 13-hydroxylabda-6,8,14-triene (**Dit27**), 13-hydroxylabda-6,8(17),14-

triene (**Dit28**), 9 α ,13-epoxy-labda-6,8(17),14-triene (**Dit29**), 6 β -acetoxy-13-hydroxylabda-8,14-dien-7-one (**Dit30**), 6 β -acetoxy-7 β ,13-dihydroxylabda-8,14-diene (**Dit31**), 6 β -acetoxy-13-hydroxylabda-7,14-diene (**Dit47**), 13-hydroxy-6 α -butyryloxy-labda-7,14-diene (**Dit48**), 13-hydroxylabda-7,14-diene-6-one (**Dit49**), 9 α ,13-dihydroxylabda-7,14-dien-6-one (**Dit50**), 6 α ,13-dihydroxylabda-7,14-dien-17-al (**Dit51**), isomanool (**Dit52**), 6 α -hydroxy-9 α ,13-epoxy-labda-7,14-diene (**Dit53**), 6 α -acetoxy-9 α ,13-epoxy-labda-7,14-diene (**Dit54**), 6 α -butyryloxy-9 α ,13-epoxy-labda-7,14-diene (**Dit55**), 5 α -hydroxy-9 α ,13-epoxy-labda-7,14-diene-6-one (**Dit56**), 6 α -acetoxy-9 α ,13-epoxy-labda-7,14-dien-17-al (**Dit57**), 6-oxo-14,15-*nor*-labda-7-ene (**Dit58**), 8 α ,13-dihydroxylabda-6,14-diene (**Dit66**), 8 α ,13-dihydroxylabda-5,14-dien-7-one (**Dit67**), *epi*-manoyl oxide (**Dit68**), 6,7-dehydro-13-*epi*-manoyl oxide (**Dit69**), 6,7-dehydro-8,13-bis-*epi*-manoyl oxide (**Dit70**), 13,17-epoxy-labda-5,7,14-triene (**Dit71**), 9 α ,13-epoxy-5 α ,8 α -dihydroxylabda-6,14-diene (**Dit72**), 5 α -hydroxy-7,8-epoxy-7,8-*seco*-6,7-dehydro-13-*epi*-manoyl oxide (**Dit73**), haploparvone (**Dit103**), 5 α -hydroxyhaploparvone (**Dit104**), haploparviolide (**Dit105**), 1,1,5,6-tetramethyl-4-[3-hydroxy-3-methyl-pent-(4)-enyl]-tetralin (**Dit106**), and 1,1,5-trimethyl-6-(3-hydroxy-3-methyl-pent-4-enyl)-tetralin (**Dit107**) (Zdero et al., 1991b).

4.17 *H. poeppigianus* (Hook. & Arn.) A. Gray

The aerial parts of *H. poeppigianus* (syn. *H. canescens* (Phil.) Reiche (Klingenberg, 2007)) contain the flavonoid compounds centaureidin (**Flv14**), myricetin (**Flv33**), chrysoeriol (**Flv56**), diosmetin (**Flv58**), hispidulin (**Flv62**), and scutellarein 6- β -D-glucoside (**Flv64**) (Oksuz et al., 1981).

4.18 *H. paucidentatus* Phil

The aerial parts of *H. paucidentatus* contain 4-hydroxyacetophenone (**Ket2**) and the terpenoids germacrene D (**Sqt7**), caryophyllene oxide (**Sqt34**), 8-oxo- β -cyperone (**Sqt45**), 18-hydroxy-friedolabd-5-en-15-oic acid (**Dit78**), 18-hydroxy-*cis*-cleroda-3-en-15-oic acid (10 β H, 16 ξ , 19 β , 17 β , 20 α form) (**Dit83**), 19-hydroxy-*cis*-cleroda-3-en-15-oic acid (10 β H, 16 ξ , 19 β , 17 β , 20 α form) (**Dit85**), 18-hydroxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (**Dit93**), and 18-acetoxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (**Dit99**) (Jakupovic et al., 1986).

4.19 *H. pulchellus* DC

Regarding the compounds identified in the aerial parts of *H. pulchellus*, those include the diterpenoids 7 α -hydroxylabd-8(17)-en-15,18-dioic acid (**Dit4**), labd-7-en-15,18-dioic acid (**Dit36**), 18-acetoxy-friedolabd-5-en-15-oic acid (**Dit76**), 18-acetoxy-friedolabd-5-en-7-one-15-oic acid (**Dit77**), 18-hydroxy-friedolabd-5-en-15-oic acid (**Dit78**), 18-hydroxy-7-oxo-friedolabd-5-en-15-oic acid (**Dit79**), friedolabd-5-en-15,18-dioic acid (**Dit80**), and 15-hydroxy-friedolabd-5-en-18-oic acid (**Dit81**) (Zdero et al., 1991a).

4.20 *H. remyanus* Wedd

The esters benzenepropanoic acid, 2-methyl-6-methylene-2,7-octadienyl ester (**Est3**), (\pm)-1-acetoxy-2-(*p*-tolyl)-2-propanol (**Est4**), 2-hydroxy-2-(4-methylphenyl)propyl benzenepropanoate (**Est5**), 2-hydroxy-2-(4-methyl-3-cyclohexen-1-yl)propyl benzenepropanoate (**Est6**), and 2-hydroxy-2-(4-methyl-3-cyclohexen-1-yl)propyl 3-phenyl-2-propenoate (**Est7**) have been detected in the aerial parts of *H. remyanus* (Zdero et al., 1991a). Regarding its terpenoid profile, the species contains uroterpenol (**Mon12**), 9-benzoyloxy-(1-formyl)- α -terpineol (**Mon13**), 9-benzoyloxy- α -terpineol (**Mon14**), 7-hydroxy-9-benzoyloxy- α -terpineol (**Mon15**), 8-hydroxy-9-acetoxy- β -phellandrene (**Mon26**), 18-hydroxylabda-7,13(*E*)-dien-15-oic acid (**Dit39**), 18-acetoxy-labda-7,13(*E*)-dien-15-oic acid (**Dit40**), and 18-dihydrocinnamoyloxy-labda-7,13(*E*)-dien-15-oic acid (**Dit46**) (Zdero et al., 1991a; Faini et al., 2011). Moreover, the following flavonoid compounds are present in *H. remyanus*: quercetin (**Flv1**), 3-*O*-acetyl-7-methylquercetin (**Flv9**), kaempferol 7,4'-dimethyl ether (**Flv27**), kaempferol 3,7,4'-trimethyl ether (**Flv29**), 3-*O*-acetyl-7,4'-dimethylkaempferol (**Flv30**), sakuranetin 4'-methyl ether (**Flv68**), eriodictyol (**Flv71**), pinostrobin (**Flv74**), 7,4'-dimethylaromadendrin (**Flv75**) and alpinone 3-acetate (**Flv83**) (Zdero et al., 1991a; Faini et al., 2011).

4.21 *H. rengifoanus* Remy

The aerial parts and/or leaves of *H. rengifoanus* are reported to contain the sesquiterpenoid liguloxide (**Sqt57**) and the flavonoids quercetagenin 3-methyl ether (**Flv12**), quercetagenin 3,7-dimethyl ether (**Flv13**), isorhamnetin (**Flv18**), isorhamnetin 3- β -D-glucoside (**Flv19**), isorhamnetin 3- β -D-galactoside (**Flv20**), apigenin (**Flv47**), luteolin (**Flv53**), and scutellarein 6- β -D-glucoside (**Flv64**) (Ulubelen et al., 1981; Zdero et al., 1991a).

4.22 *H. rigidus* Phil

The diterpenoids rigiduside (**Dit6**), 18-acetoxy-*cis*-clerode 3,13(*Z*)-dien-15 oic acid (**Dit82**), rigidusol (**Dit100**), and deacetylrigidusol (**Dit101**) are present in the aerial parts of *H. rigidus* (Morales et al., 2000a; 2000b; 2003). Furthermore, the flavonoids quercetin 3-methyl ether (**Flv2**), beturetol (**Flv15**), kaempferol (**Flv21**), isokaempferide (**Flv23**), sakuranetin (**Flv67**) and sternbin (**Flv70**) were detected in the aerial parts (Morales et al., 2000a; 2003; 2009; Schmeda-Hirschmann et al., 2015), along with 3,5-dicaffeoylquinic acid (**Cin12**) (Schmeda-Hirschmann et al., 2015).

4.23 *H. schumannii* (Kuntze) G.K. Br. & W.D. Clark

The alkanes C₂₃H₄₈ – C₃₁H₆₄ (**Ala14** – **Ala22**) and C₃₃H₆₈ (**Ala14**) have been identified in the aerial parts of *H. schumannii*, along with 1-octadecyne (**Aly1**), dihydro- α -ionone (**Ket6**), and the lactone tetrahydroactinidiolide (**Ltn2**) (Urzúa et al., 2004a). The terpenoid profile of this species includes the sesquiterpenoids β -

cadinene (**Sqt19**), β -bourbonene (**Sqt55**), and globulol (**Sqt56**), as well as the diterpenoids manool (**Dit7**), (-)-eperuic acid (**Dit21**), *epi*-manool (**Dit25**), 8 α -hydroxylabdan-15-oic acid (**Dit59**), and 2-oxoclerod-3-en-15-oic acid (**Dit86**) (Urzúa et al., 1997; 2004a). Moreover, the flavonoids quercetin (**Flv1**), isoquercitrin (**Flv10**), vicenin-2 (**Flv49**), vitexin (**Flv50**), and isovitexin (**Flv51**) are present in the leaves of *H. schumannii* (Ates et al., 1982).

4.24 *H. scrobiculatus* (Nees) DC

The presence of the terpenoids α -farnesene (**Sqt1**), 18-hydroxymanool (**Dit15**), and 2-oxokolavenic acid (**Dit94**) has been reported in the case of the aerial parts and resinous exudates of *H. scrobiculatus* (Rossomando et al., 1995; Urzúa et al., 2004b). However, the largest group of compounds in this species is that of phenolics, namely, quercetin (**Flv1**), isoquercitrin (**Flv10**), isorhamnetin (**Flv18**), isorhamnetin 3- β -D-glucoside (**Flv19**), rhamnocitrin (**Flv25**), santin (**Flv41**), eupatorin (**Flv42**), penduletin (**Flv45**), vicenin-2 (**Flv49**), vitexin (**Flv50**), isovitexin (**Flv51**), isoschaftoside (**Flv52**), eupafolin (**Flv59**), 6-methoxyluteolin 4'-methyl ether (**Flv60**), cirsiolol (**Flv61**), and esculetin (**Cum1**) (Ates et al., 1982; Rossomando et al., 1995; Urzúa et al., 2012).

4.25 *H. taeda* Reiche

The terpenoid profile of *H. taeda* includes taedol (**Mon41**), 18-hydroxylabda-7,13(*E*)-dien-15-oic acid (**Dit39**), 7,13-labdadien-15,18-dioic acid (**Dit43**), cleroda-3,13 (*E*)-dien-15,18-diol (**Dit95**), and 18-acetoxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (**Dit99**) (Marambio and Silva, 1989; Torres et al., 2005; Faini et al., 2007; 2008). However, scientific literature provides more information on the phenolic composition of this species, with the following compounds being reported: quercetin (**Flv1**), quercetin 3-methyl ether (**Flv2**), quercetin 3,7-dimethyl ether (**Flv6**), kaempferol (**Flv21**), sakuranetin (**Flv67**), sternbin (**Flv70**), eriodictyol 7,3'-dimethyl ether (**Flv72**), eriodictyol 7,3',4'-trimethyl ether (**Flv73**), 3-*O*-acetyl-7-*O*-aromadendrin (**Flv77**), padmatin (**Flv78**), 3-*O*-acetylpadmatin (**Flv79**), 9-*trans-p*-coumaroyloxy- α -terpineol (**Cin7**), 7-*trans-p*-coumaroyloxy-taedol (**Cin8**), chlorogenic acid (**Cin10**), 3,4-dicaffeoylquinic acid (**Cin11**), and 3,5-dicaffeoylquinic acid (**Cin12**) (Marambio and Silva, 1989; Faini et al., 2007; 2008; Schmeda-Hirschmann et al., 2015).

4.26 *H. uncinatus* Phil

The alkanes C₂₃H₄₈ – C₃₁H₆₄ (**Ala14** – **Ala22**) and C₃₃H₆₈ (**Ala14**) have been identified in the resinous exudates and/or aerial parts of *H. uncinatus* (Urzúa et al., 2000; 2004a; 2006), along with 2,7-dimethyl-5-(1-methylethenyl)-1,8-nonadiene (**Ale3**) and 3,5-dihydroxy-3',4',6,7-tetramethoxyflavone (**Flv40**) (Urzúa et al., 2004a; 2006). Regarding its terpenoid profile, the species is reported to synthesize 3,3,7,7-tetramethyl-5-(2-methyl-1-propenyl)-tricyclo[4.1.0.0(2,4)]heptane (**Mon53**), the sesquiterpenoids cadalene (**Sqt17**), aromadendrene (**Sqt47**), α -cubebene (**Sqt48**), β -cubebene (**Sqt49**), spathulenol (**Sqt52**), cedryl acetate (**Sqt53**), β -bourbonene

(**Sqt55**), globulol (**Sqt56**), α -copaene (**Sqt58**), as well as the clerodane diterpenoid 18-acetoxy-*cis*-cleroda-3-en-15-oic acid (10 β H, 16 ξ , 19 β , 17 β , 20 α form) (**Dit84**) (Urzúa et al., 2000; 2004a; 2006).

4.27 *H. velutinus* Remy; *H. velutinus* Remy subsp. *illinitus* (Phil.) Klingenb

Several compounds are reported to be present in both *H. velutinus* and the subspecies *H. velutinus* subsp. *illinitus*. These are the alkanes C₂₃H₄₈ – C₃₁H₆₄ (**Ala14** – **Ala22**) and C₃₃H₆₈ (**Ala14**), 5,5-dimethyl-2(5*H*)-furanone (**Fur1**), β -myrcene (**Mon3**), limonene (**Mon8**), α -pinene (**Mon37**), β -pinene (**Mon38**), labd-7-en-15,18-dioic acid-18 α -methylester (**Dit37**), β -sitosterol (**Str2**), and quercetin (**Flv1**) (Latorre et al., 1990; Marambio and Silva, 1996; Faini et al., 2002; Urzúa et al., 2004a; Echeverría et al., 2019).

In contrast, compounds solely identified in *H. velutinus* include 3-ethyl-1,4-hexadiene (**Ale2**), 2-nonyl-1-ol (**Ale3**), 2-pentadecen-1-ol (**Ale4**), *n*-dodeceny-1-ol (**Ale5**), vanillin (**Ald8**), picein (**Ket5**), lavender lactone (**Ltn1**), linalyl anthranilate (**Mon5**), davanone (**Mon6**), davana ether (**Mon7**), 1,2:8,9-diepoxy-*p*-menthane (**Mon19**), *cis-p*-menth-2-en-1-ol (**Mon22**), *trans*-pulegone oxide (**Mon23**), α -campholenal (**Mon24**), *m*-cymene (**Mon27**), α -thujene (**Mon33**), pinocarveol (**Mon39**), *trans*-2-pinanol (**Mon40**), *cis*-verbenol (**Mon47**), α -sinensal (**Sqt3**), humulene epoxide II (**Sqt6**), caryophyllene oxide (**Sqt34**), α -guaiene (**Sqt35**), (-)-oplopanone (**Sqt37**), spathulenol (**Sqt52**), patchouli alcohol (**Sqt54**), dehydropinipholic acid 19-methyl ester (**Dit11**), 4 α -hydroxy-18-norlabd-8(17)-en-15-oic acid (**Dit12**), 4 β -hydroxy-19-norlabd-8(17)-en-15-oic acid (**Dit13**), 18-hydroxylabd-8(17)-en-15-oic acid (**Dit14**), 7,13-(*E*)-labdadien-15,18-dioic-acid-18-methyl ester (**Dit45**), friedelin (**Tri1**), *epi*-friedelinol (**Tri3**), taraxerol (**Tri4**), erythrodiol (**Tri5**), stigmaterol (**Str1**), isoquercitrin (**Flv10**), isokaempferide (**Flv23**), kumatakenin (**Flv28**), luteolin (**Flv53**), and scopoletin (**Cum9**) (Urzúa and Mendoza, 1989; Urzúa et al., 1991; Urzúa et al., 1995a; 2004a; Urzúa and Mendoza, 1993; Marambio and Silva, 1996; Echeverría et al., 2019).

The group of compounds identified solely in the subspecies *H. velutinus* subsp. *illinitus* consists of 3,3,5,5-tetramethylcyclopentene (**Ale4**), methyl octanoate (**Est1**), 5-methyl-octanoic acid methyl ester (**Est2**), β -cadinene (**Sqt19**), procerin (**Mer1**), as well as the diterpenoids 7 α -hydroxylabd-8(17)-en-15,18-dioic acid-15-methylester (**Dit5**), pinifolic acid 15-methyl ester (**Dit22**), pinifolic acid 18-methyl ester (**Dit23**), pinifolic acid dimethyl ester (**Dit24**), labd-7-en-15,18-dioic acid (**Dit36**), labd-7-en-15,18-dioic acid-15-methylester (**Dit38**), and 7-oxo-labd-8(9)-en-15,18-dioic acid-15-methylester (**Dit10**), (Faini et al., 2002; Urzúa et al., 2004a).

5 Traditional uses and evidence-based pharmacological activities related to human health

5.1 Traditional uses

The plants of the genus *Haplopappus* are of high medicinal value and form essential part of the traditional medicines of the Andean

TABLE 5 Traditional uses of *Haplopappus* species.

| Species | Plant part(s) – preparation(s) | Traditional use(s) | References |
|-------------------------|---|---|--|
| <i>Haplopappus</i> spp. | whole plant (alone or combined with <i>Satureja parvifolia</i> or <i>Lycopodium Saururus</i>); aerial parts; leaf/aerial parts infusion (with or without milk); stem juice; resin (applied externally or ingested) | antidiarrheic; antiseptic; antispasmodic; antitussive; aphrodisiac; cholagogue; choleric; cicatrizant (in particular, to treat horses); digestive; disinfectant; emmenagogue; hepatic; stimulant; sudorific; against altitude sickness, abdominal colic, dysentery, chronic dyspepsia, colds, flu and urinary diseases | Alonso, 2005; de Mösbach (1992), Hoffmann et al. (1992), Mellado Campos (1996), Ministerio de Salud (2010), Montes and Wilkomirsky (1987), Ratera and Ratera (1980), Schrickel and Bittner (2001) |
| <i>H. baylahuen</i> | whole plant; aerial parts; leaf/aerial parts infusion; leaf decoction; stem juice; taken with milk | aphrodisiac; antidiarrheic; antirheumatic; antiseptic; antispasmodic; antitussive; antiviral, astringent; carminative; cholagogue; choleric; cicatrizant (in particular, to treat horses and other animals); digestive; disinfectant; emmenagogue; expectorant; hepatic; stimulant; stomachic; against altitude sickness, chronic hemorrhagic intestinal inflammation, colds, flu, flatulent dyspepsia, dysentery, gastritis, male and female hormonal disorders, pneumonia, pains provoked by air currents, genital, renal and urinary disorders | Cárdenas (1998), Del Vitto et al. (2010), Espinoza (1897), Gómez-Parra and Siarez Flores (1995), Hoffmann et al. (1992), Houghton and Manby (1985), Laval (1957), Madaleno and Delatorre-Herrera (2013), Ministerio de Salud (2010), Montes and Wilkomirsky (1987), Mostny et al. (1954), Munizaga (1963), Munizaga and Gunkel (1958), Muñoz S. et al. (1981), Murillo (1861), 1889; Remington and Woods (1918), Serracino et al. (1974), Steinmetz (1954), Vogel et al. (2005b) |
| <i>H. multifolius</i> | whole plant; leaf infusion | antidiarrheic; antiseptic; digestive; emmenagogue; hepatic; stomachic; against dysentery and urinary disorders | Muñoz S. et al. (1981), Vogel et al. (2005b) |
| <i>H. remyanus</i> | whole plant; leaf infusion | antidiarrheic; antiseptic; antispasmodic; digestive; emmenagogue; hepatic; stomachic; against dysentery and urinary disorders | Montes and Wilkomirsky (1987), Muñoz S. et al. (1981), Vogel et al. (2005b) |
| <i>H. rigidus</i> | whole plant; aerial parts infusion; taken with milk; decoction with fruits of <i>Opuntia camachoi</i> Espinosa | antirheumatic; antitussive; aphrodisiac; diuretic; febrifuge; hepatic; laxative; stomachic; against colds, flu, pains provoked by air currents, pneumonia, renal colic, cardiac pain, gastrointestinal, ovary and urinary disorders; against veterinary ailments | Aldunate et al. (1981), Gómez et al. (1997), Hoffmann et al. (1992), Mellado Campos (1996), Monterrey (1996), Montes and Wilkomirsky (1987), Muñoz S. et al. (1981), Ratera and Ratera (1980), Villagrán et al. (2003), 1998; Wickens (1993) |
| <i>H. taeda</i> | whole plant; resinous leaves; leaf infusion | antidiarrheic; antiseptic; digestive; emmenagogue; hepatic; stomachic; against dysentery, intestinal and urinary disorders | Faini et al. (2007), Vogel et al. (2005b) |

region (Chile, Argentina), where the genus presents high endemicity. *Haplopappus* species and their preparations have traditionally been associated with numerous health benefits, associated with multiple aspects of the human health and also with veterinary applications (Table 5).

The main health benefits traditionally attributed to different preparations of *Haplopappus* plants are associated with pathologies of the human alimentary tract and metabolism. Various species and preparations have widespread use as digestives, antidiarrheic, remedies against dyspepsia, dysentery and gastrointestinal ailments, in general.

Moreover, there are reported several traditional uses associated with the human genitourinary system, with *Haplopappus* preparations being considered as aphrodisiacs, emmenagogues, diuretic and as remedies against urinary and renal disorders and colics or even against male and female hormonal disorders.

Other traditional uses are associated with health benefits for the human respiratory (antitussives, expectorants, cold remedies) and nervous (stimulant, antispasmodic) system, as well as with their role as disinfectants.

Finally, it is well-documented in traditional Andean medicines the use of *Haplopappus* preparations as cicatrizants with veterinary applications, especially to treat horses' wounds.

It has to be mentioned that *H. baylahuen* Remy is recognized by the Chilean health authorities as a traditional herbal medicine against liver diseases, abdominal colics, chronic dyspepsia, kidney stones, flus and colds, as well as an aphrodisiac and wound disinfectant (Ministerio de Salud, 2010). Meanwhile, pharmaceutical products that include *bailahuén*, e.g., the formulations 'Ulcenat' and 'Ubenat' (Grüne Leben) and 'Bailahuen extracto fluido' (Knop Laboratorios S.A.) are commercialized in Chile as treatments against digestive disorders. However, there are no internationally or nationally established norms and/or protocols regarding quality, standardization, safety, and adulteration control of *bailahuén* preparations and commercial products.

5.2 Evidence-based pharmacological activity related to the human health

Scientific literature provides evidence related to various human health-promoting effects of extracts and isolated compounds of *Haplopappus* species (Table 6), with their inhibitory effect against human pathogens of bacterial origin being the most thoroughly investigated.

TABLE 6 Biological activity attributed to the species of the genus *Haplopappus*.

| Biological activity | Plant species | Plant part(s) | Type of extract and/or isolated compound | Outcome | References |
|-----------------------|---|----------------------------|--|--|--|
| Antibacterial | <i>H. anthylloides</i> | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Escherichia coli</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al. (1995b) |
| | <i>H. baylahuen</i> | aerial parts | decoction, extracts (EtOH, EtOAc) | <i>In vitro</i> growth inhibition of <i>Acremonium falciforme</i> , <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> | Lazo, (1990) |
| | | leaves | extract (H ₂ O/EtOH) | Bactericide activity against <i>Salmonella enteritidis</i> and inhibition of its ability to form biofilm, express <i>adrA/hilA</i> genes and adhere to Caco-2 cells | Elgueta et al. (2021) |
| | <i>H. chrysanthemifolius</i> | resin | extract (MeOH) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Enterococcus faecalis</i> , <i>Listeria monocytogens</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> | Urzúa et al., 2004a, 2012 |
| | <i>H. deserticola</i> | resin | 18-acetoxy- <i>cis</i> -cleroda-3,13(<i>E</i>)-dien-15-oic acid (Dit99) | Bactericidal effect against <i>Streptococcus mutans</i> | Urzúa Moll et al. (1997) |
| | <i>H. diplopappus</i> subsp. <i>diplopappus</i> | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al. (1995b) |
| | | | 13- <i>O</i> - β -xylopyranosyl- <i>ent</i> -manool (Dit8) | | Urzúa et al. (1995a) |
| | <i>H. foliosus</i> | resin | extracts (MeOH, CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. cereus</i> , <i>B. coagulans</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Micrococcus luteus</i> , <i>Proteus vulgaris</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al., 1995b, 2003; Urzúa and Mendoza, 2001 |
| | | | 2 α -hydroxy- <i>cis</i> -clero-3,13(<i>Z</i>),8(17)-trien-15-oic acid (Dit87); 2 α -acetoxy- <i>cis</i> -clero-3,13(<i>Z</i>),8(17)-trien-15-oic acid (Dit88) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. coagulans</i> , <i>B. subtilis</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> | Urzúa et al. (2003) |
| | <i>H. litoralis</i> | resin | extract (MeOH) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Enterococcus faecalis</i> , <i>Listeria monocytogens</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> | Urzúa et al., 2004, 2012 |
| <i>H. multifolius</i> | aerial parts | esculetin (Cum1) | <i>In vitro</i> growth inhibition and bactericide effect against <i>Escherichia coli</i> , <i>Sarcina lutea</i> , <i>Staphylococcus aureus</i> | Chiang et al. (1982) | |
| | | prenyletin (Cum3) | <i>In vitro</i> growth inhibition and bactericide effect against <i>Sarcina lutea</i> , <i>Staphylococcus aureus</i> | | |
| | | haplopinol (Cum4) | <i>In vitro</i> growth inhibition and bactericide effect against <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> | | |
| | aerial parts | extracts (EtOH), infusion | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> , <i>S. pyogenes</i> | Padilla et al. (2021) | |

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TABLE 6 (Continued) Biological activity attributed to the species of the genus *Haplopappus*.

| Biological activity | Plant species | Plant part(s) | Type of extract and/or isolated compound | Outcome | References |
|--|---|---|--|---|---|
| | | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Micrococcus flavus</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> | Urzúa et al. (1995b) |
| | <i>H. rigidus</i> | aerial parts | extracts (EtOH/H ₂ O, CHCl ₃ , EtOAc) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Corynebacterium minutissimum</i> , <i>Enterococcus faecalis</i> , <i>Listeria monocytogenes</i> , <i>Staphylococcus aureus</i> , <i>S. lugdunensis</i> | Morales et al., 2003; Ortiz et al., 2019 |
| | <i>H. schumannii</i> | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Escherichia coli</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Proteus vulgaris</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al. (1995b) |
| | <i>H. scrobiculatus</i> | resin | extracts (MeOH, CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. cereus</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Proteus vulgaris</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al., 1995b; Urzúa et al., 2004, 2012 |
| | <i>H. taeda</i> | aerial parts | extracts (EtOH), infusion | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Staphylococcus agalactiae</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. pyogenes</i> | Padilla et al. (2021) |
| | <i>H. uncinatus</i> | resin | extract (MeOH) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. coagulans</i> , <i>B. subtilis</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> | Urzúa and Mendoza, (2001) |
| extract (CH ₂ Cl ₂) | | | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Escherichia coli</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Proteus vulgaris</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al. (1995b) | |
| aerial parts | | resin 18-acetoxy- <i>cis</i> -cleroda-3-en-15-oic acid (10βH, 16ξ, 19β, 17β, 20α form) (Dit84) | <i>In vitro</i> growth inhibition of <i>Bacillus cereus</i> , <i>B. subtilis</i> , <i>Micrococcus luteus</i> | Urzúa et al. (2006) | |
| | <i>H. velutinus</i> | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Proteus vulgaris</i> , <i>Micrococcus flavus</i> , <i>M. luteus</i> , <i>Staphylococcus aureus</i> , <i>S. epidermidis</i> | Urzúa et al. (1995b) |
| | <i>H. velutinus</i> subsp. <i>illinitus</i> | resin | extract (CH ₂ Cl ₂) | <i>In vitro</i> growth inhibition of <i>Bacillus anthracis</i> , <i>B. pumilis</i> , <i>B. subtilis</i> , <i>Bordetella bronchiseptica</i> , <i>Micrococcus flavus</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> | Urzúa et al. (1995b) |
| Antidysenteric | <i>H. baylahuen</i> | resin | extract suspended in milk, cream or almond emulsion | Symptomatic treatment of dysentery in humans | Fingland, (1903) |
| Anti-inflammatory | <i>H. baylahuen</i> | aerial parts | aqueous extract | Inhibition of carrageenan-induced edema in rats | Adzet and Gene, (1991) |

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TABLE 6 (Continued) Biological activity attributed to the species of the genus *Haplopappus*.

| Biological activity | Plant species | Plant part(s) | Type of extract and/or isolated compound | Outcome | References |
|---------------------|-----------------------|---------------------------------|--|---|---|
| | <i>H. multifolius</i> | leaves | esculetin (Cum1); esculin (Cum2); prenyletin (Cum3); 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin (Cum6); 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin (Cum7); umbelliferone (Cum14); <i>O</i> -prenylumbelliferone (Cum15) | <i>In vitro</i> inhibition of soybean 15-lipoxygenase (15-sLOX) | Torres et al. (2013) |
| | <i>H. remyanus</i> | resin | extract | Inhibition of arachidonic acid-induced ear edema in mice | Faini et al. (2011) |
| | <i>H. taeda</i> | - | extract (EtOH); taedol (Mon41); 18-acetoxy- <i>cis</i> -cleroda-3,13(<i>E</i>)-dien-15-oic acid (Dit99); sakuranetin (Flv67) | Inhibition of arachidonic acid-induced ear edema in mice | Faini et al. (2008) |
| Antioxidant | <i>H. baylahuen</i> | commercial product (herbal tea) | infusion | Antioxidant capacity <i>in vitro</i> (ORAC, TEAC-ABTS, HClO quenching and ONOO ⁻ quenching assays) | Speisky et al., 2006; Alarcón et al., 2008 |
| | | aerial parts | infusion, extract (MeOH) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Schmeda-Hirschmann et al. (2015) |
| | | leaves | infusion, extract (MeOH, H ₂ O/EtOH, EtOH), resin | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Vogel et al., 2005a; Méttola et al., 2018; Elgueta et al., 2021 |
| | <i>H. deserticola</i> | aerial parts | infusion, extract (MeOH) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Schmeda-Hirschmann et al. (2015) |
| | <i>H. multifolius</i> | aerial parts | infusion, extract (MeOH) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Schmeda-Hirschmann et al. (2015) |
| | | aerial parts | quercetin (Flv1); isorhamnetin (Flv18); prenyletin (Cum3); haplopinol (Cum4); 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin (Cum6); 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin (Cum7); 6-hydroxy-7-[(<i>E,E</i>)-3',7'-dimethyl-2',4',7'-octatrienyloxy] coumarin (Cum8) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Torres et al. (2006) |
| | | leaves | infusion, extract (MeOH), resin | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Vogel et al. (2005a) |
| | <i>H. remyanus</i> | leaves | infusion, extract (MeOH), resin | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Vogel et al. (2005b) |
| | <i>H. rigidus</i> | aerial parts | sternbin (Flv70) | Antioxidant capacity <i>in vitro</i> (TEAC – ABTS, DPPH assay) | Morales et al. (2009) |
| | | aerial parts | infusion, extract (MeOH) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Schmeda-Hirschmann et al. (2015) |
| | <i>H. taeda</i> | resin, aerial parts | 9- <i>trans-p</i> -coumaroyloxy- α -terpineol (Cin7); 7- <i>trans-p</i> -coumaroyloxy-taedol (Cin8) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Faini et al. (2007) |
| | | aerial parts | infusion; extract (MeOH) | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Schmeda-Hirschmann et al. (2015) |
| | | leaves | infusion, extract (MeOH), resin | Antioxidant capacity <i>in vitro</i> (DPPH assay) | Vogel et al. (2005b) |
| Antitumoral | <i>H. remyanus</i> | resin | extract (CH ₂ Cl ₂) | Cytotoxic effect against T-lymphoblastic leukemia cell line (CCRF-CEM) | Faini et al. (2011) |

(Continued on following page)

TABLE 6 (Continued) Biological activity attributed to the species of the genus *Haplopappus*.

| Biological activity | Plant species | Plant part(s) | Type of extract and/or isolated compound | Outcome | References |
|----------------------------------|-----------------------|---------------|---|---|--|
| | <i>H. rigidus</i> | aerial parts | rigidusol (Dit100) | Cytotoxic effect against human breast adenocarcinoma cell line (MCF-7) | Morales et al., 2000a; Vogel et al., 2005a |
| | | | sternbin (Flv70) | Cytotoxic effect against human breast adenocarcinoma (MCF-7), human lung carcinoma (A-549) and human colon adenocarcinoma (HT-29) cell lines | Morales et al. (2009) |
| Diuretic | <i>H. baylahuen</i> | leaves | extract (EtOH) | Diuretic effect on Wistar rats | Méttola et al. (2018) |
| Hepatoprotective | <i>H. baylahuen</i> | aerial parts | infusion; 7-O-methylaromadennin (Flv76) | Decrease of glutamic pyruvic transaminase (GTP) levels in serum of rats under CCl ₄ -induced liver injury | Nuñez-Alarcon et al. (1993) |
| | | | infusion | Reduction of serum bilirubin concentration, bromosulphophthalein and alanine aminotransferase activity in dogs under CCl ₄ -induced liver injury | Martin et al. (1988) |
| Inhibitory of lipid peroxidation | <i>H. baylahuen</i> | leaves | infusion; extracts (MeOH, EtOH) | Inhibition of lipid peroxidation <i>in vitro</i> and in erythrocyte membranes | Vogel et al., 2005; Méttola et al., 2018 |
| | <i>H. multifolius</i> | leaves | infusion; extract (MeOH) | Inhibition of lipid peroxidation in erythrocyte membranes | Vogel et al. (2005a) |
| | <i>H. remyanus</i> | leaves | infusion; extract (MeOH) | Inhibition of lipid peroxidation in erythrocyte membranes | Vogel et al. (2005a) |
| | <i>H. rigidus</i> | aerial parts | sternbin (Flv70) | Inhibition of iron/ascorbate-induced lipid peroxidation in rat cells | Morales et al. (2009) |
| | <i>H. taeda</i> | leaves | infusion; extract (MeOH) | Inhibition of lipid peroxidation in erythrocyte membranes | Vogel et al. (2005a) |
| Muscle relaxant | <i>H. rigidus</i> | aerial parts | extracts (H ₂ O, MeOH, CH ₂ Cl ₂) | Relaxation of L-phenylephrine precontracted <i>corpus cavernosum</i> smooth muscles of Guinea pigs | Hnatsyzyn et al. (2003) |
| Inhibition of GLUT1 transporter | <i>H. baylahuen</i> | leaves | rhamnetin (Flv17) | Inhibition of GLUT1 transporter in human myeloid HL-60 cells, in transfected Chinese hamster ovary cells overexpressing GLUT1, and in normal human erythrocytes; inhibition of binding of cytochalasin B to GLUT1 in erythrocyte ghosts | Vera et al. (2001) |
| | | | isorhamnetin (Flv18) | | |

5.2.1 *H. anthylloides* meyen & walp

Although the bioactivity of the species *H. anthylloides* has not been extensively studied, it is reported that dichloromethane extracts of its resinous exudates present antibacterial effects, inhibiting the *in vitro* growth of several human pathogenic bacteria (Urzúa et al., 1995a).

5.2.2 *H. baylahuen* remy

Haplopappus baylahuen is the species with the highest number of bioactivity studies. Extracts and decoctions of its aerial parts are reported to have antibacterial and bactericide effects against *Staphylococcus aureus*, *Bacillus subtilis*, *Acremonium falciforme* (Lazo, 1990) and *Salmonella enteritidis* (Elgueta et al., 2021).

Moreover, emulsions of its resin have been successfully used to treat the symptoms of dysentery in affected individuals (Fingland, 1903), while extracts of the aerial parts of *H. baylahuen* have shown anti-inflammatory (Adzet and Gene, 1991), diuretic (Méttola et al., 2018) and hepatoprotective (Nuñez-Alarcon et al., 1993) effects in rat models and hepatoprotective activity in dog models (Martin et al., 1988). The hepatoprotective effect in rats under CCl₄-induced liver injury has also been confirmed in the case of 7-O-methylaromadennin (**Flv76**) isolated from the aerial parts of the plant (Nuñez-Alarcon et al., 1993). Moreover, rhamnetin (**Flv17**) and isorhamnetin (**Flv18**) isolated from the leaves of *H. baylahuen* have been found to inhibit in a dose-dependent manner the glucose transporter GLUT1 in human cell lines and *in vivo* in hamsters

(Vera et al., 2001). Finally, extracts of the aerial parts of this species have demonstrated significant antioxidant capacity as measured by various *in vitro* assays (Vogel et al., 2005a; Speisky et al., 2006; Alarcón et al., 2008; Schmeda-Hirschmann et al., 2015; Méttola et al., 2018; Elgueta et al., 2021), while also inhibiting lipid peroxidation *in vitro* and in erythrocyte membranes (Vogel et al., 2005a; Méttola et al., 2018).

5.2.3 *H. chrysanthemifolius* (Less.) DC

In the case of *H. chrysanthemifolius*, scientific evidence supports the antibacterial effect of the methanolic extracts of its resinous exudates, as this has been demonstrated through the *in vitro* growth inhibition of several Gram-positive human pathogenic bacterial strains (Urzúa et al., 2004b; 2012).

5.2.4 *H. deserticola* Phil

The diterpene 18-acetoxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (Dit99) isolated from the resin of *H. deserticola* presented a bactericidal effect against *Streptococcus mutans* (Urzúa Moll et al., 1997), while the *in vitro* antioxidant capacity of the infusion and methanolic extract of the plant's aerial parts has also been documented (Schmeda-Hirschmann et al., 2015).

5.2.5 *H. diplopappus* Remy subsp. *diplopappus*

The resin of *H. diplopappus* subsp. *diplopappus*, as well as the isolated diterpenoid 13-*O*- β -xylopyranosyl-*ent*-manool (Dit8) present antibacterial effect against various Gram-positive and Gram-negative human pathogenic bacteria (Urzúa et al., 1995a).

5.2.6 *H. foliosus* (Hook. & Arn.) Hook. & Arn

Scientific evidence supports the antibacterial effect of the resinous exudate of *H. foliosus* against several Gram-positive and Gram-negative human pathogenic bacteria (Urzúa et al., 1995a; 2003; Urzúa and Mendoza, 2001). Similar bioactivity has been attributed to the diterpenes 2 α -hydroxy-*cis*-clero-3,13(*Z*),8(17)-trien-15-oic acid (Dit87) and 2 α -acetoxy-*cis*-clero-3,13(*Z*),8(17)-trien-15-oic acid (Dit88) which were isolated from the resin of *H. foliosus* (Urzúa et al., 2003).

5.2.7 *H. litoralis* Phil

In the case of *H. litoralis*, it has been reported that its resinous exudate inhibits the *in vitro* growth of *Bacillus cereus*, *B. subtilis*, *Enterococcus faecalis*, *Listeria monocytogens*, *Micrococcus luteus*, *S. aureus* (Urzúa et al., 2004b; 2012).

5.2.8 *H. multifolius* reiche

Scientific literature provides evidence that support the antibacterial effect of *H. multifolius* resin and aerial parts extracts against a wide spectrum of Gram-positive and Gram-negative human pathogenic bacteria (Urzúa et al., 1995a; Padilla et al., 2021). Moreover, similar antibacterial activity has been documented for the coumarins esculetin (Cum1), prenyletin (Cum3) and haplopinol (Cum4) isolated from the aerial parts of this species (Chiang et al., 1982). Regarding the *in vitro* antioxidant capacity of *H. multifolius*, this has been demonstrated in the case of extracts, aerial parts infusions and resin (Vogel et al., 2005a; Schmeda-Hirschmann et al., 2015), as well as for the isolated compounds quercetin (Flv1), isorhamnetin (Flv18), prenyletin

(Cum3), haplopinol (Cum4), 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin (Cum6), 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin (Cum7) and 6-hydroxy-7-[(*E,E*)-3',7'-dimethyl-2',4',7'-octatrienyloxy] coumarin (Cum8) (Torres et al., 2006). Furthermore, the isolated compounds esculetin (Cum1), esculin (Cum2), prenyletin (Cum3), 6-hydroxy-7-(5'-hydroxy-3',7'-dimethylocta-2',6'-dien)-oxycoumarin (Cum6), 6-hydroxy-7-(7'-hydroxy-3',7'-dimethylocta-2',5'-dien)-oxycoumarin (Cum7), umbelliferone (Cum14) and *O*-prenylumbelliferone (Cum15) have demonstrated an anti-inflammatory effect associated to the *in vitro* inhibition of soybean 15-lipoxygenase (Torres et al., 2013). Finally, methanolic extracts and infusions of *H. multifolius* leaves inhibited the lipid peroxidation in erythrocyte membranes (Vogel et al., 2005a).

5.2.9 *H. remyanus* wedd

Infusions, methanolic extracts and resin from the leaves of *H. remyanus* demonstrated a significant antioxidant capacity *in vitro*, while also inhibiting lipid peroxidation in erythrocyte membranes (Vogel et al., 2005a). Furthermore, the resinous exudates of the plant exhibited an anti-inflammatory effect in mice (Faini et al., 2011) and a cytotoxic effect against T-lymphoblastic leukemia cell line (CCRF-CEM) (Faini et al., 2011).

5.2.10 *H. rigidus* Phil

Extracts of the aerial parts of *H. rigidus* have effectively inhibited the *in vitro* growth of several Gram-positive bacterial strains (Morales et al., 2003; Ortiz et al., 2019), presented a significant *in vitro* antioxidant capacity (Schmeda-Hirschmann et al., 2015) and also acted as muscle relaxants in Guinea pig models (Hnatyszyn et al., 2003). The isolated flavanone sternbin (Flv70) presented high *in vitro* antioxidant capacity, lipid peroxidation inhibitory effects in rat cells and also antitumoral effect against the human breast adenocarcinoma (MCF-7), human lung carcinoma (A-549) and human colon adenocarcinoma (HT-29) cell lines (Morales et al., 2009). The isolated diterpene rigidusol (Dit100) also had a cytotoxic effect on human breast adenocarcinoma cells line (MCF-7) (Morales et al., 2000b).

5.2.11 *H. schumannii* (Kuntze) G.K. Br. & W.D. Clark

The resinous exudates of *H. schumannii* inhibited the *in vitro* growth of several Gram-positive bacterial human pathogens (Urzúa et al., 1995a).

5.2.12 *H. scrobiculatus* (Nees) DC

Similarly, the only known bioactivity regarding the resin of *H. scrobiculatus* is that of the *in vitro* antibacterial effect against several Gram-positive bacteria (Urzúa et al., 1995a; 2004b; 2012).

5.2.13 *H. taeda* reiche

Ethanol extracts and infusions of aerial parts of *H. taeda* successfully inhibited the *in vitro* growth of several *Bacillus* and *Staphylococcus* bacterial strains (Padilla et al., 2021). Regarding the *in vitro* antioxidant capacity of the species, this has been shown to be significant in the case of aerial parts infusions, extracts and resinous exudates (Vogel et al., 2005a; Schmeda-Hirschmann et al., 2015), as well as for the isolated compounds 9-*trans*-*p*-coumaroyloxy- α -

terpineol (**Cin7**) and 7-*trans-p*-coumaroyloxy-taedol (**Cin8**) (Faini et al., 2007). Moreover, leaf infusions and methanolic extracts of *H. taeda* inhibited lipid peroxidation in erythrocyte membranes (Vogel et al., 2005a). Ethanolic extracts, as well as the isolated compounds taedol (**Mon41**), 18-acetoxy-*cis*-cleroda-3,13(*E*)-dien-15-oic acid (**Dit99**), and sakuranetin (**Flv67**) exhibited an anti-inflammatory effect against arachidonic acid-induced ear edema in mice (Faini et al., 2008).

5.2.14 *H. uncinatus* Phil

Extracts of the aerial parts and resinous exudates of *H. uncinatus*, as well as the isolated diterpenoid 18-acetoxy-*cis*-cleroda-3-en-15-oic acid (10 β H, 16 ξ , 19 β , 17 β , 20 α form) (**Dit84**) have been reported to inhibit *in vitro* the growth of various Gram-positive human pathogenic bacteria (Urzúa et al., 1995a; 2006; Urzúa and Mendoza, 2001).

5.2.15 *H. velutinus* remy, *H. velutinus* Remy subsp. *illinitus* (Phil.) Klingenb

Dichloromethane extracts of the resinous exudates of *H. velutinus* and its subspecies *H. velutinus* subsp. *illinitus* inhibited *in vitro* the growth of various Gram-positive and Gram-negative human pathogenic bacteria (Urzúa et al., 1995a).

6 Non-human health related bioactivity and toxicity

Among the pharmacological activities attributed to *Haplopappus* species and not related to the human health, the most studied is the antimicrobial effect against plant pathogens. The essential oil of the leaves of *H. baylahuen* inhibited the *in vitro* growth of the fungi *Aspergillus niger* and *Fusarium oxysporum* (Becerra et al., 2010). Moreover, the diterpenoid 7,13-(*E*)-labdadien-15,18-dioic acid 18-methyl ester (**Dit45**) was isolated from the resinous exudate of *Haplopappus velutinus* and inhibiting *in vitro* the mycelial growth of *Botrytis cinerea* (Echeverría et al., 2019). In the case of the phytopathogenic bacterium *Clavibacter michiganensis* subsp. *michiganensis*, its *in vitro* growth was inhibited by the resin (Urzúa and Mendoza, 2001) and the isolated diterpene 18-acetoxy-*cis*-cleroda-3-en-15-oic acid (10 β H, 16 ξ , 19 β , 17 β , 20 α form) (**Dit84**) (Urzúa et al., 2006) from *H. uncinatus*, as well as by the methanolic extract of the resin of *H. foliosus* (Urzúa and Mendoza, 2001).

The essential oil of *H. foliosus* also exhibited insecticide effects against house flies (*Musca domestica*) (Urzúa et al., 2010), while hydroethanolic and chloroform extracts of *H. rigidus* presented biotoxic activity against *Artemia salina* (Morales et al., 2003).

7 Concluding remarks and future perspectives

The available scientific literature on the genus *Haplopappus* can be said to support, although partially, its widespread and longstanding use as a medicinal plant. However, the results of

the present review highlight several limitations that need to be addressed.

Firstly, phytochemical and bioactivity research of the genus *Haplopappus* is largely concentrated in the 1990s and 2000s, with almost 80% of the investigation having been performed before 2010. Therefore, a revival of scientific interest and the application of modern, more advanced and diverse analytical and biological techniques can further elucidate the composition and bioactivity of *Haplopappus* plant species, thus broadening the existing knowledge and promoting its potential uses.

Furthermore, phytochemical and pharmacological evidence is available only for the 40% and 23%, respectively, of the botanical taxa of the genus *Haplopappus*, while for many of the studied taxa, the available information is rather limited. Similarly, terpenoids and phenolics correspond to approximately 70% of the compounds reported in *Haplopappus* spp., suggesting that scientific investigation up to date has possibly understudied other chemical groups. It is, therefore, suggested to extend the focus of scientific research to more, if not all, *Haplopappus* species and groups of chemical compounds, thus permitting to fully explore its promising chemical and biological prospects.

Based on the available bioactivity and pharmacological evidence, *Haplopappus* species can be considered as a valuable plant resource for health-promoting applications. However, the majority of the investigation provides evidence associated to the *in vitro* antibacterial and antioxidant activity of the genus *Haplopappus*. In contrast, there is a lack of scientific evidence to support or refute various traditional uses, while, at the same time, the limited number of *in vivo* studies and/or clinical trials hinders its wider human health-promoting application and secure use.

In this context, the information presented in the present review supports the ethnopharmacological, phytochemical and bioactive potential of the genus *Haplopappus*, while addressing the aforementioned limitations could further promote and broaden both scientific research and future applications and uses.

Author contributions

CM: Writing–review and editing, Writing–original draft, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. JE: Writing–review and editing, Writing–original draft, Supervision, Project administration, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. We gratefully acknowledge support from Comisión Nacional de Investigación Científica y Tecnológica—CONICYT PAI/ACADEMIA No. 79160109 and from Dirección de Investigación Científica y Tecnológica—DICYT USACH 022341EM_Ayudante.

Acknowledgments

CM was supported by the Scholarship Program of the Agencia Nacional de Investigación y Desarrollo de Chile (ANID Doctorado Nacional 2022/21220376).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2024.1490243/full#supplementary-material>

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