Anti-Inflammatory Activity of the Compositae Family and Its Therapeutic Potential

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ABSTRACT

Compositae is the largest family of flowering plants, with more than 1600 genera and 22 000 species. It has many economic uses in foods, cosmetics, and pharmaceutics. The literature reports its numerous medicinal benefits and recognized anti-inflammatory activity. Thus, this study evaluated the technological trends of anti-inflammatory activity of Compositae, based on the survey of scientific databases, articles, and patents, as well as the website of the Brazilian National Health Regulatory Agency (ANVISA), which is responsible for registering and controlling of healthcare and cosmetic products in the Brazil. The survey was conducted between 2008 and 2018, in the databases Science Direct, Lilacs, PubMed, and Web of Science (main collection), as well as the SciELO Citation Index. The patent survey was carried out on the basis of the Derwent Innovations Index, an important source for worldwide patent consultation, which covers 20 y of registered patents. Despite the numerous studies involving species of the Compositae family in different models of anti-inflammatory activity, there are few records of patents or products on the market from these species for that purpose. Some species have a traditional use and are present even in the Phytotherapic Summary of the Brazilian Pharmacopeia. This review confirms the therapeutic potential of Compositae for the development of anti-inflammatory drugs and reinforces the need to develop competencies and reduce technological bottlenecks to promote research and innovation in biodiversity products.

Introduction

Compositae is considered one of the most numerous and evolved families of the plant kingdom, as well as the largest family of flowering plants. Its name derives from the characteristic structure of its inflorescences, in the form of flower head [1]. Paul Dietrich Giseke stated that Compositae includes more than 1600 genera and 23 000 species [2, 3], of which 250 genera and 2000 species are found in Brazil. These plants have varied habits and may be herbs, shrubs, trees, and creepers, although small plants predominate [1].

The Compositae family has a cosmopolitan distribution and is widespread in all continents except for Antarctica [4, 5] and easily encountered in savannas, the countryside, and less frequently in humid tropical forests [2]. This family has great economic utility for food, cosmetics, and pharmaceutics as an ornamental plant

and also includes plants with phytoremediation potential [4, 6]. In addition to this strong economic impact, other species of this family have been the target of speculation because they can cure different diseases. Many have been used in popular medicine, such as arnica (*Arnica montana*), macela (*Achyrocline satureioides* (Lam.) DC.), globe artichoke (*Cynara scolymus*), and guaco (*Mikania glomerata* var *glomerata*), which are widely used, respectively, for healing, anti-inflammatory, hepatic insufficiency, and respiratory problems [7].

Individual species of the Compositae family have been the subjects of reviews about their anti-inflammatory activity. However, no review has emphasized the technological prospection of the Compositae family, including the most important species with anti-inflammatory activity, highlighting scientific articles involving the development of pharmaceutical forms, patents, and products on the market.

In Brazil, several species of the Compositae family are indicated for different pathologies in popular medicine, largely as anti-inflammatories, in official compendia such as the *Memento Fitoterápico da Farmacopeia Brasileira* (MFFB, Phytotherapic Summary of Brazilian Pharmacopoeia) [8] and in the *Formulário Fitoterápico da Farmacopeia Brasileira* (FFFB, Phytotherapic Formulations of Brazilian Pharmacopoeia) [9]. In addition, the Brazilian government, through Normative Instruction IN 02/2014 [10], lists traditional phytotherapeutic products for simplified registration, where a list of recommended species with anti-inflammatory activity, such as *Calendula officinalis, Matricaria chamomilla*, and *Arnica montana* are present [11]. The latter, in Brazil, is a substitute species, *Solidago chilensis*, which is recommended in the *Relação Nacional de Plantas de Interesse do Sistema Único de Saúde* (RENISUS, Brazilian National List of Medicinal Plants by the Unified Public Health System [12], both with anti-inflammatory activity [13].

Dutra et al. [14] recently made a survey on the use of medicinal plants in Brazil, contemplating pharmacological studies, discovery of new drugs, challenges, and perspectives. The anti-inflammatory activity was one of the relevant indices of continual study by researchers, in which some species from Compositae were included.

However, according to Carvalho et al. [15], although the market for natural products has expanded worldwide, Brazil does not seem to have participated in this expansion, since few products from Brazilian biodiversity have been licensed. Currently, one of the obstacles for finding phytotherapeutic products licensed in Brazil could be the complexity of the entire production chain for phytomedicines, as well as the transferring of basic research to the industrial scale and the communication between those involved in this process [16, 17].

Thus, one of the objectives of this work was to evaluate how much of the basic research is currently translated into products registered on the market or for perspective production, through patent protection.

Focusing on species in the Compositae family with anti-inflammatory activity, a study of the therapeutic potential was conducted by surveying scientific articles, theses, dissertations, patent applications, patents granted, and products on the market. This work surveyed the Integrity Platform databases (Derwent, Web of Science, and SciELO) in Science Direct, Lilacs, and PubMed, as well as consulted the National Health Regulatory Agency (ANVISA, *Agência Nacional de Vigilância Sanitária*) site to verify the products with valid registration of these species.

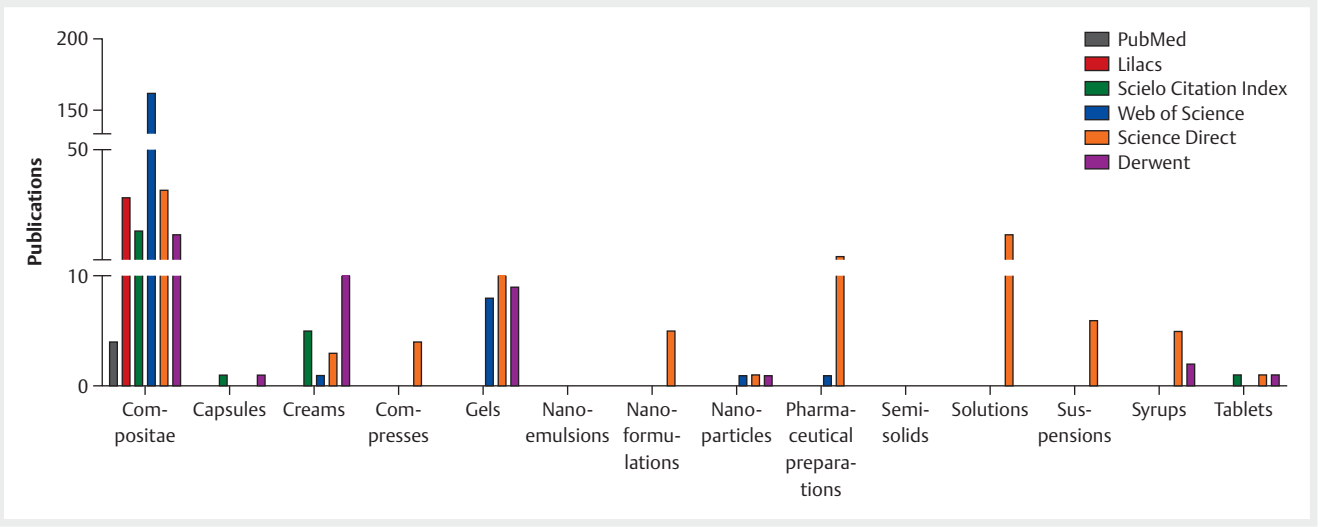
In spite of the numerous Compositae species found with anti-inflammatory activity, some were more relevant than others, especially when comparing the number of bibliographic references with the requested patents and products in the market. The majority with a registered product are already used by traditional herbal medicine and are included in official compendia or in the national list of plants of SUS interest.

This work reviews reports published between 2008–2018 in the databases Science Direct, Lilacs and PubMed, as well as in the databases of the Integrity Platform, as in the main collection of scientific articles of the Web of Science and SciELO Citation Index. Patents were also searched on the basis of the Integrity Platform, in the Derwent Innovation Index, which indexed over 62 patent authorities in the Derwent World Patent Index featuring as clients United States Patents and Trademark Office (USPTO), European Patent Office (EPO), Japan Patent Office (JPO), Brazil among others, covering over 98% of all basic patents in the world. The search covered a period from 1998 to 2018, encompassing the 20-y patent period. To obtain a scientific, patent, and market survey of the species of the Compositae family with anti-inflammatory activity, the possible products registered in Brazil were also searched on the ANVISA website.

For the databases of scientific articles, the following keywords and combinations were used: Compositae, anti-inflammatory activity, pharmaceutical preparations, tablets, capsules, syrups, compresses, nanoformulations, nanoparticles, solutions and suspensions, creams, gels, and semi-solid formulations. In general, searches were refined in terms of the Plant Science or Pharmacology and Pharmacy subjects, mainly looking for open access articles and reviews, although some computed references were not automatically available either. In addition, relevant theses and dissertations found outside the search but within the stipulated chronological period were incorporated into this research. Only studies with full descriptions were considered and presented; thus, evaluated references included part of the plant used, extraction and isolation method, and phytochemical identification about the marker through chromatographic and spectroscopic assays. Another relevant criterion evaluated was the intention to develop pharmaceutical products for internal or external use, thereby reducing the number of papers presented. In addition, references that showed *in vitro* anti-inflammatory potential and *in vivo* anti-inflammatory activity assays for extracts and/or isolated substances as well as for formulated products were considered relevant.

Patenting monitoring contemplated the same keywords or combination of these and considered formulations and compositions for the International Patent Classification (IPC) such as A61 (medical or veterinary science, hygiene), A61K (preparations for medical, dental, or hygienic), A61P (therapeutic activities of medicinal preparations), as well as the years and country of deposit.

On the Anvisa site, the products researched were the species with the greatest description of potential anti-inflammatory action observed through the articles and patents found in the databases, or its popular indication, using the word “phytoterapic”, as a regulatory category.



▶ **Fig. 1** Relation of the number of records found in the searched databases combining search terms with anti-inflammatory activity.

Metric Comparison between Databases

In all the databases surveyed, a search for the term Compositae brought up innumerable and countless references. However, this general search proved the lack of a review article on technological prospection of the Compositae family with anti-inflammatory activity that highlighted scientific articles, patents, and commercial products.

▶ **Fig. 1** shows the number of records found in the databases searched between 2008 and 2018 for scientific articles, dissertations, and theses, as well as for the years 1998–2018 for patents, when terms for anti-inflammatory activity were searched.

In most of the sources, when the terms Compositae and anti-inflammatory activity are combined, many references appear, especially in the main collection of Web of Sciences. Nevertheless, when these terms are combined with some pharmaceutical forms, few appeared, except in the Science Direct database, where for the pharmaceutical form “drug solution”, this number was quite expressive compared to the others (27). This same graph illustrates that although the number of articles is high for Compositae with anti-inflammatory activity, the patents and products from species of this family does not follow that trend, which confirms the information of Carvalho et al. [15] who mention that the market for biodiversity products is still very small.

In addition to the solutions, the most commonly cited pharmaceutical forms were gels and creams. However, when the search was carried out, generalizing the pharmaceutical forms as pharmaceutical preparations, this number was also high.

Species of the Compositae Family Found with Anti-Inflammatory Activity or with Anti-Inflammatory Potential

▶ **Table 1** shows a compilation of the references containing several Compositae species with anti-inflammatory activity as a function of different inflammation models (*in vivo*) or with anti-inflammatory potential, through the effects on mediators of the inflammatory processes (*in vitro*). All the descriptors of the mentioned species are in agreement with *The Plant List* taxonomic database.

According to Chagas-Paula et al. [18], some Compositae species act as potent inhibitors through the mechanism of dual inhibition of cyclooxygenase-1 (COX-1) and 5-lipoxygenase (5-LOX). However, other mechanisms of action for the anti-inflammatory potential of this family are discussed.

Articles strictly related to ethnobotany were evaluated and used as important reference sources even though they did not reference experimental conditions, since most of them only mentioned the popular use of the species.

The most cited species in the obtained literature for anti-inflammatory activity or anti-inflammatory potential were the different types of arnica (*Solidago, Lychnophora, Tithonia, Chromolaena, Heterotheca*). Other species mentioned in the scientific literature for anti-inflammatory activity were yarrow (*Achillea millefolium*), chamomile (*Matricaria chamomilla*), artemisia (*Artemisia* spp.), baccharis (*Baccharis* spp.), vernonia (*Vernonia* spp.), burdock (*Arctium lappa*), guaco (*Mikania* spp.), Echinacea (*Echinacea purpurea*), and Beggar-ticks (*Bidens pilosa*).

Thus, despite the vast number of species from the Compositae family reported against inflammatory processes and the traditional use of some, we highlight only those with bibliographic references that confirm their anti-inflammatory activity as important species with technological potential: *A. millefolium, A. lappa, Artemisia* spp., *Baccharis* spp., *Bidens pilosa, E. purpurea, Vernonia* spp., and 5 synonyms of arnica (*Chromolaena odorata, Heterotheca sub-*

▶ **Table 1** Compositae species with anti-inflammatory activity (*in vivo*) or with effects on mediators of the inflammatory processes (*in vitro*), under different models.

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Achillea					
A. millefolium L.	Aerial parts	Apigenin, luteolin, and its glycosidic derivatives, chlorogenic and caffeic acid	Ethanolic extract in olive and sunflower oil	Application of extracts on irritated skin by sodium lauryl sulphate	[19]
Acmella					
A. oleraceae (L.) R. K. Jansen	Aerial parts	Hydrocarbons, monoterpenes, sesquiterpenes, and arylpropanoides (genus)	Ethanolic extract	Ear edema (0.5; 2.5; 5 mg/mL/ear) Oral (300–1200 mg/kg)	[20]
A. pilosa R. K. Jansen	Stem	Rosmarinic acid and caffeic acid	Ethanolic extract	Carrageenan-induced paw edema	[21]
Ageratina					
A. pichinchensis (Kunt) R. M. King & H. Rob.	Aerial Parts	7-O-(β-D-glucopyranosyl)-galactin	Aqueous Extract	Paw edema induced by carrageenan	[22]
Ageratuam					
A. fastigiatum (Gardner) R. M. King & H. Rob.	Aerial parts (leaves and inflorescences)	α-pinene, limonene, trans-caryophyllene, α-humulene, caryophyllene oxide, 1,2-humulene-epoxide, 1,6- humulanodien-3-ol, and α-cadinol	Essential oil	Viability of peripheral blood leukocytes and effect on cytokine production (5×10^{-3}; 10^{-2}; 2.5×10^{2} µL/mL) after exposure to different concentrations of essential oil and *in vitro* effect of essential oil on the production of cytokines by human lymphocytes	[23]
Aucklandia					
A. lappa DC.	–	Terpenes, anthraquinones, MeOH extract alkaloids, flavonoids		Induced neutrophil cytokine inhibition (MeOH ext. 0.1 mg/mL) and acute and chronic inflammation-induced paw edema and peritonitis (EtOH Ext. 50–200 mg/kg)	[24]
Arctium					
A. lappa L.	Leaves	Sesquiterpenolactones	Onopordopicrin- enriched fraction	Model of colitis induced by 2,4,6-trinitrobenzene sulfonic acid	[25]
A. minus (Hill) Bernh	Leaves	Phenolic compounds expressed in terms of gallic acid	Aqueous and ethanolic extract	Carrageenan-induced paw edema	[26]
Arnica					
Arnica montana L.	Flowers	Quercetin, rutin, and apigenin and chlorogenic acid. Total sugar and total uronic acids contents	Polyphenolic and polysaccharide extract and liposomal formulations	Cell morphology model and pro-inflammatory cytokines Production	[27]
	Flower heads	Sesquiterpenelactones, helenalin, and derivatives	Different dyes and gel	Inhibition of MMP1 and MMP13 mRNA and consequent inhibition of NF-κB	[28]
Artemisia					
A. herba-alba Asso	Aerial Parts	Hispidulin and cirsilineol	Ethanolic extract (percolation)	Paw edema (100; 200 and 400 mg/Kg p. o.)	[29]
A. judaica L.	Aerial Parts	Monoterpenes (piperitone, camphor, and ethyl cinnamate)	Essential oil	NO inhibition in macrophage culture induced by (LPS)	[30]
A. pallens Wall. Ex DC.	Aerial Parts	Sesquiterpenolactones	Methanolic extract	Acetaminophen-induced nephrotic model and hepatotoxicity	[31]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Atractylodes					
A. lancea (Thunb.) DC.	Rhizomes	*β*-eudesmol	Atractylochromene, quinone, *β*-eudesmole atractylon	Inhibition of 5-LOX and COX-1	[32]
Baccharis					
B. incarum (Wedd.) Perkins, *B. boliviensis* (Wedd.) Cabrera[a]	Aerial parts (std 0.1–0.8 mg/mL flavonoids and flavoinois)	Flavonoids and terpenoids	Ethanolic extracts	Inhibition of COX-1, COX-2, and PGE2	[33]
B. uncinella DC.	Aerial parts	Non-glycosylated flavonoids, triterpenes, and phenolic derivatives	Organic fractions of ethanolic extract	Phospholipase A2-induced paw edema of rattlesnake and carrageenan	[34]
B. trimera (Less.) DC.	Aerial parts	Flavonoids, tannins, saponins, alkaloids, isoprenoids	Aqueous extract (infusion), ethanolic fraction, and aqueous fraction	Carrageenan-induced paw edema	[35]
Bidens					
B. tripartita L.	Aerial parts	Catechin, chlorogenic ac., caffeic acid, luteolin-7-O-glucoside, chicoric acid, luteolin, Hydroxycinnamic acid, luteolin glucoside, polyacetylenes	Hydroalcoholic extract	Paw edema (4, 10, and 20 ml/Kg)	[36]
			Cream containing 2.5% extract	Psoriasis	
B. pilosa L.	Whole Plant	Phenylpropanoids, sesquiterpenes, phytosterols, chalcones and terpenes, poilacetylenes and flavonoids	ECOBIDENS® glycolic extract formulated with POLOXAMER	Mucositis induced in rats with 5-fluorouracil (75; 100 and 125 mg/Kg)	[37]
B. pilosa L.	Glycolic extract	Phenylpropanoids, sesquiterpenes, phytosterols, chalcones and terpenes, poliacetylenes and flavonoids	FITOPROT mucoadhesive formulation	Mucositis induced in rats with 5-fluorouracil	[38]
Calendula					
C. officinalis L.	Flowers	Triterpenoid (esters of faradiol-3-myristic acid, faradiol-3-palmitic acid, and 4-taraxasterol)	Ethyl acetate soluble fraction of the methanol extract	Ear inflammation induced by 12-otetradecanoyl phorbol-13-acetate (TPA)	[39]
		Esters of faradiol-myristic acid, faradiol-palmitic acid, and Ψ-taraxasterol	Dichloromethane extract	Croton oil-induced edema	
			Cream containing calendula extract	Dextran and burn edemas	
Carthamus					
C. tinctorius L. (C. flos–the dried floret)	Safflower	Ginkgolide B, saffloquinoside A	Safflor yellow (25 and 50 mg/kg, intraperitoneal)	Rats of pulmonary fibrosis induced by bleomycin (*in vivo*)	[40]
Centaurea					
C. tchihatcheffii Fisch. & C. A. Mey.	Flowers, leaves, and stems	Sesquiterpenlactones	Ethanol extracts	Paw edema induced with carrageenan and PGE2 and ear edema induced with 12-O-tetradecanoyl-13-acetate (TPA)	[41]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
C. ainetensis Boiss.	Aerial parts	Guaianolide (salograviolide A)	Methanol extract	Inhibited endotoxin (ET)-induced IL-6 levels in SCp2 mammary epithelial cells model and decreased the levels of IL-1-induced COX enzyme levels in intestinal epithelial cells model.	[42]
Chiliotrichum					
C. diffusum (G. Forst.) Kuntze	Flowers	Chlorogenic acid, caffeic acid, hyperoside, isoquercetrine, quercitrin, afzelin, quercetin, apigenin, and kaempferol	Aqueous extract (Decoct)	Paw edema (30 and 100 mg/Kg)	[43]
Chromolaena					
C. odorata (L.) R. M. King & H. Rob.	Aerial Parts	Essential oils, flavonoids	MeOH extract (fatty acid, coriolic acid, methyl ester, α, 15,16-didehydrocorp, alkali, and 15,16-didehydrochloride, methyl ester, linoleamide, linolenamide	Inhibition of NO production and NF-κB activity in LPS-stimulated macrophage culture	[44]
	Leaves	Scutellarin, tetramethyl ether	Dichloromethane extract	Inhibition of NF-κB activity (10 µg/mL)	[45]
Conocliniopsis					
C.prasiifolia (DC.) R. M. King & H. Rob.	Leaves	Sesquiterpene lactones, coumarins, flavonoids	Ethanolic extract	LPS-induced neutrophil degranulation (0.1–50 µg/mL)	[46]
Dichrocephala					
D. integrifolia (L. f.) Kuntze	Whole plant	Portulide glucoside A and dichroditerpene A (diterpenes) 14-acetoxy-9-epi-britanlin A (sesquiterpene)	Extracts soluble in EtOAc and n-BuOH from partition of the MeOH: H_2O extract	Antineutrophilic inflammatory activities against superoxide anion generation and elastase release assay	[47]
Echinaceae					
E. purpurea (L.) Moench	Leaves and roots	Germacrene D, naphthalene, caryophyllene oxide, α-felandren, and α-cadinol	Essential oil	Carrageenan-induced paw edema	[48]
Echinops					
E. spinosus L.	Rhizome	–	Aqueous, ethanol, and chloroform extracts	Carrageenan-induced rat subplantar edema and arachidonic acid-induced mouse ear edema models	[49]
	Leaves	5,7-dihydroxy-8,4′-dimethoxy-flavanone-5-*O*-α-L-rhamnopyranosyl-7-*O*-β-D-arabinopyranosyl-(1→4)-*O*-β-D-glucopyranoside	Methanolic extracts	Carragenan-induced hind paw edema method	
	Whole plant	–	Ethanol extracts	Anti-inflammatory activity induced by carrageenan, formaldehyde-induced acute and chronic arthritis, and adjuvant-induced acute and chronic arthritis	
Eclipta					
E. prostrata (L.) L.[b]	Whole plants	Wedelolactone, demethylwedelolactone, oroboside	Methanol extract	Asthma induced with OVA model (i. p.)	[50]
	Leaves	Steroids, triterpenoids, flavanoids, reducing sugar, tannins and saponins	Methanol extract	Carrageenan and egg white-induced hind paw edema in rats	[51]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Egletes					
E. viscosa (L.) Less.	Seeds	Flavonoids (ternatin), saponins, catechins, xanthones, flavonoids	Aqueous extract	Formalin assay	[52]
Emilia					
E. sochifolia (L.) DC. ex DC.	Aerial parts	Quecetrin; kaemferol C-glycoside derivative; chlorophyll; carrotenoid derivatives; triterpenoids; and phenolic acids–caffeic acid derivatives	Methanol/methylene chloride extract	Levels of IL-1β and TNF-α after an intraperitoneal lipopolysaccharide challenge and TNF-α and inducible (iNO) production by LPS-stimulated bone marrow-derived macrophages (BMMDM) models	[53]
Eremanthus					
E. erythropappus (DC.) MacLeisch	Branch	Sesquiterpenoids and sesquiterpenic lactones	Ethanolic extract	Paw edema (100 and 200 mg/Kg)	[54]
Erigeron					
E. annuus (L.) Pers.	Roots	Sesquiterpenoids, diterpenoid, sterols, and triterpenoids	Methanol extract	NO Production, carrageenan-induced paw edema and carrageenan-induced acute inflammation	[55]
Eupatorium					
E. perfoliatum L.	Aerial parts	Polysaccharides, sesquiterpene lactones, and flavonoids	MeOH-, EtOH-, and DCM extracts and fractions	LPS-stimulated cells by NO/iNOS quantification, gene array, real-time PCR, and ELISA.	[56]
Felicia					
F. muricata Thunb. (Nees)	Leaves	Alkaloids, flavonoids, tannins, saponins, and phenolics	Aqueous extract	Paw edema induced by carrageenan and egg albumin	[57]
Galinsoga					
G. parviflora Cav.	Aerial parts	Flavonoids, aromatic esters, caffeic acid derivatives, diterpenoids, and phenolic acid derivatives.	Methanol, hexane extracts, and H_2O fractions	COX-1 assay and (5-LOX)	[58]
Gochnatia					
G. polymorpha (Less.) Cabrera	Trunk bark	11,13-dihydrozaluzanin C	Ethanol extract, ethyl acetate and other fractions, and the isolated compounds bauerenyl acetate and 11,13-dihydrozaluzanin C	Paw edema and carrageenan-induced air pouch inflammation models	[59]
G. pulchra Cabrera	Aerial Parts	Sesquiterpene lactone, dimeric guaianolide, bisabolines; diterpenes, triterpenes, coumarin	Alcoholic extr. and genkwanine, scutelarine, apigenin, 3,5 dicapheoilquinic	Paw edema/pleurisy (50; 100 e 500 µg/Kg)	[60]
Gynura					
G. procumbens (Lour.) Merr.	Aerial parts	–	Ethyl acetate	Ear inflammation inhibition	[61]
	Aerial parts	Essential oils, titerpenes/ steroid, bitter principles	Hexane and toluene fractions of ethyl acetate extract	Ear inflammation inhibition Less inflammatory cells at granulation tissue	
	Leaves	Flavonoids/saponins	Ethanol	Increased in release of cytokine such as IL-2 and IFNγ	
Helichrysum					
H. graveolens (M.Bieb.) Sweet[c]	Flowers	Apigenin	Methanol extract and n-hexane, CH_2Cl_2 and n-butanol fractions	Wound-healing activity and inflammatory activity using the acetic acid induced increase in capillary permeability test are different assays	[62]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
H. italicum (Roth) G. Don	Flowers	Gnaphaliol 9-O-propanoate and 5 known acetophenonones	Chloroform fraction of EtOH extract	Nitrite measurement in J774 macrophages	[63]
H. italicum subsp. *microphyllum* (Willd.) Nyman	Leaves and flower heads	Arzanol	Petroleum ether-ethyl acetate of acetone extract	Inhibition of NF-κB activation, release of proinflammatory mediators: interleukins, TNF-α, and PGE2	[64]
Heliopsis					
H. longipes (A.Gray) S. F. Blake[a]	Roots	Spilanthol	Enriched hexane extract	Freud's adjuvant-induced arthritis model (2; 6.6 e 20 mg/Kg p.o)	[65]
	Root	Alkamides	Ethanolic extract	Production of TNFα and NO by activated RAW264.7 macrophage	[66]
Heterotheca					
H.subaxillaris var. latifolia (Buckley) Gandhi & R. D. Thomas	Aerial Parts	Santin, pectolinaringenin; 3,6-dimethyl-5,7,4-trihidroxiflavone; and hispidulin	Petroleum ether, dichloromethane, and methanol extracts	Ear and paw edema	[67]
Inula					
I. cuspidata (Wall. ex DC.) C. B. Clarke	Stem and root	Alkaloids, flavonoids, triterpenoids, steroids, tannins, and phenolic compounds	Chloroform and methanol extracts	Carrageenan-induced paw edema model	[68]
I. japonica Thunb.	–	Sesquiterpene lactones	–	Inhibition of UBcH5 (suppression of the TNF-α and NF-κB gene (2.5–10 μM)	[69]
Jasonia					
J. glutinosa (L.) DC.	Plant	Sesquiterpenes (lucinone, glutinone, epi-kutdtriol, and kutdtriol)	Aqueous acetone solution, aqueous methanol solution, benzene or hydrodistillation	COX-1 inhibiting a decreasing the production of PGE2 in cells models	[70]
Jungia					
J. sellowii Less.	Leaves	Succinic acid and lactic acid	Ethanol/water extract and n-hexane, dichloromethan, ethyl acetate and n-butanol fractions, and aqueous fraction	Pleurisy induced by carrageenan	[71]
Lychnophora					
L. passerina (Mart. ex DC.) Gardner	Aerial Parts	Triterpenoids, sesquiterpenoids, steroids, and flavonoids	Ethanolic extract in lanolin-vaseline base	Inhibition of NO production, TNF-α, and stimulation of IL-10. Carrageenan-induced paw edema	[72]
		Sesquiterpene lactone (goiasenzolide)	Ethanolic extract	Carrageenan-induced paw edema	[73]
L. salicifolia Mart.	Leaves	Chlorogenic acid	(Butanol fraction of MeOH/water extract)	Inhibition of the production of interleukin, TNF-α and PGE-2 in stimulated neutrophils (50; 100 e 400 μM)	[74]
L. trichocarpha (Spreng.) Spreng. ex Sch.Bip[a]	Aerial parts	Luteolin, apigenin, Sesquiterpenolactone (lichnofolide and eremantholide C), lupeol	Ethanolic extract and fraction in ethyl acetate	Paw edema induced by urate monosodium crystal	[75]
Matricaria					
M. chamomilla L.[d]	–	α-bisabolol, bisabolol oxide A, and guaiazulene	Ethanolic extract	Formalin test	[76]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Mikania					
M. cordata (Burm.f.) B. L. Rob.	Aerial Parts	Betulinic acid derivative	Chloroform extract	Paw edema 100 mg/Kg b.w	[77]
		Mikanine, friedelin, kaurenoic acid, butynyloxy and benzyloxy, stigmasterol and sitosterol	Essential oil and chloroform and ethyl acetate extract	Paw edema (200; 400; 800 mg/Kg b.w)	[78]
M. glomerata var. *glomerata.*[e]	Leaves	Terpenes, essential oils, di and sesquiterpenolactone, flavonoids, stigmasterol, Alcohols, acids, esters, aldehydes, organic esters, and steroids	Hydroalcoholic Extract	Intra-dermal injection in rats infected with *Bothrops* venom (3.2; 6.4; 12.8 µg/mL)	[79]
M. lindleyana DC.	Aerial Parts	Stigmasterol and esters of stigmasterol, fatty acids	Methanolic extract	Carrageenan-induced peritonitis (0.5; 1.0 e 2.0 g/Kg)	[80]
M. micrantha Kunth	Stem with leaves, and inflorescences with seeds	Linalool and a-pinene	Hexane, ethyl acetate, and methanol extracts	Mouse ear edema assay induced with TPA (12-O-tetradecanoyl-phorbol-13-acetate)	[81]
Moussonia					
M. deppeana (Schltdl. & Cham.) Klotzsch ex Hanst.	Cicatrisan™/ Gastricus™, Gastinol™, and Gastrovita™	Sitosterol and stigmasterol, ursolic oleanolic, caffeic and chlorogenic acid	EtOH extracts of three dietary supplements	TPA and by carrageenan murine models	[82]
Pseudobrickellia					
P. brasiliensis (Spreng.) R. M. King & H. Rob.	Leaves	Quininic acid and derivatives, 5-caffeoylquinic acid; 3,5-dicetheoylchinic acid; flavonoids, luteolin and luteolin dihexoside	Aqueous extract, ethanolic and ethyl acetate	Inhibition of pro-inflammatory action in mononuclear cell culture (12.5–100 µg/mL extrato)	[83]
Santolina					
Santolina spp.	–	Monoterpenes and sesquiterpenes, flavonoids and coumarins	Metanol, chloroform, hexane, dichloromethane, ethyl acetate, and petroleum ether extracts	Croton oil-induced dermatitis in mouse ears; PLA2-induced mouse paw edema; carrageenan paw edema in rats; inhibition of PLA1; adjuvant carrageenan-induced inflammation, ACII, model using Wistar male rats; ionophore-stimulated mouse peritoneal macrophages; NF-κB, IL-6, IL-8, TNF-α, PGE2	[84]
Saussurea					
S.heteromalla (D.Don) Hand.-Mazz.	Whole plant	Chlorojanerin, a guaianolide type of sesquiterpene lactone	Chlorojanerin (ethyl acetate fraction from dichloromethane : methanol extract)	TNF- and IL-6 inhibition in LPS stimulated THP-1 cells and in synovial cells from a patient with rheumatoid arthritis	[85]
Scorzonera					
S. latifolia (Fisch. & C. A. Mey.) DC. *and Scorzonera mollis* subsp. *szowitzii* (DC.) D. F. Chamb.	Aerial parts	Chlorogenic acid	Methanol-water extracts	*In vivo* wound healing activity	[86]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Senecio					
S. brasiliensis (Spreng.) Less.	Flowers	Alkaloids senecionine, integerrimine, and senecionine N-oxide and mixture of 1,4-, 3,4-, 3,5- and 4,5-dicaffeoylquinic acids	Hexane, CH_2Cl_2, and ethyl acetate fractions from ethanol (96%) extract Alkaloid fraction from ethanol (96%) extract	Pleurisy induced by carrageenan	[87]
Smallanthus					
S. sonchifolius (Poepp.) H. Rob.	Leaves	Chlorogenic acid, sesquiterpene lactones	Aqueous, polar extract (MeOH) and leaf "washed" extract (acetone)	Ear edema (0.125–0.5 mg/ear) and inhibition of neutrophil migration (0.25–1.0 µg/mL)	[88]
Solidago					
S. chilensis Meyen	Rhizomes, leaves and inflorescences	Labdane diterpene solidagenone	Aqueous extracts	Mouse model of pleurisy induced by carrageenan	[89]
	Rhizome	Chlorogenic acid and caffeic acid	Aqueous extract, and its butanolic and aqueous fractions	Mouse model of the air pouch induced by carrageenan	[90]
	Aerial parts	Caffeoylquinic acid derivatives and the flavonoid rutin	Hydroalcoholic extract	Ear edema model induced by topical application of the chloroform fraction of latex-extract from *Euphorbia milii*.	[91]
	Aerial parts	Rutin and phenylpropanoids, monocaffeoylquinic acid (chlorogenic acid) and dicaffeoylquinic acid (ethanolic extract)	Gel cream containing a 5% glycolic plant extract	Clinical trial for the treatment of tendonitis of flexor and extensor tendons of wrist and hand	[94]
	Inflorescences	Quercetin, kaempferol, solidagenone, isoquercitrin, quercitrin, afzelin, chlorogenic acid, nicotiflorin, and isoquercitrin	Ether-ethanol extract	Inhibition of NO in LPS-induced macrophage culture	[95]
S. virgaurea L.	Plant	Quercetin, rutin, and kaempferol; salicylic acid derivatives; triterpene saponins, tannins, essential oils	Standardized extract in routine ≥ 0.2 mg/mL)	Inhibition and modulation of interleukin and TNF-α of LPS-stimulated fibroblasts (0.02 e 0,1%)	[96]
S. virgaurea L.	Aerial parts	3,5-O-Dicaffeoylquinic acid, 3,4-O-dicaffeoylquinic acid, 3,4,5-O-tricaffeoylquinic acid and 4,5-O-dicaffeoylquinic acid	Phenolic-rich fraction from ethanol : water 30 : 70 extract	Carrageenan-induced rat paw edema model	[97]
Sonchus					
S. oleraceus (L.) L.	Aerial parts	Flavonoids and sesquiterpenes	Hydroethanolic extract	Carrageenan-induced paw edema, peritonitis, and febrile response induced by lipopolysaccharide tests	[98]
Sphagneticola					
S. trilobata (L.) Pruski	Aerial Parts	Kaureoic acid, phenylpropanoids, and triterpene saponins	Semi-solid containing 1% dry extract standardized in kaurenoic acid	Ear edema induced by chrotonic oil, arachidonic acid, or TPA	[99]
	Stems and roots	Kaurenoic acid	Creams containing kaurenoic acid, isolated from the acetonic extract	Croton oil-induced ear edema method	[100]

cont.

▶ **Table 1** *Continued*

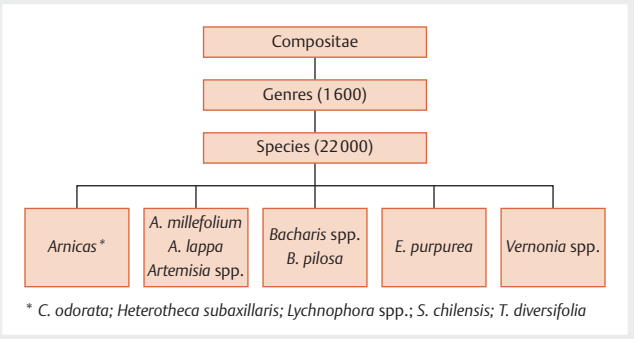
Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Silybum					
S. marianum (L.) Gaertn.	Fruits and seeds	Silymarin	Silymarin	UVB-induced edema and hyperplastic response in SKH-1 hairless mouse skin model	[101]
S. marianum (L.) Gaertn.[c]	Seed	Silibinin	Silibinin 0.2 % in hydrogel	Model of wound incision in rat	[102]
Tagetes					
T. minuta L.	Leaves	Dihydrotagetone, E-ocimene, tagetone, cis-β-ocimene, z-ocimene, limonene, epoxyocimene	Essential oil	NADH oxidase and, NO synthase measures, TNF-α mRNA expression in LPS stimulated macrophages using real time PCR	[103]
T. erecta L.	Leaves	Xanthophylls, lutein, carotenoids α-and β-carotene, lycopene, and retinoids	Chloroform, methanol, and ether extracts	Acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats	[104]
Tanacetum					
T. argenteum (Lam.) Willd.	Plant parts	Sesquiterpene lactones (Parthenolide) and pyrethrins	n-Hexane, ethyl acetate, and methanolic extracts	iNOS and NF-κB inhibition tests on RAW264.7 and HeLa cells	[105]
T. vulgare L.[a]	–	Myrtenol	Essential oils	Paw edema and articular incapacitation	[106]
Tanacetum spp.	Aerial parts	Parthenolide	Chloroform and metanol : water extracts	Wound-healing activity/inhibition of acetic acid-induced increase in capillary permeability	[107]
Taraxacum					
Taraxacum spp.[a]	Leaves and roots	Sesquiterpenes, saponins, flavonoids, and sugars, terpenes (mainly lupeol, taraxasterol and luteolin)	Extracts	Influences certain inflammatory mediators in Leukocytes (*in vitro*). Inhibits the production of inflammatory cytokines in rats, mice. Anti- inflammatory activity in disease in humans (*in vivo*).	[108]
Tithonia					
T. diversifolia (Hemsl.) A. Gray[f]	Leaves	Chlorogenic acids and sesquiterpene lactones, flavonoids	Extract of leaf washing, infusion and polar extract	Carrageenan-induced edema and Croton-oil-induced ear edema and assessment of neutrophil migration	[109]
T. diversifolia (Hemsl.) A. Gray	Leaves	Terpenoids, sesquiterpene lactones, dicafeoylquinic acid derivatives, flavonoids	Tagitinin A, C, and F	Inhibition of the production of ILs and TNF-α in culture of neutrophils induced by LPS	[110]
Tragopogon					
T. graminifolius DC.	Aerial Parts	Luteolin, vitexin, isovitexin, vicentin-1,2 and orientin, phenolic compounds	Eucerine cream containing ethanolic extract (5–10 %)	Heat-induced wound healing test	[111]
Tripleurospermum					
T. parviflorum (Willd.) Pobed. and *T. tenuifolium* (Kit.) Freyn ex Freyn	Aerial parts	Linoleic acid and palmitic acid (oil)	*n*-Hex, ethyl acetate, MeOH and aqueous extracts	Carrageenan-, and serotonin-induced hind paw edema and acetic acid-induced increase in capillary permeability models	[112]
Tussilago					
T. farfara L.	Leaves	Sesquiterpenoids	CH_2Cl_2 and MeOH extracts, CH_2Cl_2 extract without chlorophyll, MeOH extract, and detannified methanol extract	PPARs activation and on NF-κB Inhibition, LPS- or TNF-α-induced downregulation of interleukine-8 (IL-8) and E-selectin mRNA	[113]

cont.

▶ **Table 1** *Continued*

Species name by genus	Plant part used/starting material	Markers	Extract type/ Pharmaceutical form/ Isolated Substance	Experimental condition or assay carried out	Ref
Vernonia					
V. condensata Baker	Leaves	Dicafeoylquinic acid, apigenin, luteolin, chlorogenic acid	Fraction in ethyl acetate from ethanolic extract	Inhibition of cytokines and NO and TNF-α in RAW 264.7 cells induced by LPS (10 e 20 µg/mL)	[114]
V. polyanthes Less.[f]	Branches	di-O- (E) -cafeoylquinic acid, luteolin, quercetin, protocatechinic acid, quercetin-3-O-β-glucoside, apigenin, and isohamnetin	Ethanolic extract and fraction in ethyl acetate, derived from partitioning	Ear edema induced by Croton oil, arachidonic acid, and phenol	[115]
V. scorpioides (Lam.) Pers.	Leaves and flowers	Flavonoids, steroids, and polysaccharides	Ethanolic extract of leaves and flowers	Acute and chronic ear edema	[116]
Xanthium					
X. spinosum L.	Roots	Ziniolide (12,8-guaianolide sesquiterpene lactone)	MeOH and n-hexane, $CHCl_3$, and CHCl3/ MeOH (9 : 1) extracts, hydroalcoholic and n-hexane fractions, ziniolide	Determination of 5-LOX, COX-1, 12-, and 15-LOX activities. Determination of the activation of the NF-κB	[117]
X. strumarium L.	Aerial parts	Caffeic acid, reversatrol	Methanolic extract	LPS treated macrophages and an HCl/EtOH-induced mouse model of gastritis	[118]

The anti-inflammatory activity (*in vivo*) was evaluated, in most cases, in different edema models, or in specific models such as: [a] arthritis/gout; [b] anti-asthmatic; [c] wound healing; [d] inflammatory pain; [e] anti-inflammatory and antihemorrhage; [f] anti-edematogenic. The anti-inflammatory potential was evaluated, *in vitro*, through the effects on some inflammatory mediators such as NF-κB factor: nuclear factor-kappa B; LPS: lipo-polysaccharides; NO: nitric oxide; IL: interleukins; PGE2: prostaglandin-E2; TNF-α: tumor necrosis factor alpha; COX: cyclooxygenase; LOX: lipoxygenase



▶ **Fig. 2** Compositae species with anti-inflammatory activity with greater technological.

axillaris, Lychnophora spp., *Solidago chilensis,* and *Tithonia diversifolia*) (▶ **Fig. 2**).

Achillea millefolium

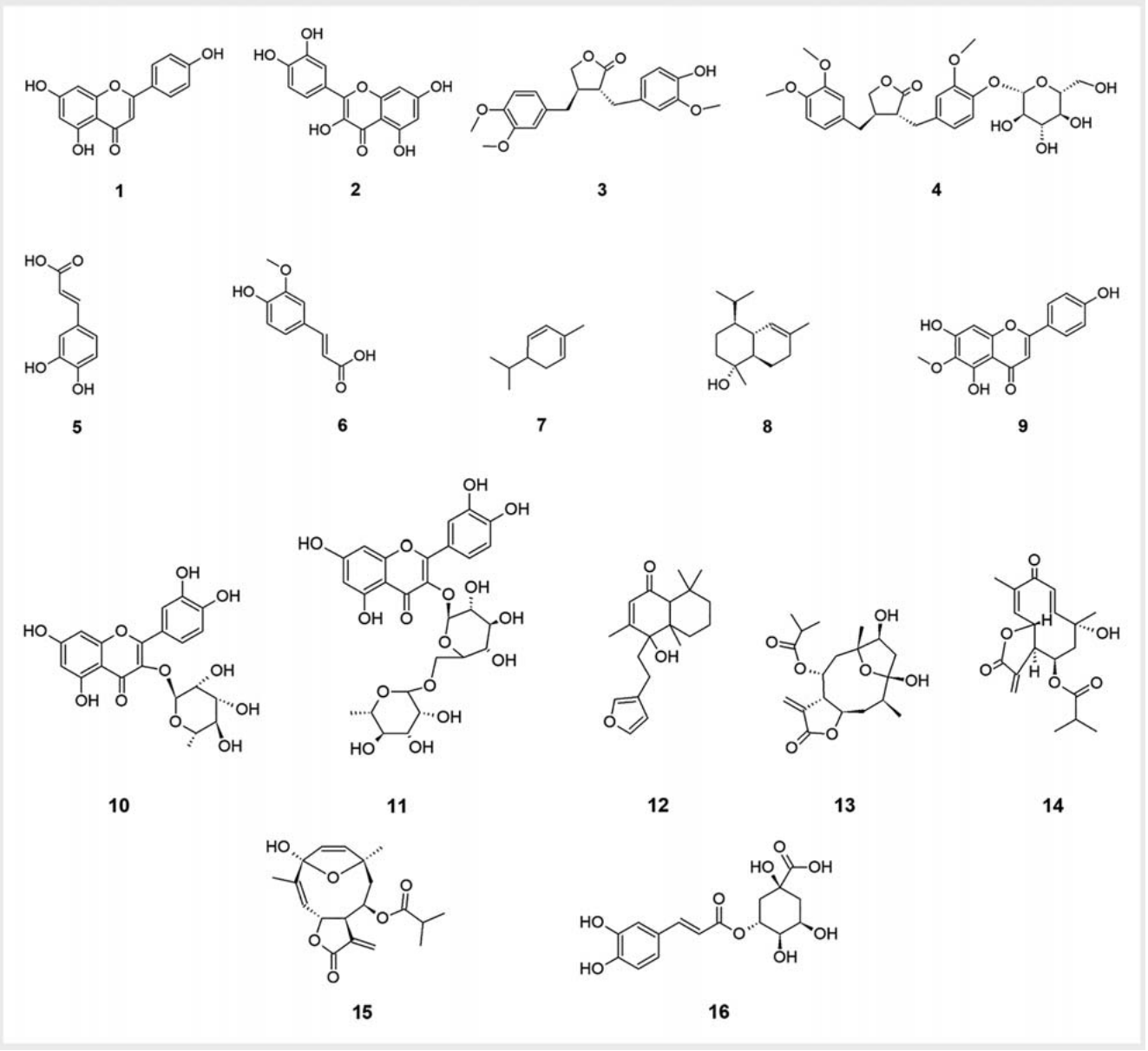
A. millefolium, popularly known as yarrow, is considered one of the most widely used medicinal plants in the world. Yarrow has been used for thousands of years to heal wounds and cure infectious diseases. The literature describes it as an anti-hemorrhagic and anti-inflammatory, and it is also used for digestive and respiratory problems. It is still referred to as a panacea [119]. It appears in official Brazilian compendia, as in the FFFB and its Supplement, for internal use, through the oral administration of infused or percolated and tincture from its aerial parts, with anti-inflammatory activity, among others [9, 120].

Tadic et al. [19] demonstrated the anti-inflammatory potential of *A. millefolium* extracts in an irritated human skin model. They attributed the topical anti-inflammatory action to its composition, which includes luteolin and its glycosidic derivatives, apigenin and its derivatives glycosides, and phenolic acids, such as caffeic and chlorogenic acids. Some metabolite structures found in the main species are shown in ▶ **Fig. 3**.

According to Bessada et al. [121], the major components found in *A. millefollium* are flavonoids, such as apigenin (1) and quercetin (2), and phenolic acids, such as caffeoylquinic acid. The phytochemical profile of *A. millefolium* also presents relevant contents of organic acids (oxalic, quinic, and citric), fatty acids (linoleic, palmitic, among others), and tocopherols (especially γ-tocopherol).

Arctium lappa

A. lappa is popularly known as "burdock" and is used in folk medicine as a diuretic, depurative, digestive stimulant, and anti-inflammatory. It has been used therapeutically for years in Europe, North America, and Asia [122], being on the list of phytotherapeutic monographs for traditional use in the European communi-



▶ **Fig. 3** Structures isolated from some Compositae species.

ty [123]. In Brazil, burdock has been indicated for internal use through its decoction and tincture based on its roots as antidyspeptic, diuretic, and anti-inflammatory, as well as for urinary disorders and inappetence. In addition, scientific studies have proven its anti-ulcerogenic, antioxidant, antiallergic, and anti-inflammatory properties by different models of *in vivo* activity. De Almeida et al. [25] investigated the effects of a fraction enriched in onopordopicrin, a sesquiterpene lactone, using a model of colitis induced by 2,4,6-trinitrobenzenesulfonic acid, to study and elucidate the involved mechanisms. The animals treated with the enriched fraction had a significant reduction in the inflammation parameters evaluated, such as myeloperoxidase (MPO) activity, TNF-α levels, edema, as well as morphological changes associated with increased mucus secretion. The decrease in neutrophil infiltration and cytokine levels was also detected. In addition, COX-2 expression decreased in the animals treated with the enriched fraction, confirming its popular use for inflammatory bowel diseases.

The main components isolated from this species are tannins, arctigenin (3), arctiin (4), beta-eudesmol, caffeic acid (5), chlorogenic acid, inulin, trachelogenin, 4-sitosterol-β-D-glucopyranoside, lappaol, and diarctigenin [122].

Artemisia spp.

The genus *Artemisia* comprises 481 species with accepted nomenclatures [124]. These include the species *A. herba-alba, A. judaica*, and *A. pallens*, with scientific evidence of anti-inflammatory activity or potential through *in vivo* and *in vitro* tests, respectively, that classify it as an important species with technological potential.

A. herba-alba, known in Egypt as "Sheh", is a well-known medicinal plant used in traditional Middle Eastern medicine to treat various diseases. This species is rich in flavonoids like hispidulin and cirsilineol, with anti-inflammatory action attributed to these components. Jaleel et al. [29] evaluated the anti-inflammatory activity of *A. herba-alba* through the reduction of carrageenan-induced paw edema, using ethanolic extract of its aerial parts.

A. pallens is a medicinal aromatic species native to Southern India, and the chemical composition of its oils has been described by some researchers. Pharmacological activities include, among others, antipyretic, analgesic, antidiabetic, antimicrobial, antioxidant, and anti-inflammatory. To prove the anti-inflammatory activity of *A. pallens*, Honmore et al. [31] evaluated the inhibition of NO production, *in vivo*, among other biochemical and molecular parameters in a nephrotic model and acetaminophen-induced hepatotoxicity in rats, where methanolic extract of its aerial parts presented good results. Analyzes reported by quantitative structure activity relationship (QSAR) demonstrated the presence of sesquiterpenolactones in *A. pallens*, which are indicated as responsible for the hepatoprotective action.

Like other Artemisias, *A. judaica* is also found in several traditional preparations to treat inflammation and other infections caused by fungi, bacteria, and viruses, being a widely used species in Jordanian folk medicine. Abu-Darwish et al. [30] demonstrated anti-inflammatory potential of its oil by *in vitro* NO inhibition assay in LPS-induced macrophages cultured, where the oil significantly inhibited their production. Among the major constituents found in the oil composition, the monoterpenes were prominent, in addition to piperitone, camphor, and ethyl cinnamate.

Baccharis spp.

Baccharis is an important genus of the Compositae family and comprises approximately 400 species, where about 120 occur in southern and southeastern Brazil. Several of its species are used in folk medicine as an antibiotic, antiseptic, and for wound healing. In South America, it is widely used to treat inflammation, headaches, diabetes, and hepatobiliary disorders. *Baccharis* spp. basically contains diterpenoids, triterpenoids, flavonoids, and chromenes [34].

Alberto et al. [33] demonstrated the anti-inflammatory potential of *Baccharis incarum* and *Baccharis boliviensis*. An immunoassay technique was employed to evaluate the percentage of inhibition of PGE2 production by inhibition of COX-1 and COX-2 by ethanolic extracts of its aerial parts, where *B. incarum* presented better results. Their chemical compositions showed high concentrations of phenolic compounds, among them flavone and flavanone.

Zalewski et al. [34] investigated the anti-inflammatory activity of dichloromethane (CH_2Cl_2) and ethyl acetate (AcOEt) fractions as well as isolated substances from ethanolic extract of *B. uncinella*. By the phospholipase A2-induced paw edema method of previously incubated and not incubated *Crotalus durissus terrificus* with the isolated fractions and substances or carrageenan, the capacity of *Baccharis uncinella* to reduce edema was determined. Chromatographic and spectroscopic methods were used to determine the presence of non-glycosylated flavonoids and triterpenes in the CH_2Cl_2 fraction (oleanolic and ursolic acids and pectolinaringenin) and the presence of phenolic derivatives in the AcOEt fraction, caffeic, and ferulic acids (6), identified as responsible for the anti-inflammatory action of the fractions.

Nogueira et al. [35] also identified the anti-inflammatory activity of *Baccharis trimera* through the reduction of paw edema induced by carrageenan, when using aqueous extract and aqueous and ethanolic fractions, in which all presented significant results. The chemical composition of the species is mostly flavonoids but also includes tannins, saponins, alkaloids, and isoprenoids. The FFFB and its supplement also present this species as infusions and tincture for internal use as antidyspeptic [9, 120].

Bidens pilosa

Bidens pilosa, popularly known as Beggar-ticks, is a native species to South America and found in most tropical and subtropical countries, as well as in some regions of Europe [125, 126].

Several studies have described the popular use of the species, including jaundice, malaria, inflammatory processes, asthma, and wound healing. Polyacetylenes and flavonoids (including chalcones and auronas) are among its chemical constituents [126].

One of the main uses found for Beggar-ticks was to treat intestinal mucositis caused by chemotherapeutic treatment of certain patients. De Ávila et al. [37] proposed a glycolic extract formulation of *B. pilosa* incorporated in polaxamer gel to treat mucositis in mice induced by 5-fluoruoracil (5-FU). In these experiments, the animals were treated by gavage with the mucoadhesive product for 6 d, while on the fourth and the sixth d, they were treated with 5-FU. On the seventh d, the animals were euthanized for histomorphometric analysis. As expected, animals treated only with 5-FU showed marked weight loss, reduction of intestinal villi, edema, inflammatory infiltrates, and intestinal vacuolization. On the other hand, the animals treated with the *B. pilosa*-based formulation attenuated the clinical and pathological changes, protecting the intestinal cells from cell death, regulating lipoperoxidation, and inflammatory infiltration.

The same research group subsequently developed and patented a mucoadhesive formulation called FITOPROT, containing *B. pilosa* and other extracts with action against 5-FU induced cellular toxicity using an *in vitro* model of oral mucositis, where the FITOPROT-treated cells demonstrated a decrease in the pro-cytokine levels (IL-1β, IL-6 and IL-8) among other actions, which were responsible for the restoration of cellular capacity [38].

Chromolaena odorata

Chromolaena odorata, also called *Eupatorium odoratum*, has been popularly used as a poultice to stop bleeding or as an anti-inflammatory. Studies have demonstrated the presence of essential oils, alkaloids, and flavonoids [44].

Hanh et al. [44] demonstrated the anti-inflammatory potential of *C. odorata* through the inhibition of NO and NF-κB in culture of macrophages stimulated by LPS against isolated substances. The organic fraction (CH_2Cl_2) of the partition of the methanolic extract in water from its aerial parts was chromatographed. Six fatty acids were identified: (S)-coriolic acid, (S)-crocylic methyl ester, (S)-15,16-didehydroxychoriolic acid, (S)-15,16-didehydroxychoriolic acid methyl ester, linoleamide, linolenamide, where the latter was more effective at inhibiting NO production when incubated with the stimulated cell culture. Other nonconclusive studies

demonstrate the modulating activity of *C. odorata* in COX [127]. Tran et al. [45] studied dichloromethane extract of *C. odorata* leaves and demonstrated the inhibition of NF-κB using TNF-α stimulated cells.

Echinacea purpurea

Echinacea purpurea, also known popularly as echinacea, is a species originally from the United States and has been used for centuries by Native Americans for combating various diseases [48]. This species appears in the list of monographs of traditional phytotherapy use of the European Medicines Agency (EMA), and it is in the MFFB for internal use to combat cold symptoms. Its main constituents are phenylpropanoids, polysaccharides, and sesquiterpenes [8].

Nyalambisa et al. [48] demonstrated the anti-inflammatory activity of the essential oil of its roots by the reduction of paw edema in mice. They also elucidated its chemical composition as mainly germacrene D, naphthalene, caryophyllene oxide, α-phellandrene (7), and α-cadinol (8).

Heterotheca subaxillaris

Heterotheca subaxillaris subsp. *latifolia*, widely distributed in the northwest and central regions of Argentina, is locally known as "camphor" due to its aromatic odor. In Mexico, it is used as an infusion of the entire plant to relieve menstrual pain. To study the possible relation of popular use with anti-inflammatory activity, Gorzalczany et al. [67] evaluated petroleum ether, dichloromethane, and methanol extracts from its aerial parts in carrageenan-induced paw edema model and 12-O-tetradecanoylforbol acetate-induced ear edema in mice. Dichloromethane extract produced significant activity in the ear test, reducing edema by 91%. Bioguided fractionation found the presence of some major flavonoids: santin, pectolinaringenine, 3,6-dimethoxy-5,7,4-trihydroxyflavone, and hispidulin (9) in the active fractions.

Lychnophora spp.

Species of the genus *Lychnophora* are popularly known as Brazilian arnicas and native to the Brazilian savanna (Cerrado) [127]. Rich in sesquiterpene lactones, they are widely used in folk medicine as anti-inflammatory, for rheumatism, insect bites, among others.

De Souza et al. [75] and Ugoline et al. [73] evaluated *Lychnophora trichocarpa* and *Lychnophora passerina,* respectively, and observed their anti-inflammatory, anti-arthritis (due to the accumulation of uric acid in the joints), antihyperuricemic, and anti-edematogenic effects in reduction of paw edema induced by monosodium crystal urate or carrageenan.

De Souza et al. [75] evaluated the antihyperuricemic activity of the ethanolic extract, the ethyl acetate fraction, and substances isolated from the aerial parts of *L. trichocarpa* through diminution of urate levels caused by uricase and xanthine oxidase inhibition in the liver of hyperuricemic mice stimulated with potassium oxonate.

Ethanolic extract and ethyl acetate fraction significantly reduced urate levels, and the extract also inhibited the enzyme xanthine oxidase. The isolated substances–luteolin, apigenin, lupeol, lychnopholide, and eremantholide C–demonstrated antihyperuricemic effect. Luteolin also had the inhibitory effect of xanthine oxidase, but the other substances did not. In extracts, the ethyl acetate fraction and the substances lupeol, sitosterol, lychnopholide, eremantholide, luteolin, and apigenin were also able to reduce paw edema induced by monosodium urate crystals. These results demonstrated that both extract and some isolated substances are promising agents in the treatment of gouty arthritis because they have antihyperuricemic and anti-inflammatory effects.

Likewise, Ugoline et al. [73] demonstrated the antigouty, anti-inflammatory, and anti-arthritis activities for both the ethanol extract of *Lychnophora passerina* (collected in different seasons of the year) and for its main isolated substance, sesquiterpene lactone goyazensolide, through inhibition of the hepatic xanthine oxidase enzyme and by inhibition of carrageenan-induced paw edema. Although goyazensolide levels showed small variations depending on seasonality, the pharmacological effects were maintained, suggesting the participation of other substances in the antihyperuricemic and anti-inflammatory effects. The extracts of the plants collected in the summer, autumn, and spring had a greater hyperuricemic effect.

Capelari-Oliveira et al. [72] also studied the *L. passerina* species. They demonstrated the anti-inflammatory action of the ethanolic extract as well as methanol and ethyl acetate fractions of its aerial parts through the inhibition of NO, decrease of TNF-α levels, and induction of IL-10 in LPS-induced macrophages. The anti-edematogenic activity of the species was also confirmed when they incorporated ethanolic extract of their aerial parts in lanolin-vaseline base and successfully reduced paw edema in mice, similar to diclofenac gel.

Hebeda et al. [74] also demonstrated the chlorogenic acid action of *Lychnophora salicifolia* on the viability, locomotion, and adherence of neutrophils, as a participation in the inflammation mechanisms. Although chlorogenic acid did not decrease the levels of inflammatory mediators, levels of adhesion molecules in neutrophils culture stimulated by LPS form diminished, which may explain the anti-inflammatory effect of the species.

Solidago chilensis

Solidago chilensis is native to Chile, and predominant in South America, mainly in the South and Southeast regions of Brazil, where it is known as "arnica brasileira" [128, 129]. This species is very common in fields, along roadsides, and in abandoned crops. It has been widely used as an unofficial substitute for *Arnica montana* by the population as well as public and private companies [13] due to similar anti-inflammatory properties [130].

In Chile, this species is used to treat gastric and intestinal ulcers, and in other South American countries to treat secretions of the upper respiratory tract and as an anti-inflammatory [131]. In Brazilian popular medicine, *S. chilensis* is used as a diuretic, analgesic, and anti-inflammatory, in the treatment of burns, rheumatic diseases, among others. [128, 130].

Several references have pointed to anti-inflammatory activity through *in vivo* assays. Goulart et al. [89] demonstrated inhibition of leukocytes, neutrophils TNF-α, IL-1β, NO, among others, through the administration of aqueous extracts of their rhizomes, leaves, and inflorescences in a pleurisy model in mice. Similar results were obtained by Liz et al. and Gastaldo et al. [90, 92] when they tested aqueous and hydroalcoholic extracts, respectively, by

applying open wound and air bag models in rats. Tamura et al. [91] demonstrated anti-edematogenic activity in an ear edema model both for topical and oral administration of hydroalcoholic extracts from its aerial parts, with inhibition of polymorphonuclear migration and decrease of circulating leukocytes adherence. Assini et al. [93] also demonstrated anti-inflammatory activity of aqueous extract of roots through the formalin test in mice, when they observed a decrease in the number of lymphocytes in the inflammatory phase. Only one reference was found about an *in vitro* assay, where the ethanolic ether extract of its inflorescences decreased NO production in LPS-induced macrophage culture [95]. In addition, a reference was found using a semi-solid formulation (gel-cream) in a clinical study for cases of tendinitis in the flexor and extensor tendons of the wrist and hand [94].

According to Valverde et al. [13], *S. chilensis* flavonoids, such as quercetin, quercitrin (10), rutin (11), clerodanic and labdanic diterpenes (solidagenone (12), deoxysolidagenone, solidagolactone and other solidagolactol derivatives) are also described for this species.

Tithonia diversifolia

Tithonia diversifolia, native to the southeastern plains of Mexico and Central America but currently scattered throughout the world [109], is recognized worldwide for its antiparasitic, antimicrobial, and anti-inflammatory activities, among others. *T. diversifolia*, is a major source of bioactive molecules, among them phenolic compounds and terpenes (sesquiterpene lactones), such as tagitinin, which has been widely studied for its pharmacological properties, mainly related to the NF-κB factor [110], although its action mechanism is still unknown.

To evaluate the tagitinins and their effects related to inactivation and neutrophil survival plus establish the mechanisms of inflammation, Abe et al. [110] investigated tagitinins A (13), C (14) and F (15) in purified and stimulated LPS neutrophils, where the enzymatic activity, apoptosis, and cytokinesterase secretion were determined after 18 h.

MPO activity was inhibited by tagitinin F, while apoptosis increased in the presence of tagitinin C. Tagitinins C, F, and A decreased production of IL-6, IL-8, and TNF-α. These results together demonstrated the anti-inflammatory potential of tagitinins, although tagitinin F was the only sesquiterpene lactone that decreased the secretion of neutrophil products, which consequently induced apoptosis.

Chagas-Paula et al. [109] also evaluated the anti-inflammatory and anti-edematogenic activity of *T. diversifolia*. Through the paw and ear edema assays and evaluation of neutrophil migration, these authors verified that polar extract and acetone washed leaf presented better results than nonsteroidal anti-inflammatory drugs (indomethacin) in reduction of ear edema and inhibition of neutrophil migration.

The major constituent isolated from the 3 extracts was chlorogenic acid (16), which presented better results when compared to literature reports that used the same experimental models.

Despite inhibiting neutrophil migration, infusion did not inhibit edema. Its composition similar to polar extract indicates that an antagonist is obtained by the extraction process. Thus, the polar extract presented high potential to develop an anti-inflammatory drug.

Vernonia spp.

Several species of *Vernonia* genus are used in folk medicine to treat various diseases. Recently studies have been published about these species for anti-inflammatory, antipyretic, anticancer, and antimalarial activities.

Vernonia scorpioides, popularly known as São Simão herb, is a Brazilian species that grows on poor and deforested soils all over the country and is widely used to treat different skin conditions such as lesions, irritations, ulcers, etc. To confirm the use of the species, Rauh et al. [116] evaluated the ethanolic extract of their flowers and leaves against 2 models of ear edema: acute, 12-tetracanoylphorbol acetate and arachidonic acid-induced and in a chronic model (with multiple applications of Croton oil), with evaluation of MPO inhibition. The ethanolic extract reduced dose-dependent edema in both cases, and MPO activity reduced in the acute model and in all evaluated parameters in the chronic model.

Da Silva et al. [114] also studied the anti-inflammatory potential of *Vernonia condensate*, popularly known as "Alumã". They evaluated, among other activities, the anti-inflammatory capacity of the species through inhibition of proinflammatory cytokines production in LPS-induced cells of the Raw 264.7 strain. The ethyl acetate fraction from the ethanolic extract was able to inhibit the NO, IL-6, and TNF-α production in concentrations between 10 and 20 µg/mL. Its major component is 1,5-dipheoylquinic acid, although apigenin, luteolin, and chlorogenic acid have also been isolated. Anti-inflammatory potential was attributed to the antioxidant or inhibitory capacity of pro-inflammatory cytokines.

To the *Vernonia patens* species, anti-inflammatory activity was also attributed, through the decrease of ear edema induced by the administration of 13-acetate, 12-O-tetradecanoylphorbol, after application of hexane, ethyl acetate, and methanol extracts of stems and leaves. The hexane, ethyl acetate, and methanol stem extracts obtained inhibitions of 75, 22, and 80% respectively. For the leaves, the inhibition results were 31, 57, and 50% in the same solvents respectively.

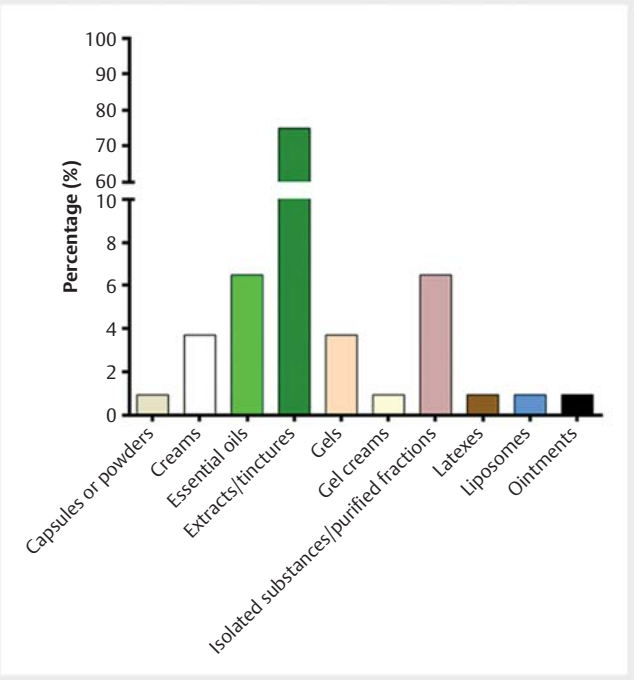
Vernonia polyanthes has been widely used in Brazil to treat inflammatory diseases and cutaneous injuries. Thus, Minateli et al. [115] proved the antiedematogenic potential of ethanolic extract and ethyl acetate fraction of *V. polyanthes* branches when topically applied to the ears of mice previously induced with Croton oil, arachidonic acid, and phenol. The anti-inflammatory response was attributed to the inhibition of inflammatory mediators, which are known to be recruited by 13-acetate-12-O-tetracanoylphorbol present in Croton oil, where the response was most evident.

Comparison between Methods Used for Pharmacological Evaluation of Anti-Inflammatory Activity or Potential in the Compositae Family

Although the *in vitro* assays present a good indication of the anti-inflammatory potential, *in vivo* assays are still the most used. De-

▶ **Table 2** *In vitro* and *in vivo* methods of the anti-inflammatory evaluation used in research with the Compositae family.

Assays	
In vitro	
Evaluation of inhibition of NO production in lipopolysaccharide-induced macrophages	[30]
Inhibition of COX and PGE	[33]
Leukocyte modulation and viability and production of cytokines and NO	[23]
Inhibition of NF-κB	[45]
In vivo	
Carrageenan-induced paw edema	[132]
Croton oil-induced ear edema	[132]
Peritonitis induced by lipopolysaccharide	[132]
Pleurisy induced by carrageenan	[89]
Model of induced arthritis	[65]
Model of induced asthma	[50]
Induced mucositis	[37]
Wound healing assay	[102]
Formalin test (inflammatory phase)	[93]
Psoriasis treatment (clinical trial)	[36]



▶ **Fig. 4** Percentage distribution of the pharmaceutical forms and inputs described in the references found for Compositae species with anti-inflammatory action.

spite all legal requirements, such as the ethics committee for animal testing, this type of experiment can evaluate the action mechanism of tested substances and consider all the variables of the living organism that act in the system.

No *in vitro* methods are available to evaluate certain pathological conditions; thus, different methods of evaluation were observed, and *in vivo* tests are required, especially when investigating specific anti-inflammatory activities such as arthritis and asthma.

▶ **Table 2** compiles the tests used in most of the references found. Among the *in vivo* methods of evaluation of anti-inflammatory activity, the most used were paw and ear edema. Another highly referenced model was carrageenan-induced peritonitis.

Only 1 reference presented a model of asthma as an allergic inflammatory condition, where the species *Eclipta prostrata* was decreased bronchial hyperresponsiveness [50].

A model of induced arthritis was also successful in the response of the species *Heliopsis longipes* when its hexane extract rich in espilantol was evaluated in rodents [65].

The *in vitro* methods of anti-inflammatory potential evaluation include leukocyte viability tests and effects on the release of inflammatory or pro-inflammatory mediators such as interleukins, cytokines, and TNF-α, evaluation of inhibition of NO, COX and PGE inhibition assay, and NF-κB assay [23, 30, 33, 45].

Pharmaceutical Forms or Types of Inputs Used in the Research about Anti-Inflammatory Activity or Potential of the Compositae Family

According to data extracted from ▶ **Table 1**, the raw extracts, prepared under different methods and with the different solvent types, according to the polarity of the phytochemicals of interest, were the most used inputs in the research of anti-inflammatory activity of Compositae species, followed by the isolated substances, and, in equal percentage, the semi-solid pharmaceutical forms as gels and creams. The percentage of distribution by pharmaceutical forms or other inputs found in the articles is present in ▶ **Fig. 4**, totaling 108 references contemplating these terms.

Few articles dealt with pharmaceutical forms in their experiments. De Carli et al. [100] demonstrated anti-inflammatory activity of *Sphagneticola trilobata* when testing kaurenoic acid, isolated from this species, from acetone extracts of roots, incorporated in base cream. Creams based on kaurenoic acid incorporated into Lanette® anionic bases, using concentrations of different types of skin permeation promoting agents, were evaluated by mouse ear edema, induced by Croton oil. Creams using kaurenoic acid with isopropyl myristate and soy lecithin as permeation enhancing agents had edema inhibition results similar to the positive dexamethasone control.

Kaurenoic acid activity was also evaluated in a semi-solid product containing 1% dry extract of *S. trilobata* standardized in kaurenoic acid. The use of the product reduced ear edema and in-

hibited neutrophil migration. Thus, it is an important prototype for the development of topical anti-inflammatory products [99].

Heidari et al. [111] incorporated ethanolic extract of *Tragopogon graminifolius* into Eucerin emulsifying base, where the recognized anti-inflammatory activity of the flavonoids present in the extract could have favored the healing of the wounds.

Samanta et al. [102] also proposed a silibinin gel of *Silybum marianum* 2%, a potent wound healing agent, where after 14 days of application in rats, the lesion was approximately 96% lower than the base gel (~ 87%) and the standard gel (~ 98%).

The search for more classic pharmaceutical forms, such as drug solutions, found ethanolic or aqueous extracts, among others, of *Smallanthus sonchifolius* for direct application as topical use, for example, in ear edema as described by Oliveira et al. [88]. Among the assayed extracts, the extract obtained by rinsing the leaves with acetone presented the highest percentage of ear edema inhibition (44%) when applied in mice induced by croton oil. This response was attributed to the sesquiterpenolactones present in the leaves of *S. sonchifolius*, as well as chlorogenic acid, although the former had a more pronounced effect.

However, for phytotherapy, the most traditionally used oral forms are teas and syrups, where there were few studies. In traditional Australian medicine, for example, species such as *Tussilago farfara* (leaves) are used in the form of teas to treat respiratory and cutaneous infections as well as for rheumatism and gout [113]. According to Brazilian legislation [10], medicinal teas can be registered as traditional phytotherapeutic products, provided they are produced in the form of infusion, decoction or maceration in water by the consumer, according to the FFFB [9], but few references were found that mention this form.

Conventional pharmaceutical forms are the most commonly found contemplating the anti-inflammatory activity of the Compositae family without major incremental innovations. Only 1 reference was found mentioning the liposomal form for extracts of *Arnica* sp., which presented superior anti-inflammatory potential to the non-encapsulated form [27]

Patents Targeting Products with Anti-Inflammatory Activity from Compositae Species

The search for patents in the Derwent database, in contrast to the searches in the other databases, was extended to 20 y, considering the period of patents' validity.

Although some patents fall into more than 1 IPC classification, only those with at least A61 (medical or veterinary science, hygiene), A61K (preparations for medical, dental, or hygienic purposes) or A61P (therapeutic medicinal preparations) were evaluated.

Not all the patents described the part of the plant used, indicating that the whole plant, or simply the plant, had been used. When the patents described the markers of the species used by the class of secondary metabolites, this information is indicated in ▶ **Table 3**. Some patents referenced the mechanism of action, where many times the species or isolated substances acted on the eicosanoid cascade.

As in the research in scientific databases, when the keyword Compositae was searched many more references were found than when the anti-inflammatory activity of the family was searched; however, this information was used as a beacon for our findings.

When the terms Compositae and anti-inflammatory activity were combined (27), a small number of patents was found compared to the same research done for articles, dissertations, and theses, which indicates the low exploitation of this research for industrial pharmaceutical market products.

Taking into consideration that this family has many records of medicinal activity, including the anti-inflammatory activity as described in the literature, and based in their traditional use, the development of their products is necessary. ▶ **Table 3** presents the data found in Derwent database for the search of patents involving Compositae species with anti-inflammatory activity and their products.

Patent research for pharmaceutical forms found a low number of registrations, as can be seen in ▶ **Fig. 1**. When patents are explored, their developments can extend and transform other pharmaceutical forms, as can be observed in ▶ **Table 3**.

One of the patents found in this search involving the terms Compositae and anti-inflammatory activity was first deposited in the United States and Australia by Koganov, where different numbers of registries occurred because filings were made along different years or using different depositors, but performed by the same inventor. Thus, Koganov initially filed in 2003 [149] the patent in the records US2003175235-A1; US7442391-B2; and AU2017202660-A1. Subsequently, beginning in 2009, Akzo Nobel started to register the same patent exclusively [150] and to maintain it in the following years, with the last filing made in 2014 [153]. It is a composition based on membrane fractions obtained from cellular juice extracted from the biomass from the fresh plants of different families, including Compositae, where *Calendula officinalis* is the representative of this group. This membrane fraction presents antiproteolytic activity, inhibits cell growth activity, can be used as a skin anti-inflammatory, incorporated in the form of hydrophilic cream for topical use, and presents as a mechanism of action the inhibition of neutrophil elastase, trypsin, and gelatinase B. This same composition was deposited under the cosmetic aspect, therefore addressing other classifications in the IPC.

Another patent found with this combination of keywords was filed in Europe and France approaching the use of the leaf extract of lettuces, such as the species *Lactuca sativa*, rich in polyphenolic compounds, with anti-inflammatory activity, which can be incorporated into creams, gels, balms, oils, and other pharmaceutical forms for topical use and incorporated into internal use pharmaceutical forms, such as capsules, tablets, syrups, etc. It was found in some of those combinations of terms [134].

One of the records found presented a patent covering species from 3 different families, among them *Bidens pilosa,* for the formation of a phytomixture to treat inflammatory conditions of the skin [166], which inhibits 5-LOX as an anti-inflammatory mechanism of action.

While using such terms, a Japanese patent was found to prevent and treat inflammation as dermatitis using *Matricaria* pref-

▶ **Table 3** List of patents found in Derwent database involving process development or products of Compositae species with anti-inflammatory activity.

Patent Number	Country of deposit	Species	Part(s) of the plant(s) used	Process/Product	Scientific Marker	Reference/ Inventor
EP3331541-A4; US2018221425-A1	Europe, United States	*Calendula* sp. *Achillea millefolium* L. *Helichrysum* sp.	–	Infuse, tincture	–	[133]
EP3042662-A1; FR3031458-A1	Europe France	*Lactuca sativa* subsp. *capitata* (L.) Schübl. & G. Martens, *Lactuca sativa* subsp. *crispa* (L.) Schübl. & G. Martens or *Lactuca sativa* subsp. *longifolia* (Lam.) Alef, among other lettuce species of other families	Leaves	Extract in form of gel, milk, cream, lotion, emulsion, oil, balm or ointment, or oral in the form of tablets, capsules, ampoules, syrups, or drops	Polyphenolic compounds (caffeoyl tartaric acid, caffeic acid, chlorogenic acid, chicoric acid)	[134]
FR3019041-B1	France	*Centaurea* sp.	Seeds	Processes of extraction The composition is in form of cream, gel, lotion, milk, etc., comprising active agent in encapsulated form, like microspheres, liposomes, nanoparticles, nanocapsules, etc.	–	[135]
BR102015024304-A2	Brazil	*Baccharis glaziovii* Baker	Leaves and flowers	Extract prepared in galenic liquid, semi-solid solutions, suspensions, emulsions, aerosol, powders, capsules, pills and tablet forms	–	[136]
ES2533200-B1; US2016213724-A1; EP3052112-A1	Spain, United States, Europe	*Calendula officinalis* L.	Whole Plant	Aqueous extract for topical composition utilization	–	[137]
US2017319467-A1; EP3250295-A2	United States, Europe	*Baeriopsis* sp.	Plant cells (*in vitro* culture), or ground material containing phytoalexin	Cosmetic composition, for topical application	phytoalexin	[138]
AU2008322737-A1; CA2705642-A1; EP2219655-A2; CN101878033-A; US2011008476-A1; JP2011503161-W; IN201001473-P2	Australia, Canada, Europe, China, United States, Japan, India	*Helianthus* sp. or *Helianthus annus* L.	–	Glucan derived from yeast derived from Compositae	Glucan	[139]
MX2009001657-A1	Mexico	*Matricaria chamomilla* L.	Plant	Extract	–	[140]
KR2014088504-A	Republic of Korea	*A. spathulifolius* Maxim., *C. morifolium* Ramat., *C. boreale* (Makino) Makino, *C. indicum* L., *C. drummondii* (D.Don) Torr. & A. Gray and *R. laciniata* L.	Plant	Extracts	–	[141]

cont.

▶ **Table 3** *Continued*

Patent Number	Country of deposit	Species	Part(s) of the plant(s) used	Process/Product	Scientific Marker	Reference/ Inventor
FR2807319-A1; AU200146631-A	France, Australia	*Arnica montana* L., *Tanacetum parthenium* (L.) Sch. Bip. or *Cnicus benedicticus* L.	Plant	Extract	Sesquiterpene lactone (helenalin, dihydrohelenalin, partheno-lide, cnicin) and their derivatives	[142]
BR200409179-A; KR2005121239-A; AU2004228021-B2; JP4769184-B2; CN1798568-B; KR1151322-B1; US9622964-B2; EP1631304-A4	Australia, Europe, Brazil, Republic of Korea, Japan, China, United States	*Achyrocline* sp., *Anaphalis* sp., *Cotula* sp., *Gnaphalium* sp., *Helichrysum* sp., *Centaurea* sp., *Eupatorium* sp., *Baccharis* sp.	Stems, roots, root barks seeds, rhizomes, flowers etc.	Pharmaceutical, dermatological or cosmetic formulation, solution, cream, lotion, ointment, gel or emulsion, liquid, paste, a soap or powder.	Gallate, acetate, cinnamoyl, hydroxyl-cinnamoyl esters, trihydroxybenzoyl esters or caffeoyl esters	[143]
JP2012158528-A	Japan	*Silybum marianum* (L.) Gaertn.	Seeds	Extracts	–	[144]
JP2017124984-A	Japan	*Cynara scolymus* L., *Centaurea cyanus* L.; *Silybum marianum* (L.) Gaertn.; *Helianthus annuus* L., *Tanacetum vulgare* L., *Tanacetum parthenium* (L.) Sch. Bip. or *Achillea millefolium* L., *Cichorium intybu* L.	Whole Plants	Internal composition or topical formulation	–	[145]
EP2436757-A2; KR1212032-B1; RU2011152866-A	Republic of Korea, Europe, Russian Federation	*Chrysanthemum morifolium* Ramat, *Artemisia* sp.	Stem cell	Capsule	–	[146]
KR1537847-B1	Republic of Korea	*Aster spathulifolius* Maxm., *Chrysanthemum morifolium* Ramat, *C. boreale* (Makimo) Makino, *C. indicum* L., *Coreopsis drummondii* (D. Don) Torr & A. Gray and *Rudbeckia laciniata* L.	Whole plant	Extracts	–	[147]
AU2003239875-A1	Australia	*Calendula officinalis* L.	Whole plant	Cell juice as formulation ingredient for topical application	–	[148]
US2003175235-A1; US7442391-B2; AU2017202660-A1	United States, Australia	*Calendula officinalis* L., dentre outras espécies de outras famílias	Flowers	Cellular juice extracted from plant biomass for topical application	–	[149]
US8101212-B2	United States	–	Whole plant	Cosmetic composition comprises a membrane fraction derived from cell juice extracted from fresh plant biomass	–	[150]
US8663712-B2	United States	*Calendula officinalis* L.	Flowers	Cosmetic formulation for topical application	–	[151]
US8734861-B2	United States	*Calendula officinalis* L.	Flowers	Cosmetic composition comprises a membrane fraction derived from cell juice extracted from fresh plant biomass	–	[152]

cont.

▶ **Table 3** *Continued*

Patent Number	Country of deposit	Species	Part(s) of the plant(s) used	Process/Product	Scientific Marker	Reference/ Inventor
US2014295004-A1	United States	*Calendula officinalis* L., among other species of other families	Flowers	Hydrophilics cream base, lotion base, surfactant base and cream base, or hydrophobic surfactant base	–	[153]
TW201521755-A; CA2900517-A1; KR2015127252-A; CN105007988-A; US2016000851-A1; SG11201506444-A1; EP2969024-A1; IN201507664-P1; AR95439-A1; JP2016516679-W; MX2015011475-A1; BR112015020178-A2; SG10201707422-A1; AU2014231030-B2; ID201703645-A	Australia, Taiwan, Canada, Republic of Korea, China, United States, Singapore, Europe, India, Argentina, Japan, Mexico, Brazil	*Calendula officinalis*, *Tanacetum parthenium* (L.) Sch. Bip., *Matricaria chamomilla* L.	Whole plant	Cream, dressing, gel, lotion, ointment, liquid, spray applicator, and their combinations, or wash-off product (liquid hand soap, bar soap, body wash, shampoo)	polyphenols	[154]
JP6246993-B2	Japan	*Anthemis* sp.; *Arctium lappa* L.	Whole plant	–	–	[155]
DE102017002005-A1	Germany	*Solidago* sp.; *Artemisia* sp.	Whole plants	Cream, paste, ointment and gel, liquid form, as emulsion, lotion, solution, tincture, extract, tea and dispersion or mixture and gel, solid form, emulsion, lotion, aerosol or spray	–	[156]
US2001024664-A1; EP1401461-A2; JP2004532811-W; AU2002230985-A8	United States, Australia, Europe, Japan	*Artemisia* sp., *Aster* sp., *Blumea* sp., *Cichorium* sp., *Crassocephalum* sp., *Silybum* sp., *Sonchus* sp. or *Taraxacum* sp.	Plant	Extracts	–	[157]
US2004185122-A1	United States	*Artemisia* spp., *Aster* spp., *Blumea* spp., *Cichorium* spp., *Crassocephalum* spp., *Silybum* spp., *Sonchus* spp., and *Taraxacum* spp.	Whole plants	Extracts	–	[158]
JP2014129253-A	Japan	*Matricaria*, preferably *M. chamomilla* L.	Whole plants	Tablet, pill, granule, capsule, emulsion, liquid agent, gel, syrup, or solid state composition	–	[159]
US2008311230-A1	United States	*Artemisia absinthium* L., *Artemisia annua* L., *Artemisia vulgaris* L., *Artemisia capillaris* Thunb.	–	–	–	[160]
MX2013004050A	Mexico	*Matricaria chamomilla* L. in association	Whole Plant	Liquid or solid form		[161]

cont.

▶ **Table 3** *Continued*

Patent Number	Country of deposit	Species	Part(s) of the plant(s) used	Process/Product	Scientific Marker	Reference/ Inventor
JP2018062468-A	Japan	Compositae family plant	Flower	Extract of flowers in the form of paste, gel. Powder, granules, tablet, capsule, chewable tablet, stick or syrup is administered by oral route	–	[162]
JP6255154-B2	Japan	*Arctium lappa* L.	Whole Plant	External preparation	glycyrrhetic acid	[163]
CN107753666-A	China	*Chrysantemum* sp.	Flowers	Liquid	–	[164]
US6749871-B2	United States	*Wyethia amplexicaulis* (Nutt.) Nutt., *Balsamorhiza sagittata* (Pursh) Nutt., *Helianthella uniflora* (Nutt.) Torr. & A. Gray, or *Tragopogon dubius* Scop.	Part of plant	Capsules	–	[165]
DE102015102020-A9; CA2976583-A1; EP3256142-A1; US2018036360-A1; CN107889461-A	Germany, Canada, Europe, United States, China	*B. alba* (L.) DC., *B.pilosa* L., among other species of other families	Whole plants	The extracts can be in a form of solution, dispersion, suspension, emulsion, tincture, syrup, juice, tea, tablet, powder, coated tablet, granule, lyophilisate, capsule, aerosol, spray, lotion or cream	Flavonoids, saponins, iridoids, polyphenols, polysaccharides, glycosylate, terpenes, monoterpenes sesquiterpenlactone, proazulene, carotenoids, vitamins A, B, C, D and E, amino acids, and/or minerals	[166]

erably, *M. chamomilla* [159]. The latter 2 were also identified in the search combining terms of Compositae and anti-inflammatory activity for pharmaceutical syrup.

No records were found using only the words "Compositae" and "pharmaceutical preparations". The same thing happened when we searched forms such as solutions or medical suspensions, as well as for compresses. Some patents consulted presented the terms in the abstract extension, such as solution and suspension, for example. However, when we exchanged these dosage forms for capsules or tablets, the same record already mentioned, based on *Lactuca sativa* [134] was found.

When the investigations involved the terms anti-inflammatory activity and semisolid, no records were observed. When we replaced the term semisolid with the pharmaceutical cream form, the number of patents for this combination increased; however, all the records found had also been observed in previous searches without involving a pharmaceutical form, but only by anti-inflammatory activity. For the gel form, the searches presented a patent that was not yet found, also from the researcher Koganov, using species like *Calendula officinalis, Tanacetum parthenium,* and *Matricaria chamomilla*, in composition, to reduce the inflammatory state of the skin [154] with an anti-inflammatory mechanism of action that inhibited of IL-8 and IL-1 secretion.

Using the terms Compositae and nanoformulations, only 1 record was found for the nanoparticle term from the researcher Bernard et al. [135]. They patented the process of obtaining extract of the species *Centaurea* sp. under the registration number FR3019041-B1 to treat and prevent inflammatory disorders of the skin and hair, among others.

In addition to these patents found in Derwent, in isolated research, we found the patent on the development of a mucoadhesive product from the *Bidens pilosa* species deposited both in Brazil and in the World Intellectual Property Organization (WIPO), which is a self-funding agency of the United Nations, with 192 member states: "Anti-inflammatory, proliferative, protective and mucoadhesive, soluble and stable pharmaceutical compositions; its use in the treatment of mucositis and the obtaining process; basic pharmaceutical composition for the preparation of the pharmaceutical compositions and process of obtaining", under registers of WO 2016065442A1 [167] and BR 10 2013 003316 A2 [168]. Articles related to this patent were also found in the bibliographic references.

Some relevant results were found by searching only for the words Compositae and the pharmaceutical forms, without involving the anti-inflammatory activity. For example, in the search for Compositae and tablets, although no results were found when contemplating the anti-inflammatory activity, a Brazilian patent appeared that described the use of the species *Baccharis glaziovii* to treat ulcers in humans and animals [136], which is an inflammatory condition. Another patent was found with these terms based on species from Compositae such as *Wyethia amplexicaulis, Balsamorhiza sagittata, Helianthella uniflora*, or *Tragopogon dubius* for cystitis [165].

▶ **Table 4** presents in the world context, the number of patents per country. For patents on products of the Compositae family with anti-inflammatory activity, Brazil, Canada, and Germany are at the same level in the ranking (3).

▶ **Table 4** Patents deposited by countries on the Compositae family, in the Derwent Innovation Index database in conjunction with isolated research.

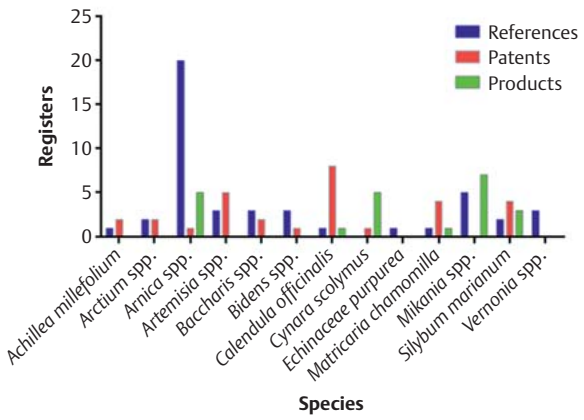
Countries (Codes)	Number of Patents
Argentina (AR)	1
Australia (AU)	7
Brazil (BR)	3
Canada (CA)	3
China (CN)	5
European Patent Organization (EP)	10
France (FR)	3
Germany (DE)	2
India (IN)	2
Japan (JP)	10
Mexico (MX)	3
Republic of Korea (KR)	5
Russian Federation (RU)	1
Singapore (SG)	1
Spain (ES)	1
Taiwan (TW)	1
United States (US)	16

As expected, the world ranking is led by the United States (16), followed by Japan and European Union (10), and Australia (7). Although these powers present expressive numbers of patents, the results are still very low when compared to the research done, demonstrating the urgent need to encourage development of technological products.

Technology Products on the Market from Compositae to Anti-inflammatory Activity

Even though countless studies evaluate the potential anti-inflammatory activity of herbal medicines from the biodiversity and companies' websites advertise producing herbal products, where descriptions of several of them were found, when consulting regulatory agencies such as the Brazilian Health Regulatory Agency (ANVISA), many products that had been registered were found to be currently in a situation of expired or canceled registration. Products based on arnica (*Arnica montana*), chamomile (*Matricaria chamomilla*), calendula (*Calendula officinalis*), guaco (*Mikania glomerata*), baccharis (*Baccharis trimera* (Less.) DC.), globe artichoke (*Cynara scolymus*), among others have been canceled [169].

Among the 23 artichoke products registered with ANVISA, only 5 have valid records, in pharmaceutical forms such as tablets and capsules. Arnica included 16 products contemplating the use of its popular synonymy; however, only 5 have valid records (ointments, gels and solutions), most of which came from *Arnica montana*, an exogenous species. The only 2 products found with its substitute *S. chilensis* were master products (cream and gel) produced by the Health Department of Rio de Janeiro [170]. Re-



▶ **Fig. 5** Comparison between bibliographic references, patents, and products of certain species from Compositae with anti-inflammatory activity: *Arctium* spp. (*A. lappa* and *A. minus*); *Arnica* spp. (*Arnica montana, Solidago chilensis, Tithonia diversifolia, Lychnophora passerina, Chromolaena odorata*); *Artemisia* spp. (*A. herba-alba, A. judaica* and *A. pallus*); *Baccharis* spp. (*B. incarum, B. boliviensis, B. trimera, B. uncinella*); *Bidens* spp. (*B. tripartita* and *B. pilosa*); *Mikania* spp. (*M. cordata, M. glomerata, M. lindleyana, M. micantha); Vernonia* spp. (*V. condensata, V. polyanthes, V. scorpioides*).

garding the guaco (*Mikania glomerata*), despite having already presented 9 records, currently 7 are valid (syrups and solutions) (*i.e,* only 2 have expired). The milk thistle (*Silybum marianum*) presented only 3 valid products such as tablets.

In addition to these, for the products based on other known anti-inflammatory species, the result of the search terms of products is closer to the number of patents and products. In spite of these numbers, several products were found being commercialized and even advertised on companies' websites, although without certainty about their proper registration.

Survey of the Technological Potential of the Compositae Family with Anti-inflammatory Activity or Potential

▶ **Fig. 5** presents a survey of the Compositae species most cited in the literature, based on the number of references that prove their action, patents requested or registered involving extraction and isolation processes or product development from these species, and commercialized technological products originated from them, whose records are valid at ANVISA. This comparison sought to diagnose commercial use for the Compositae family, based on the scientific background or portfolio, drawing attention to the technological potential of some species of this family, which have been neglected by the phytotherapeutic market.

As a result, it was possible to observe that, in terms of citations in bibliographical references, Arnica, in all its synonyms appeared in a greater number (20), which did not reflect in terms of patents (1) and its products (5) marketed. The species *Calendula officinalis* presented the largest number of patents (8); however, just 1 article proving its pharmacological activity was found and 1 officially registered product on the market. The species *Mikania* sp. presented a similar number of bibliographical citations about its activity (5) in relation to the products found in the market (7) but did not present any patent request. The *Baccharis* and *Bidens pilosa* species presented some scientific references and patent applications; however, no product was detected on the market. The species *Matricaria chamomilla* was also a surprise, since it only presented 1 reference, 1 patent application, and 1 product; nevertheless, this species is mentioned in the MFFB and FFFB [8,9] for external use as anti-inflammatory. This may be due to the traditional knowledge about these species, which are treated as medicinal herbs by traditional communities and are widely used in folk medicine.

Despite the ethnopharmacological studies that empirically prove the use of these and other Compositae species as anti-inflammatory, and the advent of herbal medicine in Brazil in the 2000 s, still more than 10 y after the main legislation and public policies that recognize and implement this therapy [171,172], many species have not been commercialized by the pharmaceutical industries.

The species *Cynara scolymus* may be an isolated fact. Although only 1 scientific article referred to its anti-inflammatory activity and no patent application, 5 products are on the market with this species. However, the commercial appeal in most of these products refers to their action for liver problems.

Conclusion

This is a consistent study that presents safe results to guide and to direct future research on anti-inflammatory agents and the technologies added to the products related to the Compositae family.

Our findings revealed that drug solutions, gels, suspensions, syrups, compresses, and creams, with minor citations, were the most cited terms in the reference survey, although creams appeared as the most cited one in the patents database. Otherwise, nanoparticles presented just 1 citation, demonstrating few studies on specific nanoformulations and that the conventional pharmaceutical forms are still the most studied ones.

These data were ratified when we found extracts, tinctures, and essential oils as the most cited inputs, followed by purified fractions and isolated substances, creams, and gels and in a minor proportion, the liposomes.

Different pharmacological assays have been performed to demonstrate the anti-inflammatory activity or potential of the Compositae family, and many of them have had their popular use ratified on a scientific basis. However, the data confirmed the predominance of certain species from Compositae family for anti-inflammatory activity, such as arnica, guaco, calendula, chamomile, artichoke, as well as also by their traditional use, being described in official compendia such as FFFB and MFFB.

Arnica spp. was the species most cited in the references while *Calendula officinalis* presented a higher number of patents. Syrups based on *Mikania* spp. were the most products found at the ANVISA website.

Although many species having scientifically proven anti-inflammatory action, no feasible products have been developed with quality control, stability, and pharmacological assays, and especially with registration with the healthcare authority in Brazil, ANVISA.

The United States holds the largest number of patents involving the searched terms, followed by the European Union and Japan, and Australia; however, the numbers were still small.

The low number of patents and products may be related to the survey having been performed in only a single database; nevertheless, it evidences minimal effort for technological development and commercial exploitation of this family. These data reinforce the need to develop skills and fill technological gaps to foment research and innovation in biodiversity products.

This study updates search results and presents products that have a valid registration today.

Contributors' Statement

Conception and design of the work: D. C. D. X. P. Lopes, E. Ricci-Junior, S. S. Valverde; data collection: D. C. D. X. P. Lopes; analysis and interpretation of the data: D. C. D. X. P. Lopes, T. Oliveira, A. L. Viçosa, S. S. Valverde, E. Ricci-Junior; drafting the manuscript: D. C. D. X. P. Lopes; critical revision of the manuscript: D. C. D. X. P. Lopes, T. Oliveira, A. L. Viçosa, S. S. Valverde, E. Ricci-Junior.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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