**Ethnopharmacology, phytochemistry and biological
activity of *Erodium* species: A review**

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Abstract

Erodium spp. is a genus that can be found in all continents that has been traditionally used in folk medicine to treat many diseases such as hemorrhage, dermatological disorders, indigestion, and inflammatory diseases. Moreover, *Erodium* leaves have been used for the preparation of salads, omelets, sandwiches, sauces and soups, among other food products. The objective of this review was to show the recent and relevant studies about extraction of bioactive compounds, the phytochemical characterization, the potential biological activities and toxicological evidence reported in both *in vitro* and *in vivo* studies from *Erodium* spp. In addition, the use of *Erodium* spp. as natural compounds against the development of diseases were also showed. This review highlights the traditional use of *Erodium* species in several countries as a therapeutic agent to treat several diseases (such as constipation, dermatological disorders, diabetes, indigestion, urinary inflammations, and as carminative agent), the factors influencing the extraction of bioactive compounds (mainly species and solvent composition on phenolic compounds) and phytochemical profile (presence of essential oils and alkaloids), the scientific evidence about its anti-inflammatory, antimicrobial (against both spoilage and pathogenic microorganisms), antiviral and other health-related activities (anti-protozoal and anti-viral activity) as well as the toxicological evidence. *Erodium* spp. is a relevant source of compounds with antioxidant, antimicrobial, and biological activity, which support its potential exploration in pharmacological and food area. Major efforts are necessary to advance the knowledge about *Erodium* genus regarding the relation between traditional use and scientific evidence, optimization of extraction conditions, the influence on biological mechanisms at animal and clinical levels, and bioaccessibility and bioavailability of bioactive compounds.

Keywords: Traditional use; phenolic compounds; antimicrobial; antiviral; anti-inflammatory; *Erodium*

1. Introduction

Erodium genus belongs to the *Geraniaceae* family and is composed of a group of more than 70 species (Fiz, Vargas, Alarcón, & Aldasoro, 2006), with some of them being represented in **Figure 1**, “*E. cicutarium*, *E. glaucophyllum* and *E. malacoides*” are among the common species of this genus. These flowering plants are composed by a five-parted long with bill-like capsules (containing the seeds) and usually are characterized by a perpendicular position of the pit on the mericarp and the absence of staminodes and rims on mericarp bristles (Aldasoro, Aedo, & Navarro, 2000; Anonymous, 1998). *Erodium* spp. are present on all continents, wherein the Mediterranean region is the location where most of the species (more than 60 species) can be found (Fiz et al., 2006). The most likely origin of *Erodium* genus in Asia (Fiz-Palacios, Vargas, Vila, Papadopoulos, & Aldasoro, 2010).

The use of *Erodium* spp. in natural medicine is a common practice in many cultures (Akaydin, Şimşek, Arituluk, & Yeşilada, 2013; Dutt, Bhagat, & Pandita, 2015). This cultural heritage has been passed through generations long before the modern practices of medicine took place and the current strategies to develop drugs were established. Preserving this knowledge is the first step to understand the preventive and therapeutic potential of using medicinal plants against diseases. In addition, the conservation of such valuable knowledge and species, not only for medicinal purposes but also for the environment as a whole, is a major issue nowadays (Chen et al., 2016; Gairola, Shariff, Bhatt, & Kala, 2010). Moreover, the exploration of bioactive components from *Erodium* genus as a potential new source of bioactive compounds has been receiving attention over the last decades (Bremner et al., 2009; Esmaeili et al., 2009; Penkov et al., 2014; Wang et al., 2016).

On the other hand, the most common species is *E. cicutarium*, with edible leaves, can be consumed raw or cooked. It can be also used with butter to prepare potherb, mainly if boiled in herbed and salted water and topped with lemon juice. Moreover, the leaves can be also added to omelets, sandwiches, sauces, and soups (Duke, 2001).

This review presents recent and relevant studies about extraction of bioactive compounds (mainly, phenolic compounds), the phytochemical characterization, the potential biological activities (anti-inflammatory, antimicrobial and antiviral activities, among others) and toxicological evidence reported in both *in vitro* and *in vivo* studies from *Erodium* spp. Future perspectives about the use as natural compounds against the development of diseases are also presented.

2. Traditional use of *Erodium* species to treat diseases

The traditional use of *Erodium* species for health purposes was reported on 18 articles (**Table 1**). The data obtained from these studies revealed that species, part of plant, preparation prior to use/ingestion, and therapeutic use are different among and within countries. The surveys carried out in Turkey revealed that several *Erodium* species are commonly used to treat indigestion, urinary inflammations, diabetes, constipation, eczemas, as carminative agent (Bulut & Tuzlaci, 2013; Cakilcioglu & Turkoglu, 2010; Dalar, Mukemre, Unal, & Ozgokce, 2018; Sargin, 2015; Sargin, Selvi, & Büyükcengiz, 2015). In addition, the population of Aydıncık district in Turkey used *E. cedrorum* to treat gastro-intestinal diseases (Sargin et al., 2015) and the population of Malatya province ingest *E. cicutarium* as tonic (Tetik, Civelek, & Cakilcioglu, 2013).

In Iraq (Al-douri, 2003) and Jordan (Al-Qura'n, 2008), local populations reported the use of *E. cicutarium* to treat hemorrhage and anasarca (generalized edema). While *E. gruinum* was reported to treat infections on urinary system and prostate in Iran (Mosaddegh, Naghibi, Moazzeni, Pirani, & Esmaeili, 2012), the aerial parts of *E. tibetanum* was reported to treat indigestion, wounds, and burns and as hair tonic in India (Angmo, Adhikari, & Rawat, 2012; Kala, 2010).

Treating circulatory system diseases, skin problems, hair loss, and burns were reported as therapeutic uses for *E. malacoides* among members of the Khattak tribe of Chonthra Karak in Pakistan (Rehman, Mashwani, Khan, Ullah, & Chaudhary, 2015). Differently, the

population of Baotou (inner Mongolia) used *E. stephanianum* to treat enteritis and diarrhea (Li et al., 2012).

In the case of South American countries, the use of *E. cicutarium* was associated to treatment of dermatological diseases among the Mapuche indigenous population, located in South American countries as Argentine and Chile (Estomba, Ladio, & Lozada, 2006; Molares & Ladio, 2009). In Ecuador, the consumption of *E. cicutarium* and *E. moschatum* was used to treat respiratory illness (Tene et al., 2007). Moreover, the infusion of *E. cicutarium* was used in cases of influenza, heart problems, and stomach pain, *E. moschatum* was reported to treat cough, pneumonia, and menstruation pain, whereas in Northern Peru, *E. cicutarium* was related to treatment of low and high blood pressure (Bussmann & Sharon, 2006). Finally, the use of *E. cicutarium* in the Canary Islands (Spain) was applied to treat wounds and hemorrhages (Darias, Bravo, Barquin, Herrera, & Fraile, 1986).

The diversity of species, locations, therapeutic uses and preparing strategies indicates the richness of knowledge about these species and their importance for local population to manage diseases. It is important highlighting that the characterization of the main information regarding the location, species, part of plant, preparation before use/consumption, and illness (particularly from the studies carried in the last decade) are necessary to preserve and improve the current knowledge of *Erodium* species.

3. Extraction of bioactive compounds and phytochemical profile

The literature about the phytochemical composition of *Erodium* spp. has been increasing in the last decades, particularly about the characterization and quantification of phenolic compounds, which have been associated with antioxidant activity *in vitro* (Table 2). An interesting approach to improve the valorization of this class of secondary *Erodium* species metabolites is by exploring the impact of extraction conditions (ratio mass/solvent, solvent composition, time of extraction and temperature) on total phenolic content and antioxidant activity of extracts (Alali et al., 2007; Jaradat, Almasri, Zaid, & Othman, 2018).

Among the several variables involved in the extraction process, the mass/solvent ratio used to extract phenolic compounds from *Erodium* spp. ranged from 1:5 to 1:40. The time required for extraction was usually 24 h (Table 2). Interestingly, a study carried out the extraction during only 10 min (Alali et al., 2007), while another experiment extracted phenolic compounds for 72 h (Jaradat et al., 2018). These two variables are considered relevant factors in the extraction of phenolic compounds from plant tissues (Azmir et al., 2013). However, the in-depth evaluation of both factors was not reported in the scientific literature. Furthermore, the differences on experimental conditions among studies does not allow direct comparison among studies.

Regarding the solvent composition used in the extraction procedure, pure solvents are the most common ones, such as benzene, chloroform, ethanol, ethyl acetate, ethyl ether, methanol, petroleum ether, and water. In fact, the solvent selection seems to influence the phenolic content and antioxidant activity of final extracts (Roselló-Soto, Martí-Quijal, et al., 2019). For instance, Alali et al. (2007) observed that total phenolic content and diphenyl picryl hydrazyl (DPPH) radical scavenge activity of aqueous and methanolic *E. bryoniifolium* extracts were influenced by solvent composition. The authors obtained 15.1 mg gallic acid equivalents (GAE)/g dry weight (DW) for total phenolic content and 45.3 µmol Trolox Equivalent (TE)/g DW for DPPH radical scavenging activity with water as solvent. Using methanol, the total phenolic content and DPPH radical scavenge activity assays revealed averaged values of 10.8 mg EAG/g DW and 25.4 µmol TE/g DW, respectively. A similar outcome was observed by El-Hela et al. (2013) with *E. bryoniifolium* extracts, who extracted more polyphenols using water than with methanol as solvent (45.4 vs. 25.4 mg GAE/100 g, respectively). Regarding the antioxidant assay, the authors observed that DPPH radical scavenge activity was improved from 11.9 to 20.1% of BHT scavenge activity by carrying out the extraction with water rather methanol. A possible explanation for the difference observed in this study could be related to the affinity between antioxidant compounds and the extracting solvent (Giacometti et al., 2018). The higher phenolic content with more affinity with water than with methanol could explain the proportional increase on antioxidant

activity between these two solvents. The relationship between phenolic content and antioxidant activity was previously reported for herbs by other authors (Agregan et al., 2019; Alali et al., 2007; Lorenzo et al., 2018; Pateiro et al., 2018; Sarikurkcu, Targan, Ozer, & Tepe, 2017).

Other studies also revealed that petroleum ether, ethyl acetate and chloroform may be interesting solvents to extract antioxidant compounds (Bouaziz, Dhouib, Loukil, Boukhris, & Sayadi, 2009; Sroka, Rzadkowska-Bodalska, & Mazol, 1994). However, the authors stated that the extraction of other antioxidant compounds of natural occurrence (not identified in this study) were dependent of solvent-solute interaction, which can explain the antioxidant potential obtained with these solvents. Overall, some studies reported that phenolic content of *Erodium* spp. varied from 15.1 mg GAE/g DW to 248 mg GAE/g DW (Table 2). In addition, the evaluation of antioxidant activity revealed that *Erodium* spp. extracts can scavenge free radicals (both lipophilic and hydrophilic) and inhibit lipid oxidation in emulsion systems (Sarikurkcu et al., 2017; Sroka et al., 1994). In addition, Sarikurkcu et al. (2017) evaluated the antioxidant potential of *E. cicutarium* aqueous methanolic extract. The authors observed that extracted compounds could prevent β -carotene bleaching up to 74% and also displayed antioxidant potential of 129.1, 90.6, 130.4, 89.6, and 6.7 mg Trolox equivalents/g extract for ABTS, DPPH, cupric ion reducing antioxidant capacity (CUPRAC), ferric reducing antioxidant power (FRAP) and nitric oxide assays, respectively.

The time required to carry out the extraction is also an important factor to be considered in the recovery of antioxidant compounds (Giacometti et al., 2018; Li et al., 2018). This is a factor that has shown conflicting results among studies. After 10 min, antioxidant compounds can be successfully extracted from *Erodium* spp. matrix (Alali et al., 2007) but extracts obtained after 24 (Hamza, Emna, & Yeddes, 2018; Sarikurkcu et al., 2017) and even 72 h (Jaradat et al., 2018) also display high antioxidant activity. The optimization of extraction time should receive more attention in order to establish time-efficient protocols and characterize the influence of this variable on the recovery of antioxidant compounds.

Similarly, the temperature is another factor poorly explored in the extraction of bioactive compounds from *Erodium* genus. Several studies extracted bioactive compounds at room temperature (**Table 2**). To the best of our knowledge, the optimization of extraction protocol aiming for extracts rich on polyphenols and elevated antioxidant activity, was not carried out on the studies with *Erodium* genus. It is worth mentioning that temperature can influence the extraction of bioactive compounds from vegetable tissues by facilitating their release from the plant matrix (Lorenzo et al., 2018) but can also induce their degradation, which can reduce the antioxidant activity of the extracts (Tan, Tan, & Ho, 2013). However, the direct comparison among studies cannot be done due to different experimental conditions. More effort is necessary to optimize these factors in order to establish more efficient extraction conditions for further experiments with *Erodium* spp.

Although phenolic compounds are the main compounds associated with antioxidant activity among natural plant extracts, the identification and quantification of *Erodium* spp. phenolic compounds were investigated by a limited number of studies. Fecka and Cisowski, (2002) indicated the presence of geraniin, dehydrogeraniin, corilagin, and isoquercitrin in *Erodium* spp. by planar chromatography, but the contents of the individual phenolic compounds of *E. ciconium*, *E. cicutarium*, *E. manescavi*, and *E. pelargoniiiflorum* were not determined. In a further study, Fecka and Cisowski (2005) elucidated the structure of the main phenolic compounds of *E. cicutarium*: gallic acid, protocatechuic acid, 3-O-galloylshikimic acid, 3-O-(6"-O-galloyl)- β -D-galactopyranoside, corilagin, dihydrogeraniin (dehydrogeraniin), geraniin, hyperin, isoquercitrin, methyl gallate 3-O- β -D-glucopyranoside, and rutin by the combination of two analytical methods, mass spectrometry and nuclear magnetic resonance.

In another study, Fecka, Kowalczyk and Cisowski (2001) indicated the presence of gallic and ellagic acids among all nine *Erodium* species. However, the predominant phenolic compounds varied among species. For instance, ellagic acid was the main phenolic compound present in *E. petraeum*, *E. botrys*, and *E. gruinum* (80.3, 17.49, and 6.81 mg/g, respectively), while brevifolin was the predominant compound in *E. cicutarium* and *E.*

manescavi (50.74 and 25.95 mg/g, respectively). Additionally, gallic acid methyl ester was absent in *E. ciconium*, *E. gruinum*, *E. pelargoniiflorum* and protocatechuic acid was not detected in *E. botrys*.

An interesting outcome was reported by Hamza et al. (2018) who evaluated the phenolic composition and antioxidant activity of *E. glaucophyllum*, *E. guttatum*, and *E. hirtum*. The results indicated that the highest polyphenolic content was obtained from *E. glaucophyllum* methanolic extract (50:50, methanol:water, v/v) in comparison to *E. hirtum* and *E. guttatum* methanolic extracts (248.1, 180.0, and 124.0 mg GAE/g dry residue, respectively). However, the results for antioxidant activity by reducing power (RP), DPPH, and inhibition of linoleic acid peroxidation assays indicated that *E. guttatum* extract contained the most potent antioxidant compounds in comparison to *E. glaucophyllum* and *E. hirtum* (**Table 2**). This scenario suggests that phenolic compounds were implicated in the antioxidant activity of *Erodium* spp. but the phenolic composition and antioxidant activity are influenced by species.

It is also relevant mentioning that *Erodium* spp. also contains essential oils. To this date, most of the studies used conventional methods of essential oil extraction. However, future research may explore the effects of emerging extraction technologies, including microwave-assisted hydrodistillation (Gavahian, Farahnaky, Farhoosh, Javidnia, & Shahidi, 2015), by supercritical CO₂ (Roselló-Soto, Barba, et al., 2019), ohmic-assisted hydrodistillation (Gavahian, Lee, & Chu, 2018), and ohmic accelerated steam distillation (OASD) (Gavahian & Chu, 2018), on the chemical composition and biological effects of the *Erodium* spp. extract. Lis-Balchin and Hart (1994) extracted methyl eugenol, geraniol, citronellol, isomenthone, and linalool (10.6, 16.7, 15.4, 11.2, and 3.1% of total oil, respectively) from leaves of *E. cicutarium*. In addition, Rodrigo et al. (2010) indicated the presence of tannins and flavonoids in the leaves of *E. cicutarium*.

The presence of alkaloids in *Erodium* spp. has not been fully confirmed. On the one hand, the presence of alkaloids was indicated for *E. cicutarium*, *E. acaule*, *E. pelargonijlorum* (Lis-Balchin & Guittonneau, 1995) and *E. laciniatum* (Al-Shamma &

Mitscher, 1979). On the other hand, negative results were reported for *E. cicutarium* (Rodrigo et al., 2010), *E. ciconium*, *E. glaucophyllum* (Al-Shamma & Mitscher, 1979), and *E. rupestre* (Viladomat, Codina, Llabres, & Bastida, 1986), which suggests that alkaloid synthesis could be influenced by *Erodium* species and environmental factors.

Over the last years, encapsulation has attracted a significant interest from food, pharmaceutical, nutraceutical, and cosmetic industries, due to its wide application in the design of functional products such as foods and/or food ingredients (Gómez et al., 2018). Encapsulation is a technology to stabilize and control the release, of high-added value compounds extracted from fruits, vegetables or waste materials (i.e. antioxidant bioactive compounds, vitamins, acidulants, flavors, aromas, enzymes, microbial cells and others) into products (Munekata et al., 2017). However, In the science literature, there are not information about the encapsulation of *Erodium* spp.

Overall, *Erodium* spp. is a rich source of natural antioxidants, phenolic compounds, and other secondary plant metabolites. Particularly for phenolic composition and antioxidant potential, the information in scientific literature indicated that *Erodium* species and solvent composition are relevant factors to be considered. It is important to highlight that the phytochemical composition of *Erodium* spp. demands more attention in order to explore polyphenols, antioxidant compounds, essential oils, and other compounds.

4. Anti-inflammatory activity

The inflammatory response is a complex protective and organized actions that activate the vascular tissues in order to prevent undesirable immune activation and the consequent response. This response can be stimulated by damaged cells, toxic compounds, and pathogens. Phenolic compounds can prevent this inflammatory response due to the modulation of enzymes responsible for the generation of prostanoids and leukotrienes (phospholipase A2, cyclooxygenases and lipoxygenases) (Azab, Nassar, & Azab, 2016; Rathee et al., 2009).

The preventive activity of phenolic compounds against inflammation also reduces the release of histamine (by the catalyzed generation of leukotrienes by lipoxygenase), which may reduce the allergy response in late stages. Likewise, the inhibition of phosphodiesterase by flavonoids has been suggested to reduce the production of cytokines and inhibit the inflammatory process of cardiovascular diseases. Another mechanism where flavonoids can inhibit inflammatory response is the preventive activity over I κ B kinase, which inactivates nuclear factor-Kappa B (NF- κ B) and its translocation to the nucleus and eventually prevents inflammatory response (Azab et al., 2016; Rathee et al., 2009). Phenolic compounds can also influence other mediators of inflammatory response such as inhibiting the biosynthesis of eicosanoids, degranulation of neutrophils, reduce the formation of free radical species and consequent lower attraction of inflammatory mediators, reducing the activity of cyclooxygenase and lipoxygenase; and preventing the activation of immune cells (Ambriz-Pérez, Leyva-López, Gutierrez-Grijalva, & Heredia, 2016; Nijveldt et al., 2001).

Some compounds involved in the inhibition of the inflammatory response have been identified in extracts of *Erodium* spp. For instance, Gohar, Lahloub and Niwa (2003) identified geraniin in *E. glaucophyllum* extracts, a compound that has been associated in the prevention of inflammation and asthma, due to its ability to inhibit the formation of 5-lipoxygenase, which is responsible to transform fatty acids into leukotrienes that in turn promote the inflammatory signal (Kimura, Okuda, Okuda, & Arichi, 1986). However, the evaluation of anti-inflammatory activity displayed contrasting results for both *in vitro* and *in vivo* experiments in addition to the currently limited number of studies carried out up to now.

Bremner et al. (2009) evaluated the anti-inflammatory activity of *E. malacoides* (using pure ethyl acetate as solvent) and other medicinal plants extracts (using either pure ethyl acetate, methanol, petroleum ether, or 80% aqueous ethanol solution as solvent) from South-Eastern Spain by means of NF- κ B and cytokine pathway. The anti-inflammatory assay indicated that *E. malacoides* extract had lower activity (data not shown by the authors) than other extracts (inhibitory activity <60%). Due to the relatively low inflammatory

potential in comparison to other herbs and plants, no further characterization was carried out for *E. malacoides* extract by the authors.

In a similar way, the study carried out by Penkov et al. (2014) evaluated the effect of *Geranium Sanguineum*, *Astragalus Glycyphyllos*, *Erodium Cicutarium*, and *Vincetoxicum officinalis* (as a single combined extract with equal amount of each plant) to inhibit inflammatory response and promote analgesic effect in male “Wistar” rats with paw edema induced by carrageenan. The combined extract displayed a limited analgesic effect that was observed after repeated intake, particularly for 2 g/kg body weight dose, against thermal irritation (55 °C for up to 30 s), which were comparable to the results obtained for rats treated with sodium metamizole. However, it is not possible to indicate which component induced the inflammatory effect or the occurrence of synergism.

Therefore, the anti-inflammatory potential of the *Erodium* spp. extracts demand more research due to the lack of definitive results obtained from the current limited number of *in vitro* and *in vivo* studies. It is also of great importance to determine which specific compounds and mechanisms are influenced by *Erodium* spp. active components. Particularly for studies dedicated to exploring phenolic composition and antioxidant activity, it is recommended to declare the entire extraction protocol.

5. Antimicrobial activity

The search for natural and safe alternatives to prevent microbial growth is a hot research topic among food researchers, processors and healthy regulatory agencies. Part of the concern has been attributed to the cumulative antibiotic resistance of pathogenic bacteria, particularly due to medicinal reasons and the prevailing outbreaks worldwide (Davies & Davies, 2010). In addition to public strategies to reduce the excessive, and sometimes unnecessary, use of antibiotics, phenolic compounds stand out as a promising alternative (Lee, Cho, Jeong, & Lee, 2013).

Over the last decades, several studies have been dedicated to clarifying the mechanisms involved in the inhibitory activity of phenolic compounds against bacteria. Two

mechanisms have been proposed to explain it: i) cell aggregation, and ii) direct antimicrobial activity (Cushnie & Lamb, 2011). In the case of cell aggregation, the access to oxygen (particularly for aerobic bacteria) and nutrients are limited, while the direct antimicrobial effect can involve the aggregation of enzymes that consequently inhibit some vital processes, such as membrane synthesis. Some promising work demonstrated the antibacterial potential of *Erodium* spp. and established a relationship with flavonoids, particularly with Geraniin (Bouaziz et al., 2009; Gohar Lahloub, & Niwa, 2003).

Rempe et al. (2017) reviewed the effects of phenolic compounds on essential bacterial functions, including the inhibitory activity over DNA gyrase and helicase (some of the enzymes responsible for DNA replication), type III secretion (a structure that facilitates invasion and also protects bacteria), multi-drug efflux pump (a protective mechanism that expels antibiotics and other harmful compounds), and endogenous enzymes (dehydratase and protein kinase, for instance).

Erodium spp. has also been reported to induce microbial death. In fact, several studies have evaluated the antimicrobial potential of *Erodium* spp. extracts, with the results varying among *Erodium* species and extracting solvents, as represented in **Table 3**. For instance, Stojanović-Radić et al. (2010) explored the impact of the essential oil obtained from three *Erodium* species (*E. absinthoide*, *E. ciconium*, and *E. cicutarium*) against the development of Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and Gram-positive bacteria *Bacillus subtilis*, *Clostridium perfringens*, and *Staphylococcus aureus*. Interestingly, the authors tested the essential oil extracted from *E. absinthoide*, *E. ciconium*, and *E. cicutarium* against two strains of *Escherichia coli* and obtained different MIC values. While the MIC values for *E. ciconium* essential oil was in the range 2.5-5 mg/mL, the essential oils of *E. absinthoide* and *E. cicutarium* achieved MIC values of 0.156-5 and 0.625-2.5 mg/mL, respectively. Particularly for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* the lowest MIC values were observed in the *E. cicutarium* and *E. absinthoides* oil, respectively (1.25 mg/mL). Differently, for *Bacillus subtilis* and *Staphylococcus aureus* the lowest MIC values were achieved by *E. ciconium* oil (0.156 and

2.5-5 mg/mL, respectively). However, the evaluation of Nystatin (a known antifungal compound) antifungal activity indicated MIC values in the range 0.039-2.5 µg/mL, which indicated a lower antimicrobial activity in comparison to *Erodium* spp. extracts.

Particularly for *E. glaucophyllum*, the hydromethanolic extract (80:20, methanol:water, v/v) obtained by Bakari et al. (2018) from flowers and leaves (75 µg extract/well) inhibited the growth of *Fusarium oxysporum*, *Fusarium* spp. and *Penicillium* spp. (19-24, 9.7-10.7, and 11.2-13 mm, respectively). Moreover, the results were lower than those obtained for chloramphenicol (15 µg/well) in the same experimental conditions (20, 18, and 18 mm for *Fusarium oxysporum*, *Fusarium* spp. and *Penicillium* spp., respectively).

Interestingly, Bouaziz et al. (2009) obtained contrasting results for the antifungal activity obtained from *E. glaucophyllum* using different solvents. While the ethyl acetate extract induced between 10 and 12 mm inhibition zone, the methanolic extract did not produce the inhibition zone. Moreover, no inhibitory effect for both ethyl acetate and methanolic extract were reported by the authors against *Candida albicans*. The authors also indicated that the *E. glaucophyllum* methanolic extract had the highest flavonol concentration and antioxidant activity in comparison to ethyl acetate extract. Comparatively, the standard antibiotic polymyxine B (dissolved in ethyl acetate, concentration not indicated) achieved inhibition zones between 10 and 15 mm against the same microorganisms. Differently than reported for *E. glaucophyllum*, polymyxine B dissolved in hexane, methanol and water also inhibited the growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella enterica*, and *Bacillus subtilis*, which indicated a lower antimicrobial activity.

Likewise, the extraction with hydromethanolic (80:20, methanol:water, v/v) solvent from *E. glaucophyllum*, *E. guttatum*, and *E. hirtum* leaves induced different levels of inhibition on *E. coli*, *Enterococcus aerogenes*, *Enterococcus faecalis*, *Serratia marcescens*, and *Staphylococcus aureus* according to Hamza et al. (2018). The larger inhibition zones were obtained from the *E. glaucophyllum* extract in comparison to *E. guttatum* and *E. hirtum* regardless of tested bacteria (concentrations not indicated). However, the values obtained

from inhibition zone using the standard antibiotic streptomycin (concentration not indicated) were reported in the range of 18.1-30.2 mm.

The effect of solvent composition in the extraction and consequent activity in bacteria seems to vary for each *Erodium* species. The study performed by Nikitina et al. (2007) evaluated the effect of solvent and extract concentration on the bacteriostatic activity of *E. cicutarium*. The authors indicated similar effect for hydroethanolic (70:30, methanol:water, v/v) and aqueous extracts at 1000 µg lyophilized extract/mL on the growth of *Azotobacter* spp., *Pseudomonas* spp., *Bacillus polymyxa*, and *Bacillus subtilis* (4 out of 5, 7 out of 7, 6-8 out of 9, and 1-4 out of 11 strains, respectively). However, non-significant differences were indicated by the authors for 500 µg lyophilized extract/mL on the growth of these microorganisms. According to authors, the differences in the antimicrobial effect of aqueous and ethanolic extract could be explained by the difference in polarity of the extracted compounds (mainly phenolic compounds) and by inhibiting the activity of microbial enzymes (phenolic compounds and quinones), which consequently impair the microbial growth. Additionally, the authors obtained similar inhibition of *B. polymyxa* (7 and 3 out of 11 strains at 15.6 and 7.8 µg/mL, respectively) and *Azotobacter* spp. (3 and 1 out of 5 strains at 15.6 and 7.8 µg/mL, respectively) using 0.0066% of the standard antibiotic furacilin in comparison to *E. cicutarium* extract at both concentrations (500 and 1000 µg lyophilized extract/mL). Interestingly, the furacilin displayed higher inhibitory activity against *B. subtilis* (10 and 8 out of 11 strains at 15.6 and 7.8 µg/mL, respectively) and lower antimicrobial activity against *Pseudomonas* spp. (not inhibited at 15.6 and 7.8 µg/mL) than *E. cicutarium* extract.

Bussmann et al. (2010) compared the antimicrobial activity of *E. cicutarium* extracts with ethanol (95:5, ethanol:water, v/v) and water. In this case, the extract obtained with water achieved lower MIC values than ethanolic solvent for both *Escherichia coli* (16 mg/mL and lack of inhibitory effect, respectively) and *Staphylococcus aureus* (4 vs. 64 mg/mL, respectively). In another study, *Erodium* extracts obtained from different extraction methods (conventional vs. ultrasound-assisted extraction) and extraction solvents (aqueous and

hydroethanolic) were evaluated in microbiological media to determine their effects on *Salmonella enterica*, *Staphylococcus aureus*, *Listeria innocua*, *Bifidobacterium lactis* and *Lactobacillus casei* (Abdelkebir et al., 2019). These authors noticed that hydroethanolic extracts (conventional extraction) exhibited the highest level of inhibition on *Listeria innocua* growth rate. A similar outcome was observed for aqueous extract (conventional extraction) to reduce the growth rate of *Staphylococcus aureus*. However, non-significant inhibitory effect was observed against *Salmonella enterica* for both extracts.

The hydroethanolic *E. laciniatum* extract (50:50, methanol:water, v/v) was associated with MIC values of 6.25-12.5 mg/mL for *Staphylococcus aureus*, 12.5 mg/mL for *Shigella sonnei* and *Enterococcus faecium*, and 25 mg/mL for *Escherichia coli* and *Pseudomonas aeruginosa* (Jaradat et al., 2018). In contrast, this study also indicated that *E. laciniatum* extract did not inhibited the growth of *Enterobacter cloacae* and *Klebsiella pneumonia* (disc-variant method), whereas standards antibiotics (such as imipenem, levofloxacin, and cefotaxime) achieved values in the range of 13-40 and 12-32 mm, respectively.

The study carried out by Gohar, Lahloub and Niwa (2003) indicated that *Erodium glaucophyllum* could be explored as a source of natural antibacterial compounds. The authors identified geraniin, by means of NMR technique, as relevant antimicrobial compound against *Staphylococcus aureus* due to similar MIC value in comparison to ampicillin (3.16 vs. 3.3 mg/mL, respectively). Conversely, geraniin achieved lower MIC value than gentamycin against *Escherichia coli* (2.5 vs. 0.125 mg/mL). Finally, the experiment carried out by Quave et al. (2008) with 95% ethanol in the extracting solvent indicated a non-significant impact on *Staphylococcus aureus* growth from *E. ciconium* and MIC₅₀ value of 128 µg/mL.

In this sense, seems reasonable to consider that some *Erodium* species can be explored as potential sources of natural antifungal and antibacterial compounds, in particular *E. absinthoides*, *E. cicutarium*, and *E. glaucophyllum*. The selection of solvent is a relevant factor to improve the extraction of antimicrobial compounds from *Erodium* spp. matrix. Diethyl ether, ethyl acetate and ethanol could be considered as relevant options to achieve

high extraction yields of antimicrobial compounds. Moreover, elucidating the main compounds associated with the antibacterial potential of *Erodium* spp. deserves more attention since few studies establish this direct connection (Bouaziz et al., 2009; Gohar et al., 2003; Stojanović-Radić et al., 2010). It is also important mentioning that direct comparison cannot be extended across different studies due to differences in the experimental designs and units used to express antimicrobial activity. It is important that further antifungal studies with *Erodium* species use the same unit and carry out the same antifungal assays in order to standardize the results.

6. Antiviral activity

Diseases caused by virus impair are on a global scale. For example, an average of 2.6 million new cases of immunodeficiency virus (HIV) infections has been annually registered between 2005 and 2015. Other alarming data are the number of carriers and associated deaths: 38.8 million cases and more than 1 million deaths due to HIV virus (Wang et al., 2016). Given the persistence of viral infections, and the complexity of the mechanisms of action, the development of new antiviral compounds is essential.

Phenolic compounds, particularly flavonoids, have been related to antiviral activity since the 1940s (Tapas, Sakarkar, & Kakde, 2008; Valcheva-Kuzmanova, Russev, Bojkova, & Belcheva, 2002). To date, several researchers proposed mechanisms to explain, at least in part, the protective activity of flavonoids against virus invasion and replication (Ahmad, Kaleem, Ahmed, & Shafiq, 2015). Flavonoids have shown *in vitro* the capacity to inhibit HIV invasion by inducing the expression of CD4 and chemokine co-receptors, antagonist activity against HIV reverse transcriptase, inhibition of DNA polymerases, and setting back HIV-1 proteinase activity (Cushnie & Lamb, 2005). For this reason, the exploration of natural sources rich in flavonoids is an interesting alternative to obtain compounds with antiviral activity.

In this scenario, the antiviral potential of *E. stephanianum* extracts against HIV Type 1 (HIV-1) was observed (Ma et al., 2002), with aqueous and methanolic extracts inhibiting

HIV-1 activity at concentrations $\geq 62.5 \mu\text{g/mL}$. In another study, the impact of *E. cicutarium* aqueous and methanolic extracts on myxoviruses, herpes virus type 1, vesicular stomatitis and vaccinia virus was studied (Zielinska-Jencylik, Sypula, Budko, & Rzadkowska-Bodalska, 1987). The results indicated that both aqueous and methanolic extracts had antiviral activity against all tested virus.

Zielinska-Jencylik, Sypula, Budko and Rzadkowska-Bodalska (1988) reported antiviral activity of *E. cicutarium* methanolic extract against Newcastle disease virus and influenza A virus on mice. The production of interferon (cellular signaling molecules associated with antiviral resistance) by the intravenous injection of *E. cicutarium* methanolic extract was observed before and after the administration of Newcastle virus. However, the authors observed that in the case of influenza A virus, the inhibition of virus infection was observed when *E. cicutarium* methanolic extract was administrated 24 and 48 h after virus infection. In a similar way, the protective effect against the invasion of hepatitis A virus and murine norovirus was associated with *E. glaucophyllum* phytochemicals (Abdelkebir et al., 2019). The authors obtained extracts using ethanol or water as solvent and observed that both extracts induced a strong inhibition against hepatitis A virus and murine norovirus.

It should be noted that polyphenols (e.g. flavan-3-ols, flavonols, condensed tannins, caffeic acid, etc.) extracted from natural sources were associated with the antiviral activity. The main effect revealed by previous studies was the ability of phenolic compounds to aggregate to viral particles, which prevented their attachment to host cells (Catel-Ferreira, Tnani, Hellio, Cosette, & Lebrun, 2015; Daglia, 2012; Sokmen et al., 2005). However, more studies are necessary to support the evidence presented in these studies, particularly related to *in vitro* and animal studies. Strengthening the role of key molecules and pathways influenced by active molecules produced by *Erodium* species tissues are of great importance to clarify and indicate the use against these diseases.

7. Other health-related potential effects

The *Erodium* spp. phytochemicals have been also related to a potential activity against *Plasmodium* spp., a parasite that infects red blood cells and causes malaria. In the study carried out by Esmaeili et al. (2009), *Erodium oxyrrhynchum* methanolic extract was tested *in vitro* against two *Plasmodium falciparum* strains: K1 (chloroquine-resistant) and 3D7 (chloroquine-sensitive). The results revealed that *E. oxyrrhynchum* extract achieved low IC₅₀ values against K1 (chloroquine-resistant) and 3D7 (chloroquine-sensitive) plasmodium strains (40.3 and 13 µg/mL, respectively). In the same way, Kaiser et al. (2007) observed a potential pathway to explain the effects of *Erodium gruinum* extract (50:50, methanol:water, v/v) on *P. falciparum* viability. The authors evaluated the effects of *Erodium gruinum* extract on the activity of 2C-methyl-D-erythritol 4-phosphate synthase (IspC), an enzyme associated with malaria infection. The results of the *in vitro* test indicated that *E. gruinum* extract displayed the high capacity to inhibit IspC activity in a concentration-dependent manner from 0.2 to 5 µL extract. For instance, the activity of IspC was reduced by 16% when 5 µL of *E. gruinum* extract was used.

However, a contradictory result has also been reported by Fokialakis et al. (2007). The authors obtained *Erodium moschatum* extract with dichloromethane as the solvent and tested its potential to inhibit the development of *Leishmania promastigotes*. The results indicated that *E. moschatum* extract was not active against both D6 (chloroquine-sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum*. It is also relevant mentioning that the study also evaluated the anti-leishmanial activity of *E. moschatum* extract. Against this protozoan disease, the extract achieved IC₅₀ value of 40 µg/mL using dichloromethane as solvent. This scenario supports the hypothesis that *Erodium* species and phytochemical composition are relevant factors to consider in the study of antiprotozoal activity and may explain, to some extent, the differences observed in these studies. The inhibitory effects against *Leishmania major* was also associated with *E. gruinum* and *E. malacoides* extracts (El-On et al., 2009). Both *Erodium* species had anti-leishmanial activity against

promastigotes (IC₅₀ values of 180 and 170 µg/mL for *E. gruinum* and *E. malacoides*, respectively) and amastigotes (IC₅₀ values of 227 and 150 µg/mL for *E. gruinum* and *E. malacoides*, respectively) forms of *Leishmania major*. Moreover, the study also revealed that *E. gruinum* (lethal concentration LD₅₀ of 190 µg/mL) and *E. malacoides* (LD₅₀ of 125 µg/mL) showed anti-leishmanial activity in isolated C3H/HeJ mouse macrophages were infected with *Leishmania major*. The isolation and posterior characterization of anti-plasmodium compounds in the composition of *Erodium* species is a necessary step to clarify these contradictory results and develop strategies for its posterior extraction and utilization.

Regarding the activity against cancer development, the antiproliferative potential of *E. cicutarium* was evaluated (Rodrigo et al., 2010). The leaves of *E. cicutarium* were defatted and then subjected to the ethanolic extraction (96:4, ethanol:water, v/v). The results of the antiproliferative analysis indicated that *E. cicutarium* extract (in the range of 1-100 µg/mL) induced a slight inhibition (up to 10%) on the proliferation of Caco-2 cells.

In a recent study, *E. cicutarium* extract inhibited the activity of some enzymes, including enzymes related to Alzheimer's disease (acetyl cholinesterase and butyryl cholinesterase) and diabetes (α-amylase and α-glucosidase) (Sarikurkcu et al., 2017). The authors observed a significant reduction of the activity of acetyl cholinesterase, butyryl cholinesterase, α-amylase, and α-glucosidase. In fact, *E. cicutarium* displayed the highest inhibitory activity against the α-glucosidase activity, comparing to other medicinal plants (such as *Lepidium sativum* and *Urtica dioica*) evaluated in that study. This evidence supports, at some extent, the traditional use of *E. cicutarium* (Sargin, 2015).

8. Toxicological evidence

The evaluation of toxicity of *Erodium* species was reported by some authors (Table 4). The results obtained from *in vitro* study with *E. stephanianum* extract with water and methanol was superior to 125 µg extract/mL in MT-4 cell line (Ma et al., 2002). Similarly, the toxicological evaluation of *E. oxycanthum* methanolic extract indicated LC₅₀ value superior

to 50 µg/mL for both human breast carcinoma and Madin–Darby bovine kidney cells (Esmaeili et al., 2009). However, the experiment carried out with *E. malacoides* extract (using ethyl acetate as solvent) indicated that more than 80% of 5.1 cell line were killed (Bremner et al., 2009).

A similar contrasting outcome can be also perceived from *in vivo* experiments. The toxicological potential of *E. cicutarium* was associated with specimen tested (Bussmann et al., 2011). While the specimens AKT1171 and ACR142 of *E. cicutarium* displayed low level of toxicity (1027 and 127 µg/mL for aqueous and ethanolic extracts, respectively), the specimen KMM578 displayed high level of toxicity (4.8 and 0.06 µg/mL for aqueous and ethanolic extracts, respectively) on Brine shrimp larvae. Conversely, the *E. cicutarium* extract (using 70% ethanol as solvent) in the range of 0.001-10 g extract/kg did not induce toxicological effects on male “Wistar” rats (Penkov et al., 2014).

It is worth mentioning that a single study reported toxic effects (skin lesions associated with photosensitivity) in two adult sheep raised in Western Cape Province of South Africa after large consumption of wild *E. moschatum* (Stroebel, 2012). The examination of epidermal tissue of affected animals revealed changes related to inflammatory response and severe necrosis associated with serocellular crust. Moreover, a small trial was carried with two animals and harvested *E. moschatum* (total of 20.9 g dried *E. moschatum*/kg body weight during 5 days) from that property followed by physiological examination of skin and liver tissues. The results indicated mild skin damaged associated with photosensitivity without damage to liver tissue in a similar fashion as observed in the animals of the grazing in the camp where *E. moschatum* grew abundantly. The authors also argued that *E. moschatum* growth stage could explain the toxic effects in sheep since the symptoms were more evident when the animals grazed on young *E. moschatum*. Conversely, the farmers reported that animals grazing on adult *E. moschatum* did not develop the skin lesions.

This scenario indicates that toxic effects related to some *Erodium* specimens and growth stage require more studies in order to identify the toxic compounds, since the investigation for the phytochemicals associated with toxic effects in this *Erodium* species was not carried

out in these studies. The absence of specific focus on the evaluation of *Erodium* species in toxicologic evaluation is major obstacle to promote advances in the field, due to simple characterization of several native plant species from a single location in the studies (screening approach). Disclosing the compounds associated with toxicity in *Erodium* species is necessary to support the selection and further investigation in this genus.

9. Conclusions and future perspectives

In conclusion, the phenolic compounds are the main phytochemicals that explain the therapeutic potential of *Erodium* spp. The successful selective extraction of these compounds is a key factor to explore this genus, which also have to consider the elucidation of compounds associated with toxicological effects reported in literature. The extraction of bioactive compounds, particularly for polyphenols, deserves more attention, which could focus on time, temperature, and mass/solvent ratio. In the same line, increase the information about the isolation and characterization of essential oils could be explored in further studies to support further commercial exploration.

Promising results were reported on antimicrobial activity, particularly against spoilage and pathogenic microorganisms (e.g. *S. aureus*, *P. aeruginosa*, *E. coli*, *S. enterica*, *B. subtilis*, *C. albicans*, and *A. niger*). The potential to reduce the viability of *Plasmodium* spp. *in vitro* is also promising. However, additional studies about the biological mechanisms influenced by *Erodium* species phytochemicals and carry out more studies at animal and clinical levels are crucial to improve the exploration of this genus as natural source of bioactive compounds. Moreover, future studies should also explore the use of advanced extraction techniques and the potential use of these plant spices as a food ingredient.

On the other hand, characterizing bioaccessibility and bioavailability of *Erodium* spp. phytochemicals also deserve attention, since the effect of digestion events and the impact of gut microbiota are unknown and necessary to develop strategies and products in food and pharmacy area. Finally, further commercial exploitation of *Erodium* genus require appropriate selection of the most promising species, which demands the throughout

characterization and quantification of target compounds (with antimicrobial or anti-plasmodial activity, for instance) as well as toxic compounds in order to establish an adequate quality standard and also prevent toxic effects when applied in the elaboration of food products or as therapeutic agent.

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889 **Figure captions:**

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2890 **Figure 1.** Some of the most popular *Erodium* specie

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Figure

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Figure 1

Table 1. Ethnopharmacological use of *Erodium* species

Location or populational group	Species	Part of plant	Traditional preparation	Therapeutic use	Reference
Turkey (Ağrı Province)	<i>E. absinthoides</i>	Leaves	Decoction	Indigestion and urinary inflammations	(Dalar, Mukemre, Unal, & Ozgokce, 2018)
Turkey (Aydıncık District of Mersin)	<i>E. cedrorum</i>	Leaves	Chewing, boiling, and in meal	Dieting	(Sargin, Selvi, & Büyükcengiz, 2015)
Turkey (Bozyazı district of Mersin)	<i>E. cedrorum</i>	Aerial parts	Infusion, boiling, and in meal	Diabetes and as carminative	(Sargin, 2015)
Turkey (Sivrice province)	<i>E. cicutarium</i>	Flowers and leaves	Infusion	Constipation	(Cakilcioglu & Turkoglu, 2010)
Turkey (Malatya province)	<i>E. cicutarium</i>	Aerial parts	Infusion	Tonic	(Tetik, Civelek, & Cakilcioglu, 2013)
Turkey (Bozyazı district of Mersin)	<i>E. cicutarium</i>	Aerial parts	Infusion, boiling, and in meal	Diabetes and as carminative	(Sargin, 2015)
Turkey (Aydıncık District of Mersin)	<i>E. gruinum</i>	Leaves	Chewing	Diabetes and as carminative	(Sargin et al., 2015)
Turkey (Bozyazı district of Mersin)	<i>E. gruinum</i>	Aerial parts	Infusion, boiling, and in meal	Diabetes and as carminative	(Sargin, 2015)
Turkey (Turgutlu province)	<i>E. moschatum</i>	Aerial parts	Ashes mixed with mud	Eczema	(Bulut & Tuzlaci, 2013)
Turkey (Bozyazı district of Mersin)	<i>E. pelargonifloru m</i>	Aerial parts	Infusion, boiling, and in meal	Diabetes and as carminative	(Sargin, 2015)
Iraq	<i>E. cicutarium</i>	Whole plant	Decoction	Metrorrhagia and treatment of anasarca	(Al-douri, 2003)
Jordan	<i>E. cicutarium</i>	Not indicated	Not indicated	Stops bleeding and uterine hemorrhage	(Al-Qura'n, 2008)

Iran (Kohghiluyeh va Boyer Ahmad province)	<i>E. gruinum</i>	Root and aerial parts	Decoction	Infection of urinary system and prostate	(Mosaddegh, Naghibi, Moazzeni, Pirani, & Esmaeili, 2012)
India (Indian trans-Himalaya region)	<i>E. tibetanum</i>	Aerial parts	Not indicated	Indigestion	(Kala, 2010)
India (Western Ladakh)	<i>E. tibetanum</i>	Stem and flower	Not indicated	Wounds, burns and hair tonic	(Angmo, Adhikari, & Rawat, 2012)
Pakistan (Khattak tribe of Chonthra Karak)	<i>E. malacoides</i>	Whole plant	Dried powder and topical use	Circulatory system diseases, skin problems, hair loss, and burns	(Rehman, Mashwani, Khan, Ullah, & Chaudhary, 2015)
China (Baotou, Inner Mongolia)	<i>E. stephanianum</i>	Whole plant	Decoction	Enteritis and diarrhea	(Li et al., 2012)
Mapuche indigenous population (South America)	<i>E. cicutarium</i>	Not indicated	Not indicated	Dermatological diseases	(Estomba, Ladio, & Lozada, 2006)
Mapuche indigenous population (South America)	<i>E. cicutarium</i>	Not indicated	Not indicated	Dermatological diseases	(Molares & Ladio, 2009)
Peru (Northern region)	<i>E. cicutarium</i>	Not indicated	Not indicated	Alterations in blood pressure	(Bussmann & Sharon, 2006)
Ecuador (Loja and Zamora-Chinchi)	<i>E. cicutarium</i>	Stem and leaves	Infusion	Stomach pain, heart problems, and influenza	(Tene et al., 2007)
Ecuador (Loja and Zamora-Chinchi)	<i>E. moschatum</i>	Leaves	Infusion	Menstruation pain, influenza, pneumonia, and cough	(Tene et al., 2007)
Canary Islands (Spain)	<i>E. cicutarium</i>	Whole Plant	Not indicated	Wounds and hemorrhage	(Darias, Bravo, Barquin, Herrera, & Fraile, 1986)

Table 2 – Extraction conditions, total phenolic content and antioxidant potential of *Erodium* spp.

Species	Part of plant	Extraction protocol ^a	Antioxidant assay	Total phenolic content ^b	Antioxidant activity	Reference
<i>E. bryoniifolium</i>	Aerial part	1:40 w/v (distilled water and pure methanol), 10 min, 25 °C	ABTS assay	15.1 (water) and 10.8 (methanol) mg GAE/g DW	45.3 (water) and 25.4 (methanol) µmol TE/g DW	(Alali et al., 2007)
	Aerial part	N.I. (distilled water and pure methanol), 24 h, N.I.	DPPH assay	45.4 (water) and 25.4 (methanol) mg GAE/100 g	20.1 (water) and 11.9% (methanol) of BHT scavenge activity (0.4 mg/mL)	(El-Hela, Abdel-Hady, Dawoud, Hamed, & Morsy, 2013)
<i>E. cicutarium</i>	Aerial parts	N.I.	DPPH assay	N.D.	25 µg/mL (DPPH ^c)	(Nikolova, Tsvetkova, & Ivancheva, 2010)
	Aerial part	N.I. (pure petroleum ether, benzene, chloroform, ethyl acetate and ethyl ether), N.I., N.I.	Inhibition of <i>Oenothera paradoxa</i> oil oxidation assay	N.D.	Inhibition: 35-95% (petroleum ether); 29-68% (benzene); 9-100% (chloroform); 0-100% (water); 18-100% (ethyl acetate); and 0-11% (ethyl	(Sroka, Rzadkowska-Bodalska, & Mazol, 1994)

								ether)	
	Aerial parts	1:20 w/v (pure ethanol), 24h, room temperature	(pure β -carotene bleaching, MC, PM, DPPH, ABTS, CUPRAC, FRAP and NO radical scavenging assay	N.D.				2.0 mmol TE/g extract (PM); 74% (β -carotene); 22.2 mg EDTAEs/g extract (MC); 129.1 (ABTS), 90.6 (DPPH), 130.4 (CUPRAC), 89.6 (FRAP), and 6.7 (NO) mg TE/g extract	(Sarikurkcü, Targan, Ozer, & Tepe, 2017)
<i>E. glaucophyllum</i>	Aerial parts	1:10 w/v (pure ethyl acetate and methanol), 24 h, room temperature	DPPH and ABTS assays	422 mg PyE/100 g extract (ethyl acetate)				1.76 μ g/mL (DPPH [°]); 0.60 mM TE (ABTS)	(Bouaziz, Dhouib, Loukil, Boukhris, & Sayadi, 2009)
				2225 mg PyE/100 g extract (methanol)				0.44 μ g/mL (DPPH [°]); 3.14 mM TE (ABTS)	
	Leaves	1.25:1 w/v (50% methanol), 24 h, N.I.	RP, DPPH, and inhibition of linoleic acid peroxidation assay	248 mg GAE/g DW				20.3 μ g/mL (DPPH [°]); 15.0 μ g/mL (RP [°]); 37.2 μ g/mL (oil peroxidation assay [°])	(Hamza, Emna, & Yeddes, 2018)
<i>E. guttatum</i>	Leaves	1.25:1 w/v (50%	RP, DPPH, and	124 mg GAE/g				56.9 μ g/mL (DPPH [°]); 28.1	(Hamza et al.,

		methanol), 24 h, inhibition of linoleic acid peroxidation assay	DW	µg/mL (RP ^c); 71.0 µg/mL (oil peroxidation assay ^c)	2018)
<i>E. hirtum</i>	Leaves	1.25:1 w/v (50% RP, DPPH, and methanol), 24 h, inhibition of linoleic acid peroxidation assay	180 mg GAE/g DW	49.5 µg/mL (DPPH ^c); 16.3 µg/mL (RP ^c); 42.5 µg/mL (oil peroxidation assay ^c)	(Hamza et al., 2018)
<i>E. laciniatum</i>	Leaves	1:5 w/v (50% DPPH assay ethanol), 72 h, room temperature	10.3 mg GAE/g extract	30.5 µg/mL (DPPH ^c)	(Jaradat, Almasri, Zaid, & Othman, 2018)

ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); DPPH: 2,2-diphenyl-1-picrylhydrazyl; CUPRAC: Cupric Reducing Antioxidant Capacity; FRAP: Ferric Reducing Antioxidant Power; MC: metal chelating; NO: Nitric Oxide; PM: Phospho-Molybdenum; RP: reducing power

w/v: weight/volume (g/mL); N.I.: not indicated; N.D.: not determined; GAE: Gallic acid equivalents; DW: dry weight; TE: Trolox equivalent, PyE: pyrogallol equivalent

^a mass/volume ratio, solvent composition, time of extraction, temperature of extraction

^b Total phenolic content or the sum of individually quantified phenolic compounds

^c Values calculated as IC₅₀

Table 3 – Antimicrobial activity of *Erodium* species

Species	Part of plant	Solvent	Microorganism	Inhibitory effect (MIC, IZ, NC and GR)	Reference
<i>E. absinthoides</i> , <i>E. ciconium</i> and <i>E. cicutarium</i>	Entire plant	Pure diethyl ether	<i>Acremonium</i> <i>chrysogenum</i> <i>Aspergillus fumigatus</i> <i>Aspergillus restrictus</i> <i>Candida albicans</i> <i>Penicillium</i> <i>chrysogenum</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Pseudomonas</i> <i>aeruginosa</i> <i>Bacillus subtilis</i> <i>Clostridium perfringens</i>	0.078 (<i>E. absinthoides</i>), 0.078 (<i>E. ciconium</i>), and 0.156 (<i>E. cicutarium</i>) mg/mL 0.078 (<i>E. absinthoides</i>), 0.156 (<i>E. ciconium</i>), and 0.156 (<i>E. cicutarium</i>) mg/mL 0.039 (<i>E. absinthoides</i>), 0.078 (<i>E. ciconium</i>), and 0.078 (<i>E. cicutarium</i>) mg/mL 0.156 (<i>E. absinthoides</i>), 0.156 (<i>E. ciconium</i>), and 0.325 (<i>E. cicutarium</i>) mg/mL 0.156 (<i>E. absinthoides</i>), 0.156 (<i>E. ciconium</i>), and 0.156 (<i>E. cicutarium</i>) mg/mL 0.156-5 (<i>E. absinthoides</i>), 2.5-5 (<i>E. ciconium</i>), and 0.625-2.5 (<i>E. cicutarium</i>) mg/mL N.I. (<i>E. absinthoides</i>), 0.156 (<i>E. ciconium</i>), and 0.156 (<i>E. cicutarium</i>) 1.25 (<i>E. absinthoides</i>), 2.5 (<i>E. ciconium</i>), and 0.312 (<i>E. cicutarium</i>) mg/mL 0.312 (<i>E. absinthoides</i>), 0.156 (<i>E. ciconium</i>), and 0.625 (<i>E. cicutarium</i>) mg/mL 0.312 (<i>E. absinthoides</i>), 0.312 (<i>E. ciconium</i>), and 0.312 (<i>E. cicutarium</i>) mg/mL	(Stojanović- Radić et al., 2010)

			<i>Staphylococcus aureus</i>	N.I.-5 (<i>E. absinthoides</i>), 2.5-5 (<i>E. ciconium</i>), and 0.312-2.5 (<i>E. cicutarium</i>) mg/mL	
<i>E. ciconium</i>	Entire plant	95% Ethanol	<i>Staphylococcus aureus</i>	N.I.	(Quave, Plano, Pantuso, & Bennett, 2008)
<i>E. cicutarium</i>	Leaves	96% Ethanol and water	<i>Escherichia coli</i>	N.I. (96% ethanol) and 16 (water) mg/mL	(Bussmann et al., 2010)
			<i>Staphylococcus aureus</i>	64 (96% ethanol) and 4 (water) mg/mL	
	Leaves, stems, and flowers	70% Ethanol	<i>Azotobacter</i> sp.	4 strains out of 5 (70% ethanol and water)	(Nikitina, Kuz'mina, Melent'ev, & Shendel', 2007)
			<i>Pseudomonas</i> sp.	7 strains out of 7 (70% ethanol and water)	
			<i>Bacillus polymyxa</i>	6 (70% ethanol) and 8 (water) strains out of 9	
			<i>Bacillus subtilis</i>	1 (70% ethanol) and 4 (water) strain out of 11	
<i>E. glaucophyllum</i>	Aerial parts	Pure ethyl acetate and metahnol	<i>Aspergillus niger</i>	12 (ethyl acetate) and N.I. (methanol) mm	(Bouaziz et al., 2009)
			<i>Candida albicans</i>	N.I. (ethyl acetate and methanol)	
			<i>Escherichia coli</i>	10 (ethyl acetate) and N.I. (methanol) mm	
			<i>Pseudomonas aeruginosa</i>	11 (ethyl acetate) and N.I. (methanol) mm	
			<i>Salmonella enterica</i>	10 (ethyl acetate) and N.I. (methanol) mm	
			<i>Bacillus subtilis</i>	10 (ethyl acetate) and N.I. (methanol) mm	

	Entire plant	95% Ethanol	<i>Staphylococcus aureus</i>	10 (ethyl acetate) and N.I. (methanol) mm	
			<i>Candida albicans</i>	1.99 mg/mL	(Gohar,
			<i>Escherichia coli</i>	2.5 mg/mL	Lahloub, &
			<i>Staphylococcus aureus</i>	3.16 mg/mL	Niwa, 2003)
	Flowers and leaves	80% Methanol	<i>Fusarium oxysporum</i>	19-24 mm	(Bakari et al., 2018)
			<i>Fusarium sp.</i>	9.7-10.7 mm	
			<i>Penicillium sp.</i>	11.2-13 mm	
			<i>Escherichia coli</i>	20-20.5 mm	
			<i>Klebsiella pneumoniae</i>	25-25.5 mm	
			<i>Salmonella enteritidis</i>	28.2-32.2 mm	
			<i>Enterococcus faecalis</i>	19.5-20.5 mm	
			<i>Bacillus cereus</i>	17.5-20.2 mm	
			<i>Bacillus subtilis</i>	15.2-17 mm	
			<i>Micrococcus luteus</i>	15.2-16 mm	
			<i>Staphylococcus aureus</i>	17-21 mm	
<i>E. glaucophyllum</i> , <i>E. guttatum</i> , and <i>E. hirtum</i>	leaves	50% Methanol	<i>Escherichia coli</i>	14.4-16.4 (<i>E. glaucophyllum</i>), 5.7-8.2 (<i>E. guttatum</i>), and 2.7-5.3 (<i>E. hirtum</i>) mm	(Hamza et al., 2018)
			<i>Pseudomonas aeruginosa</i>	2.4 (<i>E. glaucophyllum</i>), N.I. (<i>E. guttatum</i>), and N.E. (<i>E. hirtum</i>) mm	
			<i>Serratia marcescens</i>	5.2 (<i>E. glaucophyllum</i>), 3.9 (<i>E. guttatum</i>), and 2.1 (<i>E. hirtum</i>) mm	

			<i>Enterococcus aerogenes</i>	11.6 (<i>E. glaucophyllum</i>), 6.7 (<i>E. guttatum</i>), and 3.6 (<i>E. hirtum</i>) mm	
			<i>Enterococcus faecalis</i>	10.9 (<i>E. glaucophyllum</i>), 8.1 (<i>E. guttatum</i>), and 7.4 (<i>E. hirtum</i>) mm	
			<i>Staphylococcus aureus</i>	9.1 (<i>E. glaucophyllum</i>), 6.4 (<i>E. guttatum</i>), and 8.2 (<i>E. hirtum</i>) mm	
<i>E. glaucophyllum</i>	Aerial parts	Distilled water and pure ethanol	<i>Salmonella enterica</i>	0.367-0.586	(Abdelkebir et al., 2019)
			<i>Listeria innocua</i>	0.156-0.252	
			<i>Staphylococcus aureus</i>	0.327-0.608	
<i>E. laciniatum</i>	Leaves	50% Ethanol	<i>Enterobacter cloacae</i>	N.I.	(Jaradat et al., 2018)
			<i>Escherichia coli</i>	25 mg/ mL	
			<i>Klebsiella pneumonia</i>	N.I.	
			<i>Pseudomonas aeruginosa</i>	25 mg/mL	
			<i>Shigella sonnei</i>	12.5 mg/mL	
			<i>Enterococcus faecium</i>	12.5 mg/mL	
			<i>Staphylococcus aureus</i>	6.25-12.5 mg/mL	
<i>E. malacoides</i>	Leaves, stems, and flowers	50% Ethanol	<i>Staphylococcus aureus</i>	128 µg/ml	(Quave et al., 2008)

N.I.: not inhibited; N.E.: not evaluated;

MIC: Minimum Inhibitory Concentration, mg/mL; IZ: Inhibitory Zone, mm; NC: number of colonies (Nikitina et al., 2007); GR: growth rate (Abdelkebir et al., 2019)

Table 4. Toxicity of *Erodium* species (*in vitro* and *in vivo* experiments)

Species	Part of plant	Extracting solvent	Testing model	Toxicity response	Reference
<i>E. stephanianum</i>	Whole plant	Distilled water	MT-4 cells	>125 µg/mL	(Ma et al., 2002)
<i>E. stephanianum</i>	Whole plant	Pure methanol	MT-4 cells	>125 µg/mL	(Ma et al., 2002)
<i>E. oxyrrhynchum</i>	Aerial part	Pure methanol	MCF7 and Madin–Darby bovine kidney cells	LC ₅₀ >50 µg extract/mL for both cells	(Esmaeili et al., 2009)
<i>E. malacoides</i>	Entire plant	Pure ethyl acetate	5.1 cell line	50 µg extract/mL (>80% of toxicity)	(Bremner et al., 2009)
<i>E. cicutarium</i>	Leaves	Distilled water	Brine shrimp larvae, 24 h	LC ₅₀ =4.8 (KMM578 specimen) and 1075 (AKT1171 and ACR142 specimens) µg extract/mL	(Bussmann et al., 2011)
<i>E. cicutarium</i>	Leaves	96% Ethanol	Brine shrimp larvae, 24 h	LC ₅₀ =0.06 (KMM578 specimen) and 127 (AKT1171 and ACR142 specimens) µg extract/mL	(Bussmann et al., 2011)
<i>E. cicutarium</i>	Aerial parts	70% Ethanol	Male “Wistar” rats	No toxicological effects (0.001-10 g extract/kg)	(Penkov et al., 2014)

LC₅₀: median lethal concentration

MT-4: Lymphocyte cancer cell line

MCF7: Michigan Cancer Foundation-7 (a breast cancer cell line)

KMM578: registered number in the Herbarium Truxillense (Universidad Nacional de Trujillo, Peru)