Scientific basis for the industrialization of traditionally used plants of the \textit{Rosaceae} family

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\textbf{ARTICLE INFO}

Keywords:
Traditionally used plants
Ethnobotanic
Rosaceae family
Bioactive compounds

\textbf{ABSTRACT}

Plants have been traditionally used for the treatment of different types of illness, due to biomolecules with recognised benefits. \textit{Rosaceae} family is used in traditional Galician medicine. The following plants \textit{Agrimonia eupatoria}, \textit{Crataegus monogyna}, \textit{Filipendula ulmaria}, \textit{Geum urbanum}, \textit{Potentilla erecta} and \textit{Rosa canina} are usually found in treatments. The aim of this study is to perform an ethnobotanical review about the bioactive compounds of these plants and their different bioactivities, both studied in vitro and in vivo. The nature of the bioactive compounds is varied, highlighting the presence of different phenolic compounds, such as phenolic acids, flavonoids or tannins. Understanding the beneficial effects of the administration of the whole plant or target tissues from \textit{A. eupatoria}, \textit{C. monogyna}, \textit{F. ulmaria}, \textit{G. urbanum}, \textit{P. erecta} and \textit{R. canina} as well as those from their individual compounds could lead to the development of new drugs based on the use of natural ingredients.

1. Oral tradition and the knowledge based on trial and error

1.1. History of traditionally used Plants: Worldwide to Galicia (NW Spain)

Since the ancient times, people instinctively sought the remedies for pain and diverse illness in the surrounding nature (Sengupta, Gaurav, & Tiwari, 2018; Srivastava, 2018). All knowledge was based on experience, as there was no information about the reasons for the disease or which plant and its form of consumption could be useful for its treatment. After thousands of years of trial and error throughout human history, specific plants consumed via oral administration were identified for the treatment of specific diseases, therefore known as medicinal plants (Srivastava, 2018). Plants may contain diverse chemical compounds, named active or bioactive compounds, such as alkaloids or essential oils (EO) (Pérez, 1998). The correct administration of these biomolecules may have beneficial effects on health. In fact, some of these bioactive compounds are the foundation of modern medicine drugs and they represent an alternative source of innovative ingredients with further applications in food and cosmetic industries. Along the history of the traditionally used plants, at first, information was passed orally from generation to generation, until the start of writing. Numerous texts describe the use of different plants in ancient civilizations, such as the Sumerian, Egyptian, Indian, Chinese, Greek, Roman or Arab (Sengupta et al., 2018; Srivastava, 2018). The \textit{Ebers Papyrus} contains descriptions of different treatments, based on plants, to treat skin, urinary, ophthalmologic and other infections (Lennihan, 2014; Srivastava, 2018). Some of the treatments from the Ayurveda Indian medical system and Traditional Chinese medicine have similar basis and the species they described are still used today (Lennihan, 2014; Srivastava, 2018). Initially, plants were consumed raw, and later, people added them to hot water (W) to create soup and tea. As knowledge grew, different herbs were combined to elaborate more complex treatises (Lennihan, 2014). Ancient Greeks are considered the parents of modern medicine, as they combined traditional practices with scientific thinking. Hippocrates, Galen and Dioscorides, among other authors, showed their interest in the deeper application of plants by writing vast treatises (Srivastava, 2018). In \textit{Corpus Hippocraticum}, different herbal medicines and their forms of treatment were described for each disease (Lennihan, 2014; Pahlow, 1994). Galen differentiated between the use of plants “at natural” (meaning in powder form) and the galenic preparations: bioactive compounds were concentrated in W, ethanol (Et) or vinegar, then used in ointment, plasters or other galenic forms (Pahlow, 1994). Dioscorides wrote \textit{De Materia Medica}, with descriptions, modes of collection, preparation and therapeutic effects of
more than 600 MP (Srivastava, 2018). The Greek knowledge was extended by the Romans and Arabians. A scientific regression was suffered during the Middle Ages, as science and magic were mixed. Owing to their knowledge of Latin and Greek, clerics conserved the ancient knowledge (Pahlow, 1994). Until the 16th century, with the advent of iatrochemistry (chemical medicine), plants have been the major source of treatments and relief to some of the most diverse diseases, such as digestive problems, microbial infections, cancer and even neurodegenerative illness (Sengupta et al., 2018; Srivastava, 2018). Synthetic drugs were available for people with more economic resources, while remedies based on plants remained the option to treat poor people (Lennihan, 2014; Srivastava, 2018). In the 18th century, urban citizens preferred pharmaceutical drugs rather than traditional medicine. However, drug side effects became known and medicinal plans resurfaced rapidly (Lennihan, 2014). In early 19th century, the development of chemical methods allowed the discovery and isolation of alkaloids (such as morphine from *Papaver somniferum* or quinine from *Cinchona officinalis*), tannins (T), vitamins, hormones, sapponins (Sa), among other bioactive compounds from vegetal origin starting scientific pharmacy (Srivastava, 2018).

Regarding traditional Spanish medicine, it has the heritage of hundreds of years of different people that influenced the country: diverse Iberian people, Greeks, Romans, Arabs and Orientals as well as German traditions (Verde, Rivera, Fajardo, Obón, & Cebrián, 2008). Some Roman authors described the traditional use of plants by Iberian tribes (de Santayana, Morales, Tardío, Aceituno, & Molina, 2014). During Middle Ages, Ibn al-Baytar, an Andalusian doctor and botanist) wrote the *Tratado de simples*, where he described more than 1400 species with beneficial properties (de Santayana et al., 2014). However, as the Christian religion increased its influence, the human body was considered a finite recipient for a soul, which aspired to divine salvation. In these ages, people were suspicious of medicine, and healers...
were often considered heretics (Verde et al., 2008). Until the early 19th century, the Spanish Inquisition pursued and convicted many healers, men and women, of heresy (Verde et al., 2008). Little by little, science overcame religion, and two differentiated figures appeared: the physician, who carried out the diagnosis, and the pharmacist, who prepared the drugs (Mosquera Paans, 2013). After the Spanish Flu pandemic of 1918, which caused a dramatic number of deaths, traditional medicine started to grow, particularly among the population with less economic resources to obtain chemical drugs (Mosquera Paans, 2013). The botanist Pio Font Quer wrote Plantas medicinales. El Dioscórides renovado, which is the most complete text about application of Iberian plants and is still a basic reference (de Santayana et al., 2014). It includes botanic, chemical and pharmacologic data, names and local uses. He is considered one of the fathers of ethnobotany in Spain (de Santayana et al., 2014). The roots of traditional medicine lead to a new golden age of natural ingredients obtained from plants, whose use is gradually legislated more exhaustively and scientific research is favoured (Mosquera Paans, 2013).

Galicia is a region located in the NW of Spain. Not long ago, in case of ailment, the people had to seek the experience of the elders, especially in the rural areas (Rodríguez González, 2008). In these zones, visiting a doctor or buying a drug was a luxury. Healers (“mencineiros” in Galician) practiced “shamanism” and the Christian religion, integrating magic and religion. These healers used their knowledge of MP combined with spells, magic symbolism and also Christian traditions (Mosquera Paans, 2013; Rodríguez González, 2008). Actually, they were important members of the society in the rural areas, since the medical advances took a long time to arrive. Regarding the important figures, the conservation of Galician traditional medicine, Father Sarmiento (18th century) stands out. He understood the necessity to understand, recover and preserve Galician tradition and popular culture (Mosquera Paans, 2013).

As in other regions, Galician traditional medicine has almost been replaced by modern medicine. However, some people have learned and continue transmitting this ancient knowledge, thereby conserving it (González-Hernández, Romero, Rodríguez-Guitián, & Rigueiro, 2004). As popular wisdom is concentrated on in the elder population and in the rural areas, thousands of years of experience are at risk of disappearing when these people pass away. Preserving the ancient knowledge is exceedingly important, as the study of the traditional use of certain plant species could lead to the re-discovery of active compounds (initially found by our ancestors) with different applications, including medicine, nutrition, cosmetics, etc. (Franco, Guitián, & Resúa, 2013).

1.2. Current uses of natural ingredients extracted from plants

1.2.1. Food

Nowadays, the consumption of vegetal-based nutrients has been prompted by different reasons. In most of the developed countries where nutrition does not represent an issue for most of the population, consumers’ demands are focused on the improvement of the quality of the food. Some of these demands include the replacement of synthetic or artificial ingredients, additives or colorants for natural ones which are not considered to have side-effects. Other demand is to increase the presence of organic and fresh products in the market, as well as, the increment of vegetal-based products which may be included in alternative diets such as vegan or vegetarian ones. However, another important concern is about people with low economic inputs whose nutrition levels are scarce which may induce to the ingestion of unsafe products and thus cause diseases that might become chronic and even fatal. The use of vegetal-based diets has been demonstrated to be an economical approach to feed people. In this sense, since the 50’s the rise on the global population has represented a challenge due to the parallel increment of animal protein intake. Plants have been described to represent an alternative source of protein which may help to balance or even reduce the animal protein production (Astoli et al., 2017; Day, 2013; Flood, 2010). Traditionally many plants have been cultivated since ancient times, due to their nutritional and beneficial properties. Nowadays, it is very common to include some of them in our diet, as it is the case of different spices, such as thyme, rosemary, parsley, coriander; vegetables like tomatoes, garlic, pumpkins, onions, or leeks; and different fruit trees for example (López et al., 2018; Pahlow, 1994; Pinela et al., 2016; Vieira et al., 2017). Plants can be eaten raw, as in salads, cooked or in infusions and can be used in different ways: to

![Fig. 1. Different traditional and industrial uses of Rosaceae plants.](image-url)
garnish, like food ingredients, aromatize, or they can be consumed for their beneficial properties. Some herbal products are sold in pharmacies as dietary supplements, teas, capsules, extracts or powders used in self-medication to prevent diseases, soothe pains, relax, improve wellbeing, etc. Several studies have proven the efficacy of these products in health (Martín Ortega & Segura Campos, 2019; Srivastava, 2018).

Whole plants and some of their compounds could be included in foods or beverages, obtaining a “nutraceutical” food (also called nutraceutical), which, in addition to nutritional function, has different health benefits, helping in the prevention and treatment of diseases (Gulati, Ottaway, Jennings, Coppens, & Gulati, 2019; Lubbe & Verpoorte, 2011). In fact, this tendency to implement the properties of the products and the wide use of functional foods has come to blur the limits between pharma and nutrition (Corbo, Bevilacqua, Petruzzi, Casanova, & Sinigaglia, 2014). Currently, different nutraceuticals are available for consumers. One of the most well-known examples are dairy products (e.g. milk, yogurts and margarines) enriched with phytosterols, which have been proven to reduce the intestinal absorption of cholesterol (Tolve et al., 2019). Another example is folic acid, extracted from leafy green vegetables and legumes, commonly used to fortify cereal and their derivatives. This vitamin is considered to help in the prevention of central nervous system diseases (Samaniego-Vaesken, Alonso-Aperte, & Varela-Moreiras, 2016). In addition to compounds, there are also examples of products supplemented with the plant itself. For example, different plant materials are used to fortify flour, including Chenopodium quinoa, Avena sativa or Hordeum vulgare, due to the high quantity of bioactive compounds of these species (Cardoso, Fernandes, González-Paramás, Barros, & Ferreira, 2019). The toxicological and carcinogenic effects associated with synthetic ingredients have triggered the replacement with natural ones and therefore food industries and academia have prompted their deeper study. Along the last decades many applications have been developed based on the use of natural biocompounds, such as the antioxidants that are present under different chemical structures. Carotenoids, anthocyanins and betalains extracted from plants have been proven to be effective natural additives for foods with antioxidants and have less toxic effects than synthetic ones (Roviz, Barros, Prieto, Morales, & Ferreira, 2017).

The previous food applications of different species of plants are summarized in Fig. 1 and in Table 1.

1.3. Pharmacological

Pharmacological applications are the most known application of these raw materials (Pérez, 1998). Nowadays, the synthetic drugs of modern medicine have almost completely replaced the use of natural plants in developed nations and they are used mostly in traditional medicine in Third world and developing countries. In developed countries, traditional medicine is categorized as “alternative medicine” and is used not for the treatment of serious diseases, but for minor disorders (Martín Ortega & Segura Campos, 2019; Srivastava, 2018).

Natural ingredients obtained from plants can be described as being applied in different ways such as being used as direct agents or as raw materials in the manufacture of drugs. Some examples of these drugs are aspirin, which derives from willow; opium-derived morphine, obtained from poppies; or the anti-tumour drug Taxol, which derives from the Pacific yew (Lennihan, 2014; Martín Ortega & Segura Campos, 2019). In fact, it is estimated that 25–28% of drugs used in modern medicine are derived from MP, directly or indirectly (Lubbe & Verpoorte, 2011; Martín Ortega & Segura Campos, 2019). Regarding pharmacological applications, diverse compounds have been proven to be related to the health benefits of biomolecules extracted from plants. Some examples are described below and summarized in Fig. 1 and in Table 1.

<table>
<thead>
<tr>
<th>Plant Family</th>
<th>Examples</th>
<th>Compounds</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asteraceae</td>
<td>Cardamon, cinnamon, cloves, myrrh, sumac</td>
<td>PC, vitamins, terpenes, etc.</td>
<td>Diverse beneficial effects on health (Cardoso et al., 2019; Delaveau et al., 1981; Cardoso, Fernandes, González-Paramás, Barros, &amp; Ferreira, 2019)</td>
</tr>
<tr>
<td>Rutaceae</td>
<td>Bergamot, lemon, mandarin, orange</td>
<td>PC, phytoesterols, vitamins</td>
<td>Cytotoxic and antineoplastic activity (Mansfield &amp; Evans, 1968; Perez, 1998)</td>
</tr>
<tr>
<td>Fabaceae</td>
<td>Alfalfa, soybean, bean, lentil, pea, chickpea, lentil</td>
<td>Alkaloids, PC, vitamins</td>
<td>Antioxidant and anti-inflammatory activity (de Oteyza &amp; Arroyo, 2008)</td>
</tr>
<tr>
<td>Lamiaceae</td>
<td>Lavender, peppermint, rosemary, sage, thyme</td>
<td>PC, vitamin, EO</td>
<td>Antimicrobial and anti-inflammatory activity (de Oteyza &amp; Arroyo, 2008)</td>
</tr>
<tr>
<td>Zingiberaceae</td>
<td>Ginger, turmeric, cardamom</td>
<td>PC, terpenes, EO</td>
<td>Anti-inflammatory and anti-microbial activity (de Oteyza &amp; Arroyo, 2008)</td>
</tr>
<tr>
<td>Zygophyllaceae</td>
<td>Quassia, Zygophyllum, iberis</td>
<td>PC, alkaloids, PC, terpenes, etc.</td>
<td>Antimicrobial and anti-inflammatory activity (de Oteyza &amp; Arroyo, 2008)</td>
</tr>
</tbody>
</table>

Table 1. Current use of plants in different industries.
well known for their antiplatelet activity. Several bioactive compounds of these plants, specially polyphenols (Pp), flavonoids (F) and coumarins, has been proved to inhibit the ADP pathway, suppress TXA₂ formation and reduce intracellular Ca²⁺ mobilization, among other activities (El Houari & Rosado, 2016).

MP are also a great source of bioactivity compounds to treat anxiety and depression. In this case, compounds such as Sa, alkaloids, Pp, F, triterpenoids, EO, and fatty acids are involved. *Passiflora incarnata*, *Piper methysticum*, *Valeriana officinalis*, *Cimicifuga racemose*, *Hypericum perforatum* or *Melissa officinalis* are examples of plants used to treat these disorders (Martins & Brijesh, 2018). After the administration of most of the plants considered to possess medicinal properties, the anti-depressant activity is related to the increase of monoamines (serotonin, dopamine or norepinephrine) levels in the brain, inhibiting their receptor systems and transporters and also reducing the activity of monoamine oxidase enzymes, which break the monoamines (Martins & Brijesh, 2018).

Nowadays, several adverse effects of the current medication against HIV have been described. To reduce these side effects, scientists are searching for safer and more effective compounds. Several plants have shown promising anti-HIV activity (both *in vitro* and *in vivo*), such as *Rheum palmatum*, *R. officinalis*, *Trigonostemon xyphyphalloides*, *Vatica atrorhithra*, *Vernonia amygdalina*, *Hypoxis pelargonium*, *Sidoides hemocallidea* and *Sutherlandia frutescens*. The mechanism of action of most of them has not been fully disclosed, but different compounds (alkaloids, phenolic compounds (PC), terpenoids (Te) and proteins) have been proven to interrupt the life cycle of HIV and enhance the immune system (Laila et al., 2019). Other species, for instance *Sambucus nigra*, *Caesalpinia pulcherrima* and *Hypericum connatum*, are also useful against other viruses like the herpes simplex virus, influenza, hepatitis, and coxsackie virus (Akrum et al., 2018).

Antimicrobials may be obtained from plant matrixes, being alkaloids, PC and Te the responsible compounds of the activity. Generally, these compounds act through the disruption of the cell membrane and inhibition of different metabolic processes, such as the biosynthesis of nucleic acids or proteins. Species of genus *Taxus*, *Ginkgo biloba* or *Artemisia annua* have shown antimicrobial properties. *A. annua* also contains the anti-malaria compound artemisinin (Pandey & Agnihotri, 2015).

Several compounds are currently used in the formulation of drugs to treat cancer, including Te, alkaloids, Sa, glycosides (G), and PC. Briefly, these compounds act through the induction of apoptosis, autophagy or cell cycle arrest of cancer cells and also through the modification of signalling pathways (Benarba & Pandiella, 2018; Oyenihi & Smith, 2019). To give some examples, *T. brevifolia*, *Artemisia sieversiana*, *Chaenactis pulcherrima*, *Curcuma longa* or *Zingiber officinale* are MP with anti-proliferative effects *in vitro* and *in vivo* models (Benarba & Pandiella, 2018; Martín Ortega & Segura Campos, 2019; Oyenihi & Smith, 2019).

Numerous studies have demonstrated that thousands of plants contain potent antioxidant compounds, especially PC and vitamins, due to their redox properties, the ability to chelate metals and quench singlet oxygen reactive species (Borneo, León, Aguirre, Ribotta, & Cantero, 2009; Jaberian, Pirí, & Nazari, 2013; Ortega-Ramírez et al., 2014; Roleira et al., 2015). Their efficiency has been assessed through *in vitro* assays and also with *in vivo* supplementation studies in animal and human models (Oyenihi & Smith, 2019). *Menisca suaveolens*, *Thymus zygis* or *Foeniculum vulgare* are just a few examples of plants with antioxidant properties (Stanković, Radić, Blanco-Salas, Vázquez-Pardo, & Ruiz-Téllez, 2017). These compounds may be used to treat several diseases, such as diabetes, cancer, ageing and other health problems (Oyenihi & Smith, 2019).

### 1.3.1. Cosmetics

Throughout the centuries, plants have been used in the treatment of different beauty problems and disorders, such as dry skin, inflammation, eczema, psoriasis, hair loss and others. Nowadays, numerous cosmetic products contain extracts or plants-derived compounds in their formulation, such as sunscreens, moisturizers, skin cleansers, body lotions, lipsticks, etc. (Aburjai & Natsheh, 2003; Ganesan & Choi, 2016). Regarding skin products, aloe vera and cucumber are widely used, due to their anti-inflammatory, cooling and healing properties. Other examples of plants used in cosmetics are the gingenseng (anti-aging properties), tea (several bioactivities, including antioxidant, photo-protective and anti-inflammatory effects), chamomile (anti-inflammatory activity) or onion (antiallergic anti-inflammatory and antimicrobial effects) (Aburjai & Natsheh, 2003). In hair care, plants such as *Ginkgo biloba*, aloe vera, sage and rosemary have been used, especially to promote hair growth (Aburjai & Natsheh, 2003). EO are also an important cosmetic product, due to their beneficial effects for skin and hair care and relaxing properties. For instance, chamomile, lavender, eucalyptus and citron EO are appreciated in cosmetic applications for their antioxidant and anti-inflammatory properties, among others (Lubbe & Verpoorte, 2011).

In many cases, bioactive compounds are included in the formulation of cosmetics, such as PC (e.g. quercetin, gallic acid, luteolin or catechins (Ca)), vitamins, carotenes, polysaccharides (Ps) and fatty acids. Several beneficial activities of these compounds have been described, including anti-ageing, antioxidant, anti-inflammatory and anti-microbial (Ganesan & Choi, 2016). The previous food applications of different species of plants are summarized in Fig. 1 and in Table 1

### 1.3.2. Others

Currently, many consumers have a bad opinion of synthetic additives used to preserve foods. Thus, the food industry is searching new natural compounds to prevent the spoilage of food produced by pathogenic microorganisms and also the oxidation of lipids. Terpenes (e.g. geraniol, citral or carvacrol) and PC extracted from plants have been demonstrated to be effective as food additives due to their antimicrobial and antioxidant properties. Some plant compounds have been tested as food additives, such as the terpenes of *Cymbopogon citratus* and *Chenopodium ambrosiodes* and the PC of *Euphorbia stenoclada*, *Helianthemum glomeratrum* and *Gnaphalium oxyphyllum* (Ortega-Ramírez et al., 2014).

The use of plants has also been considered a promising tool for aquaculture. Microbial diseases cause high economic losses, while the inappropriate use of antibiotics could lead to negative side effects appearing in the organisms and also in the environment. Several plants have been demonstrated to exert beneficial effects on the aquatic organism and also reduction of the pathogens present in the W (Van Hai, 2015). Therefore, plants are a cheaper and more sustainable treatment, since they have numerous interesting bioactivity such us promoting anti-stress and being immune-stimulants and anti-parasitic (bacterial, fungus, virus and ectoparasites) (Reverter, Tapisier-Bontemps, Sassal, & Saulnier, 2017).

### 2. Properties of traditionally used plants from Rosaceae family

As mentioned before, the information related to traditional uses of plants is in serious danger. To record this ancient knowledge, several ethnobotanical and ethnopharmaceutical studies have been performed in different Iberian Peninsula regions, including Galicia (Franco et al., 2013; González-Hernández et al., 2004). Most of these studies are focused on the different uses of plants and their forms of consumption/application but no extensive information about the active compounds responsible of the medicinal action has been collected. Investigating the phytochemistry is necessary to understand the relationship between their traditional uses (the result of hundreds of years of trial and error) and their bioactive compounds. In addition, this study allows the exploration of possible future uses of these plants.

In ethnobotanical studies, *Rosaceae* family is found among the most frequently used plant families (Franco et al., 2013). In the present study, *Agrimonia eupatoria*, *Crataegus monogyna*, *Filipendula ulmaria*, *Zingiber officinale*...
**Geum urbanum, Potentilla erecta and Rosa canina** were chosen to perform an ethnobotanical review, because they are among the most utilised plants of this genus, and scientific studies have been carried out on their active compounds and bioactivities. All the six species mentioned can be found in the northwestern part of the Iberian Peninsula. However, the distribution of **F. ulmaria, G. urbanum, and P. erecta** have a lower density in the northwest, even though they constitute a representative flora from the northern part of the Peninsula (Castroviejo, 1986; Ministerio De Agricultura Alimentación y Medio Ambiente, 2019).

Additionally, all the species can be found in all four Galician provinces: Lugo, Ourense, A Coruña and Pontevedra (Romero, 2008). The traditional uses of the selected plants (parts used, mode of application and infections treated) are described in the following paragraphs and summarized in **Table 2**.

### 2.1. Agrimonia eupatoria

#### 2.1.1. Traditional importance

*A. eupatoria* is an indigenous plant from the middle and northern areas of Europe and also the temperate regions from Asia and North America (Al-snafi, 2015). Its aerial parts (AP) are usually collected during the flowering period, spring and summer, to be applied in different ways. Traditional uses reported along the Iberian Peninsula comprised diverse application modes, such as, infusion, decoction, dry extraction, wet extraction (using aqueous, oil or alcoholic solvents) and tincture (de Santayana et al., 2014; Escudero, 1999; Febrer, Blanquer, & Pi, 2001; Romero Martin, 1998; Verde, 2008). *A. eupatoria* has several medicinal properties: it is an astringent, hypotensive, anti-inflammatory, antiemetic, analgesic and healing. It has been used as mouthwash, to gargle and for larynges infections, to clean varicose ulcers or hemorrhoids and to control diarrhea and menstruation pain. Additional uses includes its application to detoxify blood, eliminate pimples and rashes, control headaches, reduce muscular pain, or as antihelminthic, among others (de Santayana et al., 2014; de Santayana, Morales, Tardío, Aceituno, & Molina, 2018; Escudero, 1999; Febrer et al., 2001; Romero Martin, 1998; Verde, 2008).

#### 2.1.2. Scientific studies

*Agrimonia eupatoria*, whose phytochemical composition includes compounds of interest such as carbohydrates (Carb), T, terpenes and their derivatives, PC, vitamins and oils, among other substances, has been linked to very promising biological functions at the pharmacological level, probably associated with the presence of that compounds. Some of the bioactivities *A. eupatoria* produces are antioxidant, antiviral, antibacterial, antioxidant, antidiabetic, analgesic, immunomodulatory, anti-inflammatory, anti-obesity, hepatoprotective, neuroprotective and healing activities, as demonstrated in numerous experimental studies, both in vitro and in vivo (Table 3, Table 4).

Starting with the antioxidant activity and the radical scavenging power of the extracts of *A. eupatoria*, numerous studies have demonstrated its efficacy. A study conducted on the activity of extracts against the reactive species formed during inflammation associated the antioxidant capacity observed with the presence of PC. A hydroalcoholic extract and an EA fraction were able to react with DPPH, peroxyl and hydroxyl radicals, as well as with other oxidizing species such as peroxynitrite, producing a significant radical scavenging activity and a powerful antioxidant activity. The tests carried out with polyphenol-rich extracts were the ones that showed the most efficacy (up to 97.5% in the DPPH reaction, and 79.5% in the ABTS (2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) reaction), which suggests a close relationship between the content in these compounds and the antioxidant capacity and radical scavenger (Al-snafi, 2015), as also other authors affirm that they observed a high correlation between the antioxidant function of hydroalcoholic extracts of *A. eupatoria* and their content in Pc (Muruzević, Mladenović, Stefanović, Vasić, & Ćomić, 2016). Some of the PC associated with this capacity are certain phenolic acids,
<table>
<thead>
<tr>
<th>Study</th>
<th>Solvent</th>
<th>Compounds</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agrimonia eupatoria</strong></td>
<td>HA, EA</td>
<td>Antioxidant</td>
<td>DPPH, peroxyl, peroxynitrite and hydroxyl radical neutralization. Protective effect against DNA damage.</td>
</tr>
<tr>
<td></td>
<td>Ac, Acetone</td>
<td>Antibacterial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC, Et, F, PA, K</td>
<td>Anticoagulant</td>
<td>Total inhibition of blood coagulation cascade.</td>
</tr>
<tr>
<td></td>
<td>W, B</td>
<td>Neuroprotective</td>
<td></td>
</tr>
<tr>
<td><strong>Crataegus monogyna</strong></td>
<td>PC, Et, PA</td>
<td>Antioxidant and photoprotection</td>
<td>UV DPPH radical scavenging effect, reducing power, inhibition of β-carotene bleaching and inhibition of lipid peroxidation of brain cells.</td>
</tr>
<tr>
<td></td>
<td>PC, Et</td>
<td>Photoprotection at cellular and mitochondrial level.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC</td>
<td>Antitumor</td>
<td>Inhibition of HepG2, NCI-H460, HeLa and MCF-7 cells.</td>
</tr>
<tr>
<td></td>
<td>PC, F</td>
<td>Anti-inflammatory</td>
<td>Decrease in the biosynthesis of 12-HETE and PGE2.</td>
</tr>
<tr>
<td><strong>Filipendula ulmaria</strong></td>
<td>W</td>
<td>Antioxidant</td>
<td>DPPH and reducing power.</td>
</tr>
<tr>
<td></td>
<td>F, T</td>
<td>Anti-inflammatory</td>
<td>Inhibition of UVB-induced inflammation.</td>
</tr>
<tr>
<td><strong>Geum urbanum</strong></td>
<td>HA, EA, PA</td>
<td>Antioxidant</td>
<td>DPPH, FRAP and linoleic acid peroxidation test.</td>
</tr>
<tr>
<td></td>
<td>PC, Et, T</td>
<td>Anti-inflammatory</td>
<td>Inhibition of COX-1, COX-2 and of 5-LOX-mediated leukotriene B4 formation.</td>
</tr>
<tr>
<td></td>
<td>Et</td>
<td>Anti-microbial</td>
<td>Inhibition of Gram+ bacteria from the genus Staphylococcus.</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>Anti-inflammatory</td>
<td>Inhibition of COX enzyme.</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>Anti-microbial</td>
<td>Inhibition of several Gram+ and Gram– bacteria.</td>
</tr>
<tr>
<td><strong>Rosa canina</strong></td>
<td>HA, Et, F</td>
<td>Antioxidant</td>
<td>Reduction of ROS in HepG2 and SH-SY5Y cells.</td>
</tr>
<tr>
<td></td>
<td>Et</td>
<td>Anti-inflammatory</td>
<td>Inhibition of COX-1, COX-2 and of 5-LOX-mediated leukotriene B4 formation.</td>
</tr>
<tr>
<td></td>
<td>DMSO, PC</td>
<td>Anti-tumor</td>
<td>Inhibition of WiDr cells by induction of cell phase arrest and apoptosis.</td>
</tr>
</tbody>
</table>

**Notes:** Ac, Acetone; AE: alkaline extraction; CA, Caffeic acid; CO, CO2 supercritical; DMEM, dexamethasone; EA, Ethanol; Et, Ethanol; K, kaempferol; NA, not analysed; PA, proanthocyanins; PC, Phenolic compounds; Pp, polyphenols; PS, Polysaccharides; Sa, Saponins; T, Tannins; TEAC, Trolox equivalent antioxidant capacity; VC, vitamin C.
procyanidin, flavan-3-ols, tannins, proanthocyanidins (PA), Ca, quercetin, apigenin, kaempferol (K) and their O-glycosidic derivatives, having been reported to be up to 220.31 mg of the total PC per gram of extract (Al-snaïf, 2015; Muruzović et al., 2016).

Regarding the anti-inflammatory capacity, it was possible to inhibit the production of pro-inflammatory cytokine and nitric oxide of microglial cell in vivo by applying the aqueous extract of *A. eupatoria* (Bae et al., 2010; Yoon et al., 2012). This extract also achieved a reduction in the increase in serum aminotransferase activity, as well as in the production of tumor necrosis factor α (TNF-α) in rats to which 10, 30, 100 and 300 mg/kg/day of aqueous extract had been orally administered, in addition to imposing a chronic consumption of alcohol. It was also observed that the extract produced a protective effect against chronic liver damage caused by Et (Al-snaïf, 2015). Luteolin 7-glucuronide is an active molecule that is present in the extract and is associated with the decreases in the inflammatory process, an effect probably caused by the inhibition of oxidative stress and inflammation signaling mediated by TLRs (Yoon et al., 2012). On the other hand, the ethyl extract of *A. eupatoria* managed to reduce peripheral edema in in vivo models by 43.2% (when applying a single dose) and 52.2% (when a second dose was applied). Likewise, in this study the analgesic capacity of the ethyl extract was tested, resulting in the fact that it did not produce effects of general anesthesia, but was verified by the formalin and the writhing test, which produced an inhibitory effect of 43.5% in a single dose and 49.8% when applying a second dose (Al-snaïf, 2015).

The cytotoxic effects of the aqueous and methanolic extracts of *A. eupatoria* were tested in vitro tests on human RD, HeLa and mouse embryo fibroblast cell lines, using different concentrations (6, 12, 24, 48 and 96 μg/mL) of the extracts, and throughout three rounds. In the results, it was observed that all the concentrations analyzed achieved the antitumor effect, although proportionally to the concentration, and that the methanolic extract achieved better results in the RD and HeLa cell lines than the aqueous extract, since the percentage growth inhibition was greater (Al-snaïf, 2015; Tsiiritogis-Maniecka et al., 2019). Some authors associate the antitumor activity observed in the RD and HeLa tumor cell lines with the presence of F and T in the extracts obtained from *A. eupatoria* (Ad'hiah, Al-Bederi, & Al-Sammarrae, 2013).

Immunomodulatory capacity was demonstrated using a hydroalcoholic extract in the peritoneal cavity of mice, which resulted in immunostimulatory activity through the activation of phagocytes, lysiszyme and peroxidase (Al-snaïf, 2015).

In addition, the methanolic extract of *A. eupatoria* was shown to have neuroprotective activity by decreasing the damaging oxidative impact on HT22 cells of the mouse hippocampus produced by glutamate (Al-snaïf, 2015; Lee et al., 2010). This effect was associated with various compounds present in the extract with antioxidant capacity. Among these compounds, a new flavonoid that was not previously characterized as standing out, was identified as kaempferol 3-O-β-D-((2′-O-acetyl-6′-O-p-coumaroyl)-glucopyranoside. Other nine R known as F were found in the methanolic extract (Lee et al., 2010).

The antibacterial properties of the aqueous and ethanolic extracts of *A. eupatoria* were tested against several clinically important strains, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. In this case, the ethanol (Et) extract was the one that showed the greatest inhibitory efficacy, specifically against *E. coli*, followed by *S. aureus*, with a 15 mm inhibition halo. *P. aeruginosa* was the most resistant strain to the extract. The effect of the EO of *A. eupatoria* was also tested, reported to be active against *Bacillus subtilis* (Al-snaïf, 2015). In another study, 24 species of microorganisms were tested, both bacteria, for which ampicillin and tetracycline were used as control, as fungi, whose control substances were itraconazole and amphotericin B. The extract that showed the greatest antimicrobial potential was acetone (Ac) one (Mimimal Inhibitory Concentration of 4469.5 μg/mL for *P. aeruginosa* and 4315 μg/mL for *P. mirabilis*), followed by aqueous, Et and, finally, diethyl ether. Additionally, Ac extract also produced a significant inhibition of biofilm formation from *P. aeruginosa* and *Proteus mirabilis* (Muruzović et al., 2016).

In addition to all these bioactivities, anti-diabetic properties are also associated with *A. eupatoria*, since the aqueous extract of this plant (1 mg/mL) achieves an antihyperglycemic effect in mice, producing insulin released by the β cells of the pancreas and the stimulation of glucose transporters. Furthermore, the extract reduced symptoms of this disorder characterized as weight loss, hyperphagia and polydipsia (Al-snaïf, 2015).

Other activities related to the compounds present in this plant are healing, analyzed in comparison with fucidin, which achieved complete healing in rats in 14 days, while the aqueous extract achieved it in 12 days, and the ethanolic in just 10 days; antihypertensive effect, since it manages to lower blood pressure by 40% by administering the extract intravenously in cats; uricolytic capacity, by providing infusions or decoctions at 15% w/v in male rats in doses of 20 mL/kg (Al-snaïf, 2015); anticoagulant function, tested in vitro using an extract of the AP of *A. eupatoria* rich in Pp and Ps that managed to totally inhibit the blood coagulation cascade and, therefore, the formation of clot plasma, at a concentration of 500 μg/mL (Tsiiritogis-Maniecka et al., 2019); or a lipid lowering activity, observed in healthy patients who were supplied with *A. eupatoria* tea, which produced an increase in high density lipoprotein (HDL) cholesterol, also achieving an improvement in lipid profiles (Ivanova, Vankova, & Nashar, 2013).

The European Medicines Agency (EMA) considered the properties of the herbal preparations (comminuted, tinctures or liquid extracts) and its pharmaceutical forms (comminuted for oral use or as infusion or decoction preparations for oromucosal and cutaneous uses). The uses included in the EMA report are the relief of mild diarrhea (oral administration), mild inflammation of the mouth and throat (used for gaggles), and minor skin inflammation and small superficial wounds (topic administration). It has been recommended to be applied in adults and children over 12 years (EMA/HPMC/680595/2013, 2015).

### 2.2. Crataegus monogyna

#### 2.2.1. Traditional importance

*C. monogyna* is widely distributed. It is considered native to Europe, but not in the northeastern part and the Mediterranean coast of North Africa. Roots (R), flowers (FL), leaves (L) and fruits (FR) from *C. monogyna* have different traditional uses in Iberian Peninsula (Garmandia & Castroviejo, 1998). Tinctures, infusions, or liquid extractions are the most typical ways of application (Font Quer, 2001). Even though L and FR are not considered to possess a high nutritional value, they have been also used as food (de Santayana et al., 2014). L and FL from *C. monogyna* have been found to have circulatory properties, improving blood circulation and being cardiotonic and hypotensive (Font Quer, 2001). FR and FL have been used at digestive levels to prevent diarrhea and used to protect the liver in hepatitis processes. FR and R were applied in bronchitis and respiratory infections. For nervous system infections, all plant parts were mostly utilized, usually to treat insomnia, and as anxiolytic, to calm and sedate (de Santayana et al., 2014; Escudero, 1999; Franco et al., 2013; Soutullo, Muñoz, Pazó, Alonso, & Boente, 2015; Verde, 2008).

#### 2.2.2. Scientific studies

There are many studies that have been conducted of the bioactivities of *C. monogyna*, in which its antioxidant, cardioprotective, antinociceptive, anti-inflammatory, anticoagulant and antimicrobial capabilities are proven, among others (Table 3, Table 4). The content of PC in this species is variable depending in the analyzed tissue, ranging from 55 in FR up to 377 μg GAE/g in stems (Luis, Domingues, & Duarte, 2011). Thus, this plant is rich in PC, such as phenolic acids, F, PAs and Ca, as well as tocopherols, ascorbic acid (AA), β-carotene and both saturated fatty acids (hexadecanoic and tricosanoic acid) and polyunsaturated (9Z, 12Z)-octadeca-9,12-dienoic and (9Z, 12Z, 15Z)-octadeca-9,12,15-trienoic); as well as inorganic compounds such as Cu, Fe, Mg, Mn, Zn, etc. (Barros,
The antioxidant activity of \textit{C. monogyna} extracts has been demonstrated \textit{in vitro} using four methodologies applied to animal cell lines: DPPH radical scavenging effect, reducing power, inhibition of β-carotene bleaching and inhibition of lipid peroxidation of brain cells. All the analyzed extracts showed antioxidant capacity, being especially apparent when using the extracts of unripe FR (EC50 between 5.42 and 20.83 µg/mL), which coincides with the high amount of PC and F that contain these extracts. (Barros et al., 2011). Interestingly, in an essay on the effect of the inclusion of extracts in W-soluble gels with the intention of incorporating them into cosmetic and/or pharmaceutical preparations, the antioxidant capacity was verified, using the same methodologies mentioned above. The results showed a decrease of this property, but not significant regarding the use of isolated extracts (Barreira, Rodrigues, Carvalho, & Ferreira, 2013). The antioxidant compounds contained in \textit{C. monogyna} also have a high potential for protection against UV radiation, both UVB and UVA, experimentally tested \textit{in vitro} at the cellular and mitochondrial level, as well as high photostability (Jarzycka et al., 2013; Pawlaczyk-Graja, 2018). In addition, these compounds are associated with a cardioprotective effect, thanks to the limitation of free radical formation, reducing possible damage to the heart and the deposition of cholesterol in the arteries, as it has been demonstrated \textit{in vitro}. In rat models, a protective effect of myocardial dysfunction and the occurrence of infarction was observed (Shortle, Kerry, Furey, & Gilroy, 2013). Moreover, the extracts achieved a vasodilator effect and an isotropic effect that affected sodium–potassium (Na+/K+) ATPase and that favored the Ca2+ ions transport in cardiomyocytes. In ventricular myocytes of guinea pigs, a decrease in arrhythmia was observed through a mechanism of actions similar to that of class III antiarrhythmics (Pawlaczyk-Graja, 2018), as well as a negative chronotropic effect at the cellular and mitochondrial level, as well as high photostability (Jarzycka et al., 2013; Pawlaczyk-Graja, 2018). In vivo studies of \textit{Agrimonia eupatoria}, \textit{Crataegus monogyna}, \textit{Filipendula ulmaria}, \textit{Geum urbanum}, \textit{Potentilla erecta}, \textit{Rosa canina} as a source of bioactive compounds.

### Table 4

<table>
<thead>
<tr>
<th>Effects</th>
<th>Study</th>
<th>Solvent</th>
<th>Compounds</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{Agrimonia eupatoria}</td>
<td>Anti-inflammatory: Carrageenan-induced rat paw edema test in mice</td>
<td>W</td>
<td>PC</td>
<td>(Santos et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Analgesic: Depression of the central nervous system</td>
<td>W</td>
<td>N.A.</td>
<td>(Can, Özkay, Öztürk, &amp; Öztürk, 2010)</td>
</tr>
<tr>
<td></td>
<td>Lipid lowering: Increase in high density lipoprotein (HDL) cholesterol in humans</td>
<td>W</td>
<td>N.A.</td>
<td>(Ivanova et al., 2013)</td>
</tr>
<tr>
<td>\textbf{Crataegus monogyna}</td>
<td>Anti-inflammatory: 72.4% inflammation decrease in rats</td>
<td>70% Et</td>
<td>Te</td>
<td>(Tadić et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>Antithrombotic: Inhibition of platelet aggregation in mice</td>
<td>50% Et</td>
<td>PC, F</td>
<td>(Arslan et al., 2015)</td>
</tr>
<tr>
<td></td>
<td>Anti-arrhythmic: Vasodilator effect and an isotropic effect in guinea pigs</td>
<td>A.E</td>
<td>PC, F</td>
<td>(Pawlaczyk-Graja, 2018)</td>
</tr>
<tr>
<td>\textbf{Filipendula ulmaria}</td>
<td>Antioxidant and hepatoprotective: Hepatic oxidative stress reduction in Wistar rats</td>
<td>M</td>
<td>Pp</td>
<td>(Katanić et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory: Reduction carrageenan-induced paw edema in rats</td>
<td>M</td>
<td>Pp</td>
<td>(Katanić et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic: Inhibitory effect of colorectal carcinogenesis in rats</td>
<td>W</td>
<td>PC</td>
<td>(Bespalov et al., 2018)</td>
</tr>
<tr>
<td></td>
<td>Gastroprotective: Acute stomach damage caused by Et reduction</td>
<td>W</td>
<td>F, T, AA</td>
<td>(Sparatedov et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>Immunomodulatory: Complementary immune system activation</td>
<td>W</td>
<td>W-soluble Ps</td>
<td>(Olenenikov et al., 2017)</td>
</tr>
<tr>
<td>\textbf{Geum urbanum}</td>
<td>Hypotensive: Intravenous injection, has been reported to produce a reduction in blood pressure in cats</td>
<td>W</td>
<td>N.A.</td>
<td>(Petkov, 1979)</td>
</tr>
<tr>
<td>\textbf{Potentilla erecta}</td>
<td>Vasoconstrictive: Occlusive patch test in humans</td>
<td>Et</td>
<td>N. A.</td>
<td>(Wölfle et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Anti-diarrhoeic: Reduction of diarrhea caused by rotavirus in children</td>
<td>CE</td>
<td>T</td>
<td>(Subbotina et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>Anti-ulcerogenic: Inhibition of ulcerative colitis in humans</td>
<td>CE</td>
<td>T</td>
<td>(Huber et al., 2007)</td>
</tr>
<tr>
<td>\textbf{Rosa canina}</td>
<td>Antioxidant: Has the power to reduce pain and stiffness on human patients with osteoarthritis</td>
<td>–</td>
<td>N.A.</td>
<td>(Nadpal et al., 2016; Turan et al., 2018)</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory: Carrageenan-induced and PGE1-induced hind paw edema models, as well as on acetic acid induced increase in a capillary permeability model</td>
<td>W, Et</td>
<td>PC and VC</td>
<td>(Deligriman Orhan et al., 2007; Ouerghemmii et al., 2016)</td>
</tr>
<tr>
<td>\textbf{Rosa canina}</td>
<td>Antinociceptive: ρ-Benzoquinone-induced abdominal constriction test</td>
<td>W, Et</td>
<td>PC and VC</td>
<td>(Deliorman Orhan et al., 2007)</td>
</tr>
<tr>
<td>\textbf{Rosa canina}</td>
<td>Anti-tumor: Inhibited melangenosis in mouse melanoma cells and guinea pig skin, and could be useful as a skin-whitening agent when taken orally</td>
<td>Et, F</td>
<td>PA</td>
<td>(Fujii et al., 2011)</td>
</tr>
<tr>
<td>\textbf{Rosa canina}</td>
<td>Anti-obese: Inhibitory effect on the body weight gain and in the visceral fat gain in mice</td>
<td>Ac</td>
<td>F</td>
<td>(Ninomiya et al., 2007)</td>
</tr>
</tbody>
</table>

Ac, Acetone; AE: alkaline extraction; CE, commercial extract; Ch, chloroform; CO2 e: CO2 supercritical; DMSO, dimethylsulfoxide; EA, ethyl acetate; Et, ether; Et, ethanol; H, hexane; M, methanol; W, water.

AA, ascorbic acid; Ca, Catechins; Carb, carbohydrates; EQ, essential oil; Fl, flavonoids; G, glycosides; K, kaempferol; NA, not analyzed; PA, proanthocyanidin; PC, Phenolic compounds; Pp, polyphenols; Ps, Polysaccharides; Sa, saponins; T, tannins; Te, terpenoids; To, tomentoside; Tt, Trans-tilitoside; VC, vitamin C.

Carvalho, & Ferreira, 2011; Jarzycka, Lewińska, Ganczarz, & Wilk, 2013. The antioxidant activity of \textit{C. monogyna} extracts has been demonstrated \textit{in vitro} using four methodologies applied to animal cell lines: DPPH radical scavenging effect, reducing power, inhibition of β-carotene bleaching and inhibition of lipid peroxidation of brain cells. All the analyzed extracts showed antioxidant capacity, being especially apparent when using the extracts of unripe FR (EC50 between 5.42 and 20.83 µg/mL), which coincides with the high amount of PC and F that contain these extracts. (Barros et al., 2011). Interestingly, in an essay on the effect of the inclusion of extracts in W-soluble gels with the intention of incorporating them into cosmetic and/or pharmaceutical preparations, the antioxidant capacity was verified, using the same methodologies mentioned above. The results showed a decrease of this property, but not significant regarding the use of isolated extracts (Barreira, Rodrigues, Carvalho, & Ferreira, 2013). The antioxidant compounds contained in \textit{C. monogyna} also have a high potential for protection against UV radiation, both UVB and UVA, experimentally tested \textit{in vitro} at the cellular and mitochondrial level, as well as high photostability (Jarzycka et al., 2013; Pawlaczyk-Graja, 2018). In addition, these compounds are associated with a cardioprotective effect, thanks to the limitation of free radical formation, reducing possible damage to the heart and the deposition of cholesterol in the arteries, as it has been demonstrated \textit{in vitro}. In rat models, a protective effect of myocardial dysfunction and the occurrence of infarction was observed (Shortle, Kerry, Furey, & Gilroy, 2013). Moreover, the extracts achieved a vasodilator effect and an isotropic effect that affected sodium–potassium (Na+/K+) ATPase and that favored the Ca2+ ions transport in cardiomyocytes. In ventricular myocytes of guinea pigs, a decrease in arrhythmia was observed through a mechanism of actions similar to that of class III antiarrhythmics (Pawlaczyk-Graja, 2018), as well as a negative chronotropic effect \textit{in vitro}, reducing the contraction of cardiomyocytes through the activation of muscarinic receptors. Certain F isolated from \textit{C. monogyna} such as...
luteolin-7-glucoside, hyperoside, and rutin produced a cardioprotective effect in the hearts of isolated guinea pigs, favoring coronary flow (186%, 66%, and 66%, respectively) and velocity of relaxation (104%, 62%, and 73%, respectively) in doses of 0.5 mmol/L (Nabavi et al., 2015).

Going deeper into the content of the extracts, (Pawlaczky-Graj, 2018) polyphenol-polysaccharide conjugates were isolated and characterized by using various spectrophotometric methods such as GLC-MS, FT-IR and NMR techniques. These were Pp matrices, including some F and poorly esterified Ps rich in galacturonic acid, capable of increasing blood clotting time with very low concentrations (31.25 μg/mL), as verified in vitro, although the FL extract was the one that showed an action with greater selectivity (Pawlaczky-Graj, 2018). The antithrombotic effect of the methanolic extract was tested in mouse tail models injected with a carrageenan, using heparin as the control substance. Extract doses of between 200 and 300 mg/kg were the most effective, achieving an inhibition of platelet aggregation with a high significance (Arslan, Bektas, Bor, & Sener, 2015; Nabavi et al., 2015).

The oral administration of C. monogyna extracts to rats with edemas demonstrated the anti-inflammatory effect of this plant, even surpassing what was produced by indomethacin, a drug used as a positive control, since a 72.4% decrease in inflammation was reported when the extract was used, compared to 50% achieved by the control. This activity is associated with the presence of triterpenes, especially cyclonactarol (Nabavi et al., 2015).

The antioxidant properties of C. monogyna extracts, highly related to the antiproliferative and the apoptotic effect of PC, was tested in four human tumor lines: NCI-H460, HepG2, HeLa and MCF-7, resulting in extracts obtained from FL being the most effective. HPLC–DAD–ESI/MS analyzes of the extracts revealed a predominance of F (Rodrigues et al., 2012). An interesting fact is that, in addition to not producing toxicity in non-tumor cells, the aqueous extract of C. monogyna is capable of exerting a protective effect against the toxicity caused by doxorubicin, a broad-spectrum chemotherapeutic drug whose use has been restricted (Shalizar Jalali & Hasanzadeh, 2015).

The antibacterial activity produced by the extracts of C. monogyna is moderate, especially against Gram-positive bacteria, such as Lysteria monocytogenes, Micrococcus flavus and B. subtilis (Nabavi et al., 2015). Another capacity that deserves to be highlighted is the regulation of the central nervous system, since it depresses its functionality as observed in mice, whose locomotor activity decreased after the administration of C. monogyna. An analgesic effect associated with the activation of opioid receptors was also observed; as well as a gastro-protective effect against the toxicity caused by doxorubicin, a broad-spectrum chemotherapeutic drug whose use has been restricted (Shalizar Jalali & Hasanzadeh, 2015).

The EMA report for Crataeagus monogyna offers a wide range of optional herbal preparations and pharmaceutical forms (comminuted/powdered, dry and liquid extracts using different extraction ratios and solvents, such as ethanol, methanol or sweet wine, juices, and tinctures). Leaf and flower preparations have been associated with the relief of nervous-based temporary heart complaints, such as palpitations, but it requires the previous exclusion of medical major and serious conditions. Same preparations may also relieve mild symptoms of mental stress and to aid sleep. Their use is contemplated for adults and children over 12 years (EMA/HPMC/159076/2014, 2016).

2.3. Filipendula ulmaria

2.3.1. Traditional uses

F. ulmaria is a common and widespread plant, native to Europe and Western Asia, while it has also been introduced but naturalized to North America, including some states from the United States (US) and Canada, where it has become naturalized. Flowered apexes from F. ulmaria, preferably collected when flowering is beginning, are consumed as an infusion, decoction, dry or liquid extract, tincture or syrup (Escudero, 1999). Antiseptic, analgesic, anti-inflammatory, antipyretic, anti-rheumatic, astringent, diaphoretic and diuretic properties have been associated with this species (Escudero, 1999; Franco et al., 2013; Rivera & Obón, 1998). Pharmaceutical industries utilized this plant as a precursor to aspirin since it contains salicylic acid. In addition, it has been applied for the treatment of cystitis and rheumatic pain (Font Quer, 2001). L and FL of F. ulmaria have been also used for aromatizing soups or wine and beers, respectively. It is a useful resource of ocher colors and Eos in cosmetics (Escudero, 1999).

2.3.2. Scientific studies

F. ulmaria is known to possess many biological activities, among which antioxidant, anti-inflammatory, antimicrobial and anti-proliferative capacities stand out (Kataneci et al., 2017) (Tables 3 and 4). Another interesting property that has been associated with this MP is a healing function. PC are the constituents of F. ulmaria that mostly related to bioactive potentials, and can be divided into three main groups: phenolic acids (salicylic acid, gallic acid, ellagic acid, salicylaldehyde, etc.), F and their G (K, rutoside, epicatechin, Ca, quercetin, spiraeoside, apigenin, hyperoside, astragalin, etc.), and T (rugosin A, B1, B2, D, E1 and E2, tellimagrandin I and II, etc.) (Kataneci et al., 2016).

The antioxidant properties of F. ulmaria extracts have been reported and demonstrated by many studies (Neagu, Paun, Albu, & Radu, 2015; Olennikov, Kaschenko, & Chirikova, 2017). A recent investigation analysed the radical scavenging activity of lyophilized FL infusions, in which the potential for in vitro neutralization of DPPH and OH radicals was evaluated, as well as the reducing power through the FRAP assay, obtaining IC50 values of 8.45 μg/mL for DPPH and a FRAP value of 4.46 mmol Fe2+/g. However, the results suggest that this extract has no potential to neutralize OH radicals (Samardzić et al., 2018). Taking into account the aerial part and the root of F. ulmaria, the methanolic extracts of these parts achieved potent antioxidant effects demonstrated in vivo Wistar rats, since the administration of such extracts for 10 consecutive days reduced the hepatic oxidative stress induced by cisplatin, a drug used in antitumor therapies and that of which is related to numerous adverse effects. An increase in the activities of catalase and superoxide dismutase, and a reduction of lipid peroxidation and suppression of DNA damage in normal cells was observed (Kataneci et al., 2017).

Regarding the anti-inflammatory activity of the extracts of F. ulmaria, results obtained both in vitro and in vivo show an important potential. FL extracts achieved a moderate effect of the activation of PPARs (Kataneci et al., 2016). The infusion of lyophilized FL studied ex vivo in human platelets achieved a decrease in the biosynthesis of 12-HETE and PGE2 with IC50 values of 3415 and 6768 μg/mL, respectively (Samardzić et al., 2018). The inhibition of NF-κB achieved by extracts from other plant parts of F. ulmaria was potentially significant (Kataneci et al., 2017). Likewise, it was demonstrated that the extracts of F. ulmaria managed to reduce the production of cytokines in vitro, IL-1β, IL-6 and TNF-α, in addition to the inhibition of the activity of 15-LOX. The tests carried out with the extracts (50 μg/mL) of the AP and R of F. ulmaria achieved a significant inhibition of COX-1 and COX-2, being the predominant inhibitory effect of the extract of the AP (62.84% COX-1 inhibition and 46.43% COX-2 inhibition), and, therefore, comparable to the inhibitory values achieved using the control substances, indomethacin and NS-398 at concentrations of 1.25 μM and 5 μM, respectively (Kataneci et al., 2016). In vivo trials in rats, in which carrageenan had been injected, causing tail edema, it was observed that the administration of 100 mg of AP extract and 200 mg of R extract per kg of body weight, was capable of significantly reducing inflammation, thereby achieving the maximum peak of action at 24 h (Kataneci et al., 2016).

Immunomodulatory properties of F. ulmaria have also been demonstrated. W-soluble Ps obtained from F. ulmaria FL have the ability to activate the complementary immune system in a dose-dependent manner. This system is related to the beginning of inflammatory processes, leukocyte activation and degranulation of basophils and mast
cells. (Oleninikov et al., 2017).

Similarly, the hepatoprotective and neuroprotective properties of *F. ulmaria* have been investigated. The hepatoprotective capacity of an Et extract was tested in vivo, resulting in the aforementioned beneficial action, which was closely related to the antioxidant properties of the plant, as well as the ability to stabilize membranes. The characterization by LC-DAD-MSn of the extracts of AP and R allowed the broad phenolic composition present in this plant to be elucidated, among which the quercetin stands out, being identified in both plant parts, and related to strong antioxidant properties (Katanic et al., 2017). The neuroprotective capacity was tested through the inhibitory effect of the AChE and tyrosinase enzymes, using aqueous and ethanolic extracts. At concentrations of 3 mg/mL, ethanolic extract achieved a greater inhibition of AChE, 98.3% versus an inhibition of 77.03% produced by the aqueous extract. In the case of tyrosinase, the inhibitions achieved showed fewer differences: 90.65% for ethanolic extract and 87.88% for W extract. The PC associated with this bioactivity were Pp such as quercetin and rutin, and chlorogenic acid (Neagu et al., 2015).

On the other hand, the anti-tumor effects of *F. ulmaria* extracts, such as those produced by FL extracts, which inhibit the proliferation of NCI-H460 tumor cells and cause an increase in p21 levels (at G1-checkpoint cyclin-dependent kinase inhibitor) have also been reported. In addition, concentrations between 10 and 50 μg/mL of the ethanolic extracts of *F. ulmaria* produced cytotoxicity in Burkitt lymphoma cell lines (Lima et al., 2014). Additionally, the inhibitory activity of a decoction of *F. ulmaria* in colorectal tumor processes was evaluated in vivo in female rats to which carcinogenosphere had been induced using methyl nitrosourea. A potent inhibitory effect of colorectal carcinogenesis was observed, probably related to the anti-inflammatory potential of *F. ulmaria* extracts in certain stomach and intestinal pathologies (Bespalov et al., 2018). Another study that corroborates the antimutator action of the extracts of *F. ulmaria* was performed in mice with cervical dysplasia, to which extracts obtained by decoction of FL were locally administered. The extracts were able to reduce the frequency of occurrence of carcinoma of the cervix and vagina, induced by 712-dimethyl-benz(a) anthracene (Lima et al., 2014).

Other effects related to *F. ulmaria* extracts are gastroprotective capacity, demonstrated in animal models with acute stomach damage caused by ethanol, to which oral infusions of lyophilized FL (100–300 mg/kg) were orally administered (Samardzic et al., 2018). Likewise, some PC belonging to the group of T, found in EA extracts (100–300 mg/kg) were orally administered (Samardžić et al., 2018). A further study that corroborates the antimutator action of the extracts of *F. ulmaria* was performed in mice with cervical dysplasia, to which extracts obtained by decoction of FL were locally administered. The extracts were able to reduce the frequency of occurrence of carcinoma of the cervix and vagina, induced by 712-dimethyl-benz(a) anthracene (Lima et al., 2014).

Regarding anti-inflammatory properties, *Geum urbanum* is widely extended throughout Europe, where it can reach elevations up to 2100 m over sea level. It is also considered to be native to North Africa (Algeria, Morocco, Tunisia), and temperate Asia from Anatolia, Syria and Caucasian areas up to further occidental and central zones. References about Iberian traditional uses of *Geum urbanum* are not easily found. Nevertheless, scientific references from other geographical areas point out that all parts of the plant have anti-inflammatory properties. Mostly, infusions of dried or fresh FL and R are valued since they were demonstrated to be astringent, anticholesterolemic, antihypertensive, sedative and haemostatic. Mouth, throat and gastrointestinal tract affections, such as loss of appetite or diarrhea have been treated using infusions. In addition, these infusions can be externally applied to wash hemorrhoids, genital discharges and skin infections (Al-Snafi, 2019; Singh et al., 2019).

2.4.2. Scientific studies

*G. urbanum* has been used for a long time in folk medicine due to its astringent and antisepctic properties. More recent studies have shown that its traditional use makes sense, considering *G. urbanum* is rich in PC like gallic, caffee and chlorogenic acids, and also eugenol, carotenoids, F, T and vicianose sugar, which is a very rare disaccharide that can be isolated from its R (Al-Snafi, 2019; Owczarek, Gudej, & Olszewska, 2015) (Table 3, Table 4). Other studies also found ellagitannins and proycyanidins located in the R of *G. urbanum* and the EO extracted from the AP have also been studied (Al-Snafi, 2019; Dimitrova et al., 2017).

Total phenolic acids, F and PA content were evaluated in aqueous extract and ethanolic *G. urbanum* extracts. In the first, total phenolic acids were 768.2 GAE/L, total F were 14.7 mg RE/L and PA were 37.5 mg CE/L, whereas in the second, total phenolic acid was 1261.5 mg GAE/L, a total flavonoid, 49.9 mg RE/L and PA, 60.1 mg CE/L (Al-Snafi, 2019). Ellagitannins and gallotannins are also known constituents of *G. urbanum*, and ellagic acid is also present. Ellagic acid is a potent antioxidant properties with beneficial properties to human health, such as hepatoprotective, cardioprotective, and chemopreventive effects (Owczarek, Olszewska, & Gudej, 2014). Another potent antioxidant detected in high amounts is gallic acid, which also showed antiviral activity (Owczarek et al., 2014).

The antioxidant activity of different *G. urbanum* extracts has been demonstrated in several studies. (Mantle, Edde, & Pickering, 2000) analysed a hydroalcoholic extract of *G. urbanum* L, demonstrating a powerful antioxidant effect through the ABTS assay, with values of 1.67 mmol Trolox/equivalent/mg of dry weigh. Hydromethanolic extracts of the underground and AP were evaluated trough FRAP, DPPH, and linocelic acid oxidation assays. The assays had similar antioxidant activities, which the author correlates with the presence of PC (Owczarek et al., 2015). Aqueous and Et extract also showed a remarkable scavenging activity against 2, 2-diphenyl-1-picrylhydrazyl with values of IC50 7.8 μg/mL and IC50 1.3 μg/mL, respectively (Al-Snafi, 2019).

Regarding anti-inflammatory properties, *Geum urbanum* was able to inhibit prostaglandin biosynthesis and platelet-activating factor-induced exocytosis in vitro tests. Different extracts, in a concentration of 10 mg/mL, were tested on PPAR-α and PPAR-γ activation as well as on NF-xB inhibition. The best results were obtained with the dichloromethane extraction, which possessed moderate to strong effects (Al-Snafi, 2019).

*G. urbanum* was also tested trough R infusions and decoctions. These extractions have been used externally for reducing gingivitis (bleeding and inflammation of gums), and other membranes mucous membranes (Granica et al., 2016). This action is attributed to its high content in Gemin A. This compound significantly affects the functions of stimulated neutrophils by reducing the surface expression of CD11b, and inhibiting the release of reactive oxygen species, and proteases (elastase, matrix metallopeptidase-9), chemokines and cytokines (interleukins IL-8, IL-1β), besides it also stimulates the release of TNF-α, which may be one of the stimulators of the apoptosis of neutrophil cells (Granica et al., 2016).

*G. urbanum* extracts were also tested for their in vitro neuroprotective effect via the inhibition of AChE and tyrosinase. The aqueous extract had an AChE inhibitory activity of 27.03%; 36.48% and 79.11% at concentration of 0.75 mg/mL, 1.5 mg/mL and 3 mg/mL respectively. The IC50 was 2.3 mg/mL for this extract. For the ethanolic extracts,
AChE inhibitory activities were 54.74; 73.53 and 86.77 for the same concentrations. The IC₅₀ was 0.5 mg/mL. Even though all concentrations of the aqueous extracts inhibited tyrosinase in more than 50%, ethanolic extracts were more potent than the aqueous ones (Al-Snafi, 2019).

Furthermore (Dimitrova et al., 2017), also studied the antimicrobial potential of extracts from G. urbanum against Gram-positive. EA fractions from the AP and R had a MIC of 78 µg/mL and 156 µg/mL, respectively, and inhibited the visible growth of the bacteria tested, suppressing their respiratory activity up to 26.2–28.9%. The minimal bactericidal concentration calculated was 625 µg/mL (Dimitrova et al., 2017).

The presence of Lewy bodies and Lewy neuritis is thought to be a major pathological hallmark of Parkinson’s disease and is also linked to the disease’s development. These aggregations of protein primarily consist of fibrillated α-Synuclein; and for now, there is no treatment available targeting stabilization of α-Synuclein in its native state. In the study of (Lobbens et al., 2016), an ethanolic extract of G. urbanum was found to inhibit α-Synuclein fibrillation in a concentration-dependent way and to partly disintegrate preformed α-Synuclein fibrils.

Finally, in vivo studies performed in cats have shown that a 20% aqueous decoction of G. urbanum, administered by intravenous injection, produced a reduction in their blood pressure (Al-Snafi, 2019).

2.5. Potentilla erecta

2.5.1. Traditional use

P. erecta is a Euroasiatic plant widely spread throughout Europe, Caucasus, Anatolia and Western Siberia, up to 2,300 m above sea level. It can be also found in the northwest parts of Africa, Azores and Madeira and, as F. and P. erecta, has been naturalized in North America (Guillén & Rico, 1998). R from P. erecta are usually applied orally as an infusion to treat diarrhea and intestinal colic, due to its astringent properties. The decoction of the same part of plant can be topically used for skin infections and also hemorrhoids (Font Quer, 2001). P. erecta is also considered to be hypotensive, improve blood circulation and to control urinary incontinence, menorrhagia, and arthritic pain (Febrer et al., 2001; Tobyn, Denham, & Whitelegg, 2011).

2.5.2. Scientific studies

P. erecta is an interesting plant with different confirmed bioactivities, such as antioxidant, antimicrobial, anti-inflammatory and anti-diarrheal properties (Table 3, Table 4). These properties are mostly associated with the presence of different molecules like F, triterpenoids and phenolic acids, which are usually extracted from the R and rhizomes of this plant, being the most abundant T, with 15 to 25% of dry weight. The rhizome of this plant is rich in PA and hydrolysable T, mostly agrimonin, a dimeric ellagitannin that represents about 2% of the dry mass (Wölfe, Hoffmann, Haarhus, Rao Muttapalli, & Schempp, 2017). These compounds are thought to be beneficial for human health due to their antioxidant properties and because PA are capable of complex macromolecules and metal ions. In addition, they have been proven to play an important role in the anti-inflammatory activity of several diseases, probably due to their scavenging and antioxidant activities (Mari, Eletto, Pizza, Montoro, & Picente, 2013).

A P. erecta rhizome extract showed antioxidant effects in cell-free oxidant- generating systems and in inflamed human colorectal cells, reducing the production of oxygen radicals (Tomczyk & Latté, 2009).

A study from (Wölfe et al., 2017) determined the anti-inflammatory activity of P. erecta in irradiated HaCaT keratinocytes, by measuring the formation of IL-6 and PGE2. They also analysed the effect on TNF-α induced NF-κB activation, both tests having demonstrated great results in the reduction of inflammation. In this study, P. erecta also showed a blanching effect comparable to hydrocortisone, that it is thought to be partly attributable to a scavenging effect of NO and inhibition of eNOS.

However, compared to glucocorticoids, P. erecta was not able to cause nuclear translocation of the glucocorticoid receptor in HaCaT cells.

In a different study, extracts from P. erecta combined with a hydrolysable tannin Agrimonin, known to be a potent radical scavenger, were able to reduce the inflammation caused by UVB-rays in HaCaT keratinocytes through the inhibition of cyclooxygenase-2 in a dose-dependent manner (Hoffmann et al., 2016; Wölfe et al., 2017). A further experiment demonstrated that the extracts produced a dose-dependent inhibition of UVB-induced inflammation in a in vivo model (Hoffmann et al., 2016).

The cytotoxic properties of P. erecta have been evaluated. (Tomczyk & Latté, 2009) studied the crude extract of P. erecta rhizome in 40% Et and determined that concentrations of 10 and 50 µg/mL were able to inhibit lymphoma cell growth. They also studied the effect of the extract on the herpes virus types I and II in vitro and it revealed a moderate antiviral effect, as well as its cytotoxic activity against Cowpox and the influenza virus type A2 (Tomczyk & Latté, 2009).

(Synowiec, Gniewosz, Bączek, & Przybyl, 2014) evaluated the antibacterial properties of an aqueous extract of P. erecta rhizome and it displayed an inhibiting effect against Gram-positive bacteria, like B. subtilis ATCC 6633 and S. aureus ATCC 25923, and also against yeast-like Hansenula anomala R 26 and Candida lipolitica KRP 322.

As mentioned before, P. erecta presents anti-diarrhoea properties, which have been corroborated by different studies. The oligomeric and polymeric flavan-3-ols (also known as condensed T or PA) have shown therapeutic properties in the treatment of diarrhoea, by complexing secretory compounds such as cholera toxin. Moreover, they also created an unspecific complexation of mucosal proteins in the gut, forming a protective layer and inhibiting the intestinal motility associated with the secretory compounds (Tomczyk & Latté, 2009). This action was tested with a rhizome dry extract and the results showed a high efficacy in the therapy of children’s diarrhoea due to Rotavirus. The treatment ensured a shorter duration of the diarrhoea (three days) compared with the placebo group (five days). In the treated group, 40% of the children were diarrhoea free 48 h after admission to the hospital. In the placebo group this only happened to 5% of the children, which leads the authors to assume that there is an interaction between the T and the Rotavirus proteins that contributes to the high efficacy of this extract, but they also admit that another unknown ingredient might also be involved (Tomczyk & Latté, 2009).

Another use for the P. erecta extract is in the treatment of active ulcerative colitis. Sixteen patients were treated with the extract for three weeks with a dosage of 2,400 mg/day, resulting in a significant decline in the colitis activity index (Tomczyk & Latté, 2009).

Besides, P. erecta even decreased the biochemical indices of lipid metabolism in the blood, specifically of malonaldehyde and endogenic lipids, after three administrations of a spirituous tincture from the rhizome, on albino rats under normal physiological conditions. The tincture was administered intragastrically for 14 days at 0.05 and 0.1 mL per 100 g of the animals’ body weight (Tomczyk & Latté, 2009).

2.6. Rosa canina

2.6.1. Traditional uses

R. canina belongs to Europe, Caucasus, central area of Asia (Pakistan, Afghanistan, Iran, Iraq, Anatolia, Syria, Lebanon, and Palestine), and the northwest of Africa, Canary Islands and Azores Islands. Like the last three species, it was naturalized in North America, as well as in Chile, and in Southern Australia. Different parts of Rosa canina are used and are recommended to be collected during diverse seasons. Petals (P) should be collected before the flower blooms, rose hips (RH) by the end of summer or autumn, and L during spring. RH are the most used part of Rosa canina and can be infused, decocted, extracted as a liquid, tinctured or consumed as syrup. Anti-diarrheic, astrigent, healing, depsychotic, diuretic, venotoxic, and vitamin properties are associated with this species. Respiratory infections, such as a cough, cold or sore throat, have been treated with RH infusions, which
can be mixed with other plants (Origanum spp., Laurus nobilis, Ficus carica and Citrus limon). RH are well-known to be a vitamin C (VC) source, so infusions are used for treating anemia and to control diarrhea. Jams using RH and P are valued for their high vitamin content. In gastronomy, P are also a decoration element in salads. I have been used as tea substitute, L, and dried hip roses have been added to beverages to provide aroma, color and taste. Rose water, which has been described as a collyrium, has been widely applied in cosmetics for providing aroma or color as well as for its astringent properties. Indirect uses of this plant can be applied, one example is the honey obtained from rose P (Blanco, Maca, & Morales, 1999; Escudero, 1999; Verde, 2008).

2.6.2. Scientific studies

Numerous studies have tried to determine the mechanisms of the action of R. canina of the different antioxidant, anti-inflammatory and diuretic properties (Tables 3 and 4). The anti-inflammatory activities observed in vitro were related to the inhibition of pro-inflammatory enzymes such as cycloxygenases, lipooxygenases, cytokines, chemokines, metalloproteases, nitric oxide synthase, and related stress factors such as NF-kB or C-reactive protein levels (Gruenwald, Uebelhack, & Moré, 2019). Among its different constituents, PC and VC stand out, due to their interesting properties (Cosmulescu, Trandafir, & Nour, 2017; Gruenwald et al., 2019). The nutritional content of R. canina has been described and characterized as follows: 643.38 ± 138.4% of ascorbic acid, 28.78 ± 2.07 of carotenes, 13.28 ± 0.85 of total sugars and 0.36 ± 0.03 of protein (all the values are expressed in mg per 100 g of fresh weigh) (Rosu et al., 2011). Regarding antioxidant properties, several compounds with high antioxidant proprieties have been identified in R. canina extracts: PC, such as quercitrin, gallic, and protocatechic acids, and also VC. These compounds are known for their potent antioxidant radical scavenging effects and their capacity for neutralizing reactive oxygen and nitrogen species (Gruenwald et al., 2019). EA extracts of this plant have a total phenolic content of 197 µg GAE/mg of dry content. Methanolic extracts have shown a wide variety of results depending on the pre-treatment of the sample. Fresh biomass displayed a lower phenolic amount, 7.27 µg GAE/mg, than when using dry biomass which concentration was estimated in 255 µg GAE/mg (Cosmulescu et al., 2017; Ouerghemmi et al., 2016). The antioxidant properties of the more concentrated extracts, both the EA and the methanolic, were tested by using different methods. The methanolic extract showed better results for the TEAC, FRAP and DPPH assays, while the EA showed good results for the ORAC assay (Ouerghemmi et al., 2016). This activity has also been studied in vitro, on HepG2 and SH-SYSY cells against intracellular reactive oxygen species (Fetni, Bertella, Ouahab, Martinez Zapater, & De Pascual-Teresa Fernandez, 2017).

(Gruenwald et al., 2019) also determined that R. canina has different anti-inflammatory effects: reduces the pro-inflammatory molecules and C-reactive protein levels, diminishes NF-kB signalling, inhibits pro-inflammatory enzymes, including COX1 and 2, 5-LOX and iNOS, reduces the chemotaxis and chemoluminescence of polymorphonuclear cells, and inhibits pro-inflammatory metalloproteinases. The anti-inflammatory properties of a R. canina ethanolic extract were demonstrated in vivo models. The extract was able to significantly inhibit the inflammation in the studied models: carrageenan-induced and PGE1-induced hind paw edema models, on an acetic acid-induced increase in a capillary permeability model and on a pain-model based on the inhibition of p-benzoquinone-induced in writhing mice (Deliomann Orhan, Hartevioğlu, Küpeli, & Yesilda, 2007). Besides, it has been reported that in humans, R. canina has the power to reduce pain and stiffness in patients with osteoarthritis (Ouerghemmi et al., 2016).

Numerous studies have reported good cytotoxic activity against HeLa, MRC-5, human colon (HT-29) and breast (MCF-7) cancer cells as well anti-proliferative effects on human colon cancer (Caco-2) cells by increasing the number of apoptotic cells and cell cycle arrest at the S phase (Nadal et al., 2016; Turan et al., 2018). Through the inhibition of tyrosinase, ethanolic extract of R. canina has cytotoxic effect on mouse melanoma. This extract also has a selective cytotoxic effect on WiDr cells compared with normal colon cells, inducing cell cycle arrest at the S phase and apoptosis via reduced matrix metalloproteinases. In addition, an inhibition in the expression of telomerase was observed in WiDr cells at 48 and 72 h of treatment (Turan et al., 2018).

(Fuji, Ikeda, & Saito, 2011) suggested that PA present in orally administered R. canina extract were the compounds responsible for the skin pigmentation’s inhibition of tyrosinase activity on the skin of brown guinea pigs.

Finally, different works point to R. canina as a source of biomolecules which may improve nutritional pathologies. A study conducted on mice demonstrated the anti-obese properties of R. canina. Acetone extracts of FR (with a concentration of 50 mg/kg/dw) and seeds (with a concentration of 12.5 and 25 mg/kg/dw) were tested on mice. These extracts were found to have a substantial inhibitory effect on weight gain and in visceral fat gain without affecting the food intake in mice for two weeks after the administration of the extracts. The study attributed these proprieties to trans-tiliroside (0.1–10 mg/kg/d) present in the R. canina extract, and this compound also significantly reduced blood glucose levels after glucose loading (1 g/kg) in mice (Ninomiya et al., 2007). W fractions of R. canina, mostly containing vitamins, carotenoids, flavonoids, tannins, sachharies and pectins, were demonstrated to have hypoglycaemic activity in induced diabetic rats. The administration of these extracts triggered an increment in the number of active islets of pancreas while reducing necrotic ones islets. Another functions related with the consumption of R. canina were the prevention of ulcer formation and anti-diarrheal. The antioxidant effect of extracts obtained from this plant has been also displayed to reduce the peroxidation of lipids or unsaturated fatty acids which action in hepatic and renal tissues have demonstrated to attenuate their associated diseases (Ayati et al., 2018; Márml, Sánchez-de-Diego, Jiménez-Moreno, Ancín-Azpilicueta, & Rodríguez-Yoldi, 2017).

3. Conclusion

Although modern medicine has almost replaced the traditional use of plants, they are still a source of healing. The numerous studies compiled in this review confirm the knowledge obtained from the trial and error of thousands of years: the six plants selected possess compounds with many health benefits that justify their use in traditional medicine. Understanding the knowledge that has been revealed to us through popular wisdom is important, since this information may be the key to the development of different drugs, foods and other products in the future. Thus, conducting more studies about the phytochemical composition and the mechanisms of the actions of the compounds is essential.

CRediT authorship contribution statement

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