Genus *Retama*: A review on traditional uses, phytochemistry, and pharmacological activities

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Abstract

Plants of the genus *Retama* (Fabaceae) are used in traditional medicine of the Mediterranean Basin as an emetic, purgative, and vermifuge. Certain *Retama* species are also employed to treat a multitude of disorders, including diabetes, hepatitis, jaundice, sore throat, skin diseases, joint pain, rheumatism, fever, and inflammation.

This review deals with updated information on the distribution, botanical characteristics, ethnopharmacology, phytochemistry, pharmacological activities, and toxicity of the *Retama* species in order to support their therapeutic potential and to provide an input for future research prospects.

The *Retama* species are mainly employed as ethnomedicinal remedies in Mediterranean countries, including Algeria, Egypt, Italy, Lebanon, Libya, Morocco, and Spain. Previous phytochemical studies show a complex composition, rich in carbohydrates (galactomannans), polyols (pinitol), fatty acids, phenolic compounds (genistein, daidzein) and alkaloids (retamine, lupanine). The pharmacological activity of their various extracts has been widely studied, revealing, among others, the anti-microbial, anti-inflammatory, and anti-diabetic effects of these species. The potential toxicity of these medicinal plants has also been discussed. Although recent experimental evidence confirms the pharmacological interest of this genus, further studies are necessary.

Key Words: *R. monosperma, R. raetam, R. sphaerocarpa,* quinolizidine alkaloids, isoflavones

Abbreviations:

GLC-MS: Gas Liquid Chromatography Mass Spectrometry

MIC: Minimum Inhibitory Concentration

RP-HPLC: Reversed Phase High Performance Liquid Chromatography

HCMV: Human Cytomegalovirus

MSSA: Methicillin Sensitive *Staphylococcus aureus*

MRSA: Methicillin Resistant *Staphylococcus aureus*

ROS: Reactive Oxygen Species

DPPH: 1,1-Diphenyl-2-Picrylhydrazyl

IC_{50}: 50 % Inhibitory Concentration

TAC: Total Antioxidant Capacity

AGE: Advanced Glycation End Product

SOD: Superoxide dismutase

GPx: Glutathione peroxidase

MDA: Malondialdehyde

NSAID: Non-Steroidal Anti-inflammatory Drug

LOX: Lipoxygenase

TNBS: Trinitrobenzene Sulfonic acid

TNF-α: Tumour Necrosis Factor alpha

COX: Cyclooxigenase

iNOS: Inducible Nitric Oxide Synthase

INTRODUCTION

Retama Raf. (Fabaceae) nomen conservandum, previously named Lygos Adanson, also known as rtem or ratam, constitutes a monophyletic taxon, and is comprised of four closely related endemic species of the Mediterranean Basin: *R. monosperma* (L.) Boiss., *R. raetam* (Forsk.) Webb., *R. sphaerocarpa* Boiss. and *R. dasycarpa* Coss. This genus is distributed over several climates and ecosystems including coastal dunes, maquis, and even deserts, since *Retama* species tolerate extreme drought conditions. The similarities between the phenotypic characteristics of those four species hinder their taxonomical determination. Species differ in banner colour, which is white in *R. monosperma* and R. *raetam* and yellow in *R. sphaerocarpa* and *R. dasycarpa* (Belmokhtar and Harche 2012; Boulila et al. 2009; Cardoso et al. 2013; Greuter et al. 1989).

Plants of the genus *Retama* are perennial and unarmed shrubs, with evergreen cladodes (photosynthetic stems), grow to between 2-4 m in height, and are many-branched, with simple and deciduous leaves, which fall rapidly after emergence. Flowers in racemes include those of calyx urceolate, campanulate or turbinate, bilabiate, with white to yellow corolla. Stamens are monadelphous and the style is filiform and incurved. The fruit is an ovoid to globose legume, indehiscent or finally incompletely dehiscent along the ventral suture with one or two seeds (Heywood 1968; Villar et al. 2013).

Retama raetam, grows in Israel, and is believed to be the juniper of the Bible: in Kings 19:4–5, it is called rotem in the Hebrew singular; and in Job 30:4, it is called retamim in the plural (Hehmeyer and Schönig 2012).

Plants from the genus *Retama* have shown great homogeneity regarding their medicinal use (Bellakhdar 1997). They have traditionally been used by local people to treat several ailments, such as diabetes, rheumatism, and inflammation (Ali-Shtayed et al. 1998; Abouri et al. 2012; Telli et al. 2016).

With the increasing interest in the exploration and exploitation of natural sources, a number of studies related to phytochemical and pharmacological aspects of *Retama* spp. have been conducted on *R. monosperma*, *R. raetam*, and *R. sphaerocarpa*. In roots, flowers, seeds and cladodes, the presence of carbohydrates, fatty acids, phenolic compounds as phenolic acids, flavonols, flavones, flavanones, chalcones, aurones, isoflavones and phenylpropanoids, terpenes, steroids and alkaloids has been described.

Indeed, most of the traditional uses of *Retama* spp. have been substantiated by pharmacological studies.

The literature reveals that *Retama* spp. shows several biological activities, including antibacterial (Hammouche-Mokrane et al. 2017), anti-inflammatory (González-Mauraza et al. 2014), antioxidant (El-Toumy et al. 2011), anti-proliferative (Belayachi et al. 2013) anti-ulcer (El-Toumy et al. 2011), anti-viral (Edziri et al. 2008), and hepatoprotective activities (Omara et al. 2009b; Korien et al. 2010).

In this review, the traditional uses, chemical constituents, pharmacological activities and toxicology of the *Retama* genus are highlighted. A critical evaluation of pharmacological studies in terms of their relation to ethnopharmacology is also provided.

ETHNOBOTANY of *Retama* spp.

Origin and geographic distribution

Fabaceae is a widely distributed family of flowering plants with 730 genera and 19,400 species divided into three subfamilies: namely Faboideae, Mimosoideae, and Caesalpinioideae (Kirkbride et al. 2003). The *Retama* genus belongs to the family Fabaceae, subfamily Faboideae, tribu Genisteae and comprises four species that are mainly distributed in the Mediterranean Basin (Greuter et al. 1989) (Table 1). *R. sphaerocarpa* is largely distributed throughout the Iberian Peninsula and North Africa. *R. monosperma* is native to the coastal sandy areas of SW Spain and NW of Africa. *R. dasycarpa* is restricted to the Atlas Mountains in Morocco. *R. raetam* has an amphi-Mediterranean distribution. *R. raetam* subsp. *gussonei* is endemic to Sicily.

Studies on genetic diversity and relationships among and within three populations of *R. raetam* collected in different habitats in southern Tunisia were conducted by Abdellaoui et al. (2014). Research indicates that most variation occurred within populations and that genetic differentiation had occurred between populations. These findings are crucial for a better understanding of the adaptive strategy of this plant in this geographical area and to help in the creation of an effective strategy to protect this important species.

Economic relevance

The most commonly used species in North Africa is *R. raetam*, and thus the one with major economic relevance. This specie is widely utilized by local population for construction and ornamental purposes, and for healing or ameliorating several diseases (Barakat et al., 2013). *Retama* plant species are also used in pastures to provide shade and shelter for animals, especially on hot dry days (Obón et al. 2011, Barakat et al. 2013).

Agro-climatic preference

The *Retama* genus occupies a wide range of habitats. The plants of this genus grow preferably in coastal areas and deserts. They are plants that resist winter low temperatures and summer extreme hot. *Retama* spp. could grow up in low fertility and drought soils (Muñoz Valles et al. 2013; Barakat et al., 2013).

Ethnopharmacological uses

Plants belonging to *Retama* genus have been used traditionally for the treatment of different diseases in many parts of Mediterranean Basin, especially in North Africa and the Middle East (Table 2). Literature revealed that *R. raetam* is the most widely used species.

R. raetam has a long history of use by desert Berbers and in Jewish traditional medicine, where it is used as a treatment for several diseases. Plant parts such as cladodes, fruits, seeds and roots are involved in different traditional remedies.

R. raetam (Forsk.) Webb. (commonly known in English as white broom or white weeping broom) grows in countries of North Africa such as Morocco, Algeria, Tunisia, Libya, and Egypt, and in certain Middle Eastern countries, such as Lebanon, Palestine, Jordan and Israel. The cladodes (photosynthetic stems), flowers, seeds and roots are employed such a powder, in an infusion or decoction for external use such as a cataplasm or poultice, as a bath, or in oral use.

The Moroccan pharmacopoeia has been developed and enriched by knowledge from several ethnic groups that migrated to Morocco from many areas, including Arabs from the Middle East, Andalusians from Spain, and Jews from Europe (Tahraoui et al. 2007). In Morocco, powdered cladodes from *R. raetam*, *R. monosperma* and *R. sphaerocarpa,* mixed with honey, are orally administered as an emetic, and a decoction of cladodes constitutes a useful enema utilized as purgative and vermifuge. In Tissint, powdered cladodes and flowers of *R. raetam* are employed for their healing properties in circumcision, and as a vulnerary, antiseptic and sedative in local wound care, skin ulcers and infected pimples. In Marrakech, *R. raetam* crushed with milk or butter is used with the same indications, while decoctions are applied in frictions to relieve pruritus, and human and animal scabies (Bellakhdar et al. 1991; Bellakhdar 1997). Roots are employed as enemas or as an abortifacient by fumigation. An infusion of cladodes and flowers taken orally is also used as an abortive medicine, however it is widely known that a considerable risk of poisoning exists. In Sahara, roots are employed in diphtheria and cladodes as fire spikes in neuralgias such as sciatica neuralgia. In Tata, a south-eastern Moroccan province that borders Algeria, this plant is commonly used for the treatment of scorpion bites, skin diseases, wounds healing, and rheumatism. In Algeria it is prescribed to relieve inflamed eyes, fever, stomach-ache, back pain and diarrhoea (Abouri et al. 2012; Mouhajir 2002; Bellakhdar 1997). The Ouargla region includes the most popular oasis in the Algerian Sahara in south-eastern Algeria where a decoction or infusion of fruits and seeds from *R. raetam* is used for the treatment of diabetes (Telli et al. 2016). In the Al-Jabal Al-Akhdar region of Libya, it is also recommended for the treatment of diabetes and sinusitis (El-Mokasabi 2014). In Tunisia, this is externally dispensed in scabies as a poultice (Viegi and Ghedira 2014).

In the Middle East, a decoction of cladodes and flowers of *R. raetam* is used to treat syphilis and female infertility (Yaniv and Dudai 2014). In Israel, a decoction of cladodes is employed as a bath for joint pain, back pain and skin bruising (Said et al. 2002). Jordan is a relatively small country, and it is characterized by a weak biodiversity. The inhabitants of the Mujib area use *R. raetam* on fractures and burns as a poultice, mainly for animals. A decoction of cladodes is made to treat burns (Hudaib et al. 2008). In Lebanon, this plant is also employed for joint pain (El Beyrouthy et al. 2008). In Palestine, it is prescribed against eye inflammation, sore throat, rheumatism, infertility, paralysis, and stomach ache (Ali-Shtayeh et al. 1998). In Yemen, traditional medicinal uses of this plant have been introduced from Israeli and Yemenite Jews; these populations use an infusion as a remedy for hepatitis and jaundice (Hehmeyer and Schönig 2012).

R. monosperma (in Spanish known as *Retama de olor*, *Retama blanca* and in English as *White bridal broom*) is native to the coastal sandy areas of SW Spain, NW Morocco, Algeria and Egypt. The Algerian Berbers use an extract from cladodes for the prevention of hydrophobia (rabies) (Helmstädter 2016).

A decoction of *R. sphaerocarpa* roots is used in the Errachidia province of Morocco, in the treatment of diabetes (Tahraoui et al. 2007). In the Sahara, roots are employed as a diphtheria remedy (Mouhajir 2002). In Algeria, it is used to cure rabies (Louaar et al. 2005). In the western part of the province of Granada (Andalusia, southern Spain), an infusion or decoction of cladodes and flowers is applied as a poultice or cataplasm to relieve joint pains, contusions, and luxations, and the for the healing of skin wounds and warts. Moreover, in oral administration, a decoction of cladodes and flowers is used in the treatment of diabetes and fever; the fresh ingestion of fruits is employed to stem diarrhoea; and an infusion of flowers to treat liver diseases (Benitez Cruz 2007; Benitez Cruz et al. 2010).

R. dasycarpa is an endemic plant of the high Atlas Mountains used by the Ishelhin people, a southern Moroccan Amazigh (Berber) ethnic group, in urological and nephrological diseases (Teixidor-Toneu et al. 2016).

CHEMICAL CONSTITUENTS of *Retama* spp.

Alcohols and aldehydes

The main component of the essential oil from *R. raetam* flowers is nonanal or pelargonaldehyde. Aldehydes are highly aromatic compounds: octanal (caprylic aldehyde), dodecanal (lauraldehyde) and undecanal have also been identified (Touati et al. 2015).

Cyclitols

Pinitol has been isolated from cladodes and quantified in *R. raetam* (1.8%), *R. sphaerocarpa* (1.9%) and *R. monosperma*, which has the highest concentration (2.3%) of this compound (González-Mauraza et al. 2016). Quinic acid was identified as one the main components in seeds and cladodes of *R. sphaerocarpa* (Touati et al. 2017)

Polysaccharides

Two homogeneous galactomannans were isolated from seeds of Libyan *R. raetam* (Ishurd et al. 2004)

Fatty acids

The chemical analysis of seeds and cladodes from *R. monosperma* led to the identification of 11 saturated (2.3 % w/w) and 5 unsaturated fatty acids (El Hamdani and Fdil 2015). Similarly, Touati et al. (2015) identified 14 fatty acids and quantified 2.3 % w/w of saturated fatty acids and 14 % of unsaturated fatty acids from *R. sphaerocarpa* seeds and cladodes (Table 3).

Phenolic Compounds

Isoflavones

In *R. sphaerocarpa*, *R. monosperma,* and *R. raetam,* isoflavones, such as genistein, genistin, daidzin, and daidzein and other isoflavones, such as biochanin A, 6'-methoxypseudobaptegenin and puerarin, have been isolated and identified (Lopez-Lázaro et al. 1998; Djeddi et al. 2013; Abdalla and Saleh 1983). Two new furanoisoflavones have been isolated from *R. raetam* cladodes derrone and 5” hydroxyl-derrone (Xu et al. 2015).

Dihydrochalcones and aurones

Phloretin belongs to the chemical group of dihydrochalcones, found in apple trees and pear trees (Huang et al. 2016). Hispidol has been isolated for the first time in soybean seedlings (*Soja hispida)* and could originate from the oxidative cyclization of chalcone, which is an intermediate step in aurone biosynthesis (Wong 1966).

Terpenoids

Monoterpenes

The essential oil of *R. monosperma* cladodes is rich in hydrocarbons, mainly: alkanes (31.8 %), norisoprenoids (25.4 %) oxygenated diterpenes (11.6 %) and oxygenated sesquiterpenes (10.5 %). Flower oil revealed the presence of alkanes (25.8 %), fatty acids (56.7 %) and norisoprenoids (3.1 %) as the main subclasses. Hexadecanoic acid was the main compound in the essential oil of flowers (0 - 30.6 %) while heptacosane was in the essential oil of cladodes (13 %). The ionones and damascones showed low presence in flower oil in contrast to branch oil. The pleasant aroma of *R. monosperma* during full flowering is due to the presence at significant levels of norterpenoids. The main components in the essential oil of *R. raetam* flowers are β-linalool, nonanal and α-humulene (Edziri et al. 2010).

Triterpenes

Touati et al. (2015) reported the identification and quantification from cladodes of triterpene β-amyrin (0.06 %).

Steroids

Belayachi et al. (2014) and Touati et al. (2015) identified β-sitosterol, stigmasterol and campesterol from the cladodes and seeds of *R. monosperma* and *R. sphaerocarpa.* Touati et al. (2015) quantified total phytosterols in *R. sphaerocarpa* (2.5 %). El-Sherbeiny et al. (1978) identified β-sitosterol, a phytosterol in *R. raetam*.

Alkaloids

El-Shazly et al. (1996) reported the presence of 31 bipiperydine and quinolizidine alkaloids by GLC-MS in different plant parts (cladodes, roots, fruit, and seeds) of three *Retama* species: *R. monosperma, R. sphaerocarpa,* and *R. raetam* (Table 3). The bipiperydine alkaloid ammodendrine, which shares part of the biosynthetic pathway with quinolizidine alkaloids, was detected in the three species. Alkaloidal profiles of these *Retama* species are rather similar; typical for *Retama* is the occurrence of retamine, which is uncommon in other Fabaceae, although it appears in relatively higher concentrations in *R. sphaerocarpa* and *R. raetam* than in *R. monosperma.* The tetracyclic quinolizidine alkaloids (sparteine, lupanine and retamine) represent the major components of roots and cladodes. The α-pyridone alkaloids, such as cytisine, methylcytisine and anagyrine, derive from the tetracyclic alkaloid lupanine and were detected in high concentrations in flowers and seeds. These results have been confirmed by various authors (Table 3).

PHARMACOLOGICAL ACTIVITY

Antibacterial and antifungal activity

Many studies have focused on the antibacterial activity of *Retama* spp. extracts; in the majority of instances this activity was evaluated by means of the disc diffusion method, measuring the diameter of inhibition zones, or by determining the Minimum Inhibitory Concentration (MIC).

The methanol-water (50:50) polyphenol-rich extract of *R. sphaerocarpa* stems exerted a significant antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacterial strains. The major components of this polyphenol-rich extract were piscidic and quinic acids and the flavonoid morin (Touati et al. 2017).

The alkaloid extracts obtained from seeds, leaves and stems of *R. monosperma* were tested against *Aspergillus niger*, *Candida albicans* and *Candida tropicalis*. The antifungal activity of the leaves and stems was related to their higher content of sparteine, ammodendrine and anagyrine, whereas no activity was observed on seed extract, with a major content of cytisine and its derivatives (El-Hamdani et al. 2016).

The aqueous and ethanolic extracts of the aerial parts of Palestinian *R. raetam* did not affect the viability of *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris*, *Pseudomonas aeruginosa* or the yeast *Candida albicans* (Ali-Shteveh et al. 1998). However, the ethyl acetate extract of aerial parts of *R. raetam* from Tunisia, rich in flavonoids, tannins and alkaloids, showed significant antibacterial activity against Gram-positive microorganisms, especially methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA, MRSA), thereby suggesting that the use of intermediary polarity solvents is necessary for the extraction of bioactive components with antibacterial activity (Edziri et al. 2007). This hypothesis is also supported by Mariem et al. (2014), who observed that the moderately polar fraction of Tunisian *R. raetam* shoots, obtained after ethyl acetate extraction, not only exerted the highest antibacterial activity, especially against *E. coli* and *B. cereus*, but also presented the highest polyphenol content, whereby syringic acid and coumarin were the most abundant compounds detected by RP-HPLC.

The results obtained with extracts from the flowers of *R. raetam* are along the same lines, since the most active extracts from the flowers of Tunisian *R. raetam* were those obtained with ethyl acetate and butanol, rather than with methanol and chloroform. Butanol extract exerts high activity, with MICs in the range of 0.256–0.512 mg ml^{-1} against Gram-positive bacteria, including *Bacillus subtilis*, *Enterococcus faecium*, *Streptococcus* spp., *Corynebacterium* spp., MSSA, and MRSA. This capacity of the extracts was correlated with a higher content on total polyphenols and flavonoids; whereas the ethyl acetate extract of the flowers, with appreciable activity against Gram-positive bacteria and the ability to inhibit the cytopathic effect of human cytomegalovirus (HCMV) strain, presented the highest tannin content (Edziri et al. 2008). Two isolated flavonoids from the ethyl acetate extract of *R. raetam* flowers, namely licoflavone C and derrone, exerted good antibacterial activity against *E. coli* and *Pseudomonas aeruginosa* and significant antifungal activity against *Candida* species (Edziri et al. 2012).

Two separate studies focused on the chemical composition and antimicrobial activity of the essential oils obtained by the Clevenger apparatus from the flowers of *R. raetam* collected in Tunisia and Libya, respectively. The Tunisian essential oil was rich in oxygenated monoterpenes (59.73 %) and sesquiterpene hydrocarbons (32.39 %), whereby the major detected components were nonanal, α-humulene, acetaldehyde, and linalool, and this oil exerted a moderate antibacterial and antifungal activity, with MICs in the range between 0.625 and 5 mg ml^{-1} (Edziri et al. 2010). The Libyan essential oil presented a similar composition in oxygenated monoterpenes (62.0 %) and a MIC of 3 and 6 mg ml^{-1} against *S. aureus* and *S. pyogenes*, respectively, whereas the isolated compound linalool presented MICs of 250 and 375 μg ml^{-1}, respectively (Awen et al. 2011).

Taken together, the studies focused on the antibacterial activity of *Retama* spp., mainly *R. raetam*, support the ethnopharmacological use of this plant in the treatment of infectious diseases. Notably, the studied extracts exerted significant activity against pathogens responsible for skin and soft-tissue infections, such as *S. aureus* and *S. pyogenes*. These results justify the use of this plant in traditional medicine, which is included in the special medicinal herbal powder (locally named rshush, rishush, or dhrur) used in Bedouin indigenous medicine in the Middle East for the healing of the skin after circumcision (Abu-Rabia 2015). The antibacterial activity of *Retama* spp. has been related to the presence of polyphenols, alkaloids and essential oils; however, further research is necessary in order to determine the main active principles and their mechanism of action, as well as the optimization of the extraction methods in order to obtain extracts of a more standardized nature.

Antioxidant and chemoprotective activity

High levels of reactive oxygen species (ROS) are involved in the development of the majority of chronic diseases, including cancer and neurodegenerative and cardiovascular diseases, due to their ability to damage biomolecules by inducing lipid peroxidation or DNA oxidation, and to modulate redox-sensitive pathways involved in the pathogenesis of these diseases (Valko et al. 2007). Natural products, including polyphenols, are known to exert antioxidant properties, by means of ROS scavenging, chelating transition metals, or modulating the activity of redox-sensitive enzymes (León-González et al. 2015). Numerous studies have evaluated the antioxidant activity of *Retama spp.* extract, as summarized in Table 4. Most of these studies determined the anti-radical activity *in vitro* against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical via a spectrophotometric method and expressed it as IC_{50} values, thereby indicating the concentration of extract required to scavenge 50 % of the DPPH radical. The IC_{50} results ranged between 25 and >1000 µg ml^{-1}, which correspond to the methanol extract of *R. raetam* seeds (Tlili et al. 2015) and the aqueous extracts of *R. raetam* (Djeddi et al. 2013), respectively. This variability could be correlated with the alternative extraction methods and/or the part of the plant or species employed in each study. The lower antioxidant activity of aqueous extracts suggests that the use of more intermediate polarity solvents, such as hydro-alcoholic mixtures or ethyl acetate, is more effective for the extraction of *Retama spp.* antioxidant molecules.

Belmokhatar and Harche (2014) determined the antioxidant capacity of the *R. monosperma* 70 % aqueous methanol extracts of seeds, stems and flowers and of their fractions (toluene, chloroform, ethyl acetate, and butanol) by means of the DPPH and the phosphomolybdenum total antioxidant capacity (TAC) assays. Results showed that the ethyl acetate fractions were the most active for each part and that the extract from the ethyl acetate seeds presented the highest antioxidant capacity from among all the plant parts (DPPH IC_{50}, 150 µg ml^{-1}). A linear regression analysis showed a significant Pearson's coefficient of correlation between flavonoid content and the DPPH and TAC values, which suggests they are major contributors to the antioxidant activities (Belmokhtar and Harche 2014).

In another study, Boussahel et al. (2017) reported the antioxidant and antiglycative properties of methanol and aqueous *R. sphaerocarpa* fruit extracts. The methanol extract presented a higher content on flavonoids, including the isoflavones daidzein and genistein. This extract exerted a noticeable antioxidant activity in the chemical assays performed, especially in the oxygen radical-absorbance capacity assay (ORAC), which suggests that the antioxidants of *R. sphaerocarpa* fruit are more soluble in organic solvents than in water, and that they predominantly act as hydrogen atom transfers. The methanol extract also induced a major decrease in the formation of advanced glycation end products (AGE), which are related with oxidative stress, inflammation and insulin resistance, which suggests that this flavonoid-rich extract is able to prevent the reactions between reducing sugars and proteins that lead to non-enzymatic glycation or browning.

The chemoprotective effect of the aqueous methanol extract of *R. raetam* seeds against the damage induced by formalin, indomethacin and cadmium chloride has been studied in various *in vivo* models. Formalin is a mixture of formaldehyde and methanol that mimics the effects of pollutants on humans. Formalin induced blood, liver and kidney toxicity in Sprague Dawley albino rats, by inducing a high increase in serum glucose, transaminases, bilirubin, urea, creatinin, red blood cells, and hemoglobin, an increase in white blood cells, and in liver and kidney dysfunction. The administration of *R. raetam* seed extract restored liver and kidney injuries and blood parameters to the normal levels, also increasing the blood levels of antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) and lowering lipid peroxidation (malondialdhyde (MDA)) in serum (Koriem et al. 2010). Similar results were obtained by this extract against the kidney and liver toxicity induced by cadmium chloride (Koriem et al. 2009). Furthermore, treatment with 25 mg kg^{-1} indomethacin, a non-steroidal anti-inflammatory drug (NSAID), induced severe gastric damage to male albino rats due to the lipid peroxidation of the membranes. The administration of 25 mg kg^{-1} *R. raetam* seed extract significantly reduced the ulcer area and the gastric MDA levels, whereas it increased the levels of antioxidant enzymes SOD and GPx, thereby exerting a gastroprotective effect comparable to the histamine-2 (H_2) blocker ranitidine (El-Toumy et al. 2009).

Analgesic and anti-inflammatory activity

Although there is no a specific ethnobotanical use of *Retama* spp. as an anti-inflammatory, they are used in the treatment of ailments that involved inflammation. For example, *R. sphaerocarpa* crushed shoots, are traditionally applied as a poultice to the skin to treat rheumatism or as analgesic for menstrual pain in Southern regions of Spain (Obón et al. 2011; Martínez-Lirola et al. 1997; Rivera et al. 1994). The anti-inflammatory activity was confirmed *in vitro*, as pre-incubation of human monocytes with different *R. sphaerocarpa* extract fractions for 30 mins before stimulation with LPS (10 ng ml^{-1}) significantly prevented the release of the inflammatory cytokine tumour necrosis factor-alpha (TNF-α) (Bremner et al. 2009). The methanol and ethyl acetate fractions were the most active.

Lipoxygenase (LOX) is an enzyme that catalyses the reaction of fatty acids to hydroperoxides, which can be converted into other products that play a key role in the inflammatory process; the molecules that inhibit LOX are thus considered to have anti-oxidant and anti-inflammatory properties (Steinhilber 1999). Miguel et al. (2014) studied the capacity of various medicinal plants to inhibit LOX, showing that *R. raetam* extract significantly inhibited this enzyme and that this anti-inflammatory activity was correlated with the free radical scavenging capacity (Miguel et al. 2014).

The anti-inflammatory activity of *R. monosperma* was evaluated *in vivo* in a murine Crohn's disease model, by intra-colonic administration of trinitrobenzene sulfonic acid (TNBS) in rats. Oral administration of this extract significantly prevented the TNBS-induced intestinal damage and increased the production of colonic mucus. This action was due, at least in part, to a decreased neutrophil infiltration and cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) overexpression. The mechanism of action probably involves a reduction of p38 mitogen-activated protein kinase activation, thus preventing the inhibitory protein IκB degradation in colonic mucosa (González-Mauraza et al. 2014).

The anti-inflammatory effect of *R. raetam* extracts must be mediated by the presence of the isoflavones, including genistein, 6-hydroxygenistein, 3'-O-methylorobol, pratensein, and biochanin, since Djeddi et al. (2013) showed that 1 mg kg^{-1} of these isolated compounds significantly reduced the amount of abdominal writhing induced by intra-peritoneal acetic acid injection. They suggested that these active components might inhibit the cyclo-oxygenase or other enzymes involved in the synthesis or release of inflammatory prostaglandins (Djeddi et al. 2013).

Anticancer activity

Even though no species of the genus *Retama* are traditionally used to treat cancer, several studies have tested the cytotoxic activity of crude extracts, fractions and isolated compounds.

In a screening of anticancer plant materials from Moroccan folk medicine, the methanol extract of *R. monosperma* aerial parts exerted an IC_{50} of almost 100 µg ml^{-1} against both SiHa and HeLa cell lines, from human cervical cancer (Merghoub et al. 2009). This crude extract was further fractionated, whereby the dichloromethane fraction was the most active, and presented an IC_{50} of 14.57±4.15 µg ml^{-1} and 21.33±7.88 µg ml^{-1} against SiHa and HeLa cell lines, respectively. The cytotoxic activity was mediated by the induction of caspase-dependent apoptosis, which involved an increase in ROS production and depolarization of mitochondrial membrane potential (Benbacer et al. 2012). The dichloromethane fraction also exerted significant activity against Jurkat (acute T cell leukemia) and JeKo-1 (non-Hodgkin lymphoma) (Belayachi et al. 2013). This activity was correlated to the presence of alkaloids, quantified by GC/MS (Benbacer et al. 2012). Furthermore, the hexane extract obtained by Sohxlet of *R. monosperma* aerial parts was tested against a panel of cancer and non-transformed cell lines and exerted a dramatic decrease in the cell viability of Jurkat cells, with almost no effect in the other tested cell lines. Induction of apoptosis was observed, accompanied by cell-cycle arrest, DNA damage induction, and the activation of the JNK/Fas-L/caspase 8/caspase 3 pathway. However, in this study, the chemical analysis by GC/MS revealed a major composition in α-linoleic acid (13.97 %), stigmasterol (10.34 %), β-sitosteryl (7.92 %) and campesterol (11.09 %) (Belayachi et al. 2014).

The methanol extract from the Italian endemism *R. raetam* subsp. *gussonei* exerted a cytotoxic activity against large lung carcinoma cell (COR-L23, IC_{50}: 40 μg ml^{-1}), along with antioxidant activity (Conforti et al. 2004).

Genistin, daidzin and 6´-methoxypseudobaptigenin-7-O-β-glucoside, are glucosylated isoflavons isolated from *R. sphaerocarpa* cladodes that have the ability to stabilize topoisomerase II-DNA cleavage complex, by acting as topoisomerase II poisons (Martín-Cordero et al. 2000b). Even though genistin is not a potent topoisomerase II poison, this ability could explain, at least in part, this flavonoid cytotoxic activity over the TK-10 cell line (IC_{50} 27 μM) (López-Lázaro et al. 2000).

Effect on the cardiovascular system

Aqueous extracts of *R. raetam* leaves exhibit antihypertensive and diuretic effects on hypertensive rats, by increasing sodium, potassium and chloride excretion, as well as acting as an enhancement of the glomerular filtration rate. On the other hand, the diuretic action in normotensive rats induces a significant increase on urinary potassium elimination (Eddouks et al. 2007).

Along the same lines, the intravenous administration of aqueous extracts of aerial parts of the same species showed a diuretic effect in normal rats. Again, a rise in the glomerular rate was detected, but in this case a significant decrease of urinary osmolality was found. The authors suggest that *R. raetam* metabolites could act synergistically or individually as angiotensin-converting enzyme inhibitors. This enzyme converts angiotensin I into angiotensin II. Angiotensin II is a powerful vasoconstrictor which causes an elevation of blood pressure. Thus, inhibition of this enzyme is a key way to reduce hypertension (Maghrani et al. 2005a; Patten et al. 2016).

Hypoglycemic activity

Aqueous leaf extract of *R. raetam* was able to reduce blood glucose levels with an extra-pancreatic mechanism, since plasma insulin levels remained unaffected. It is suggested that the extract inhibited renal glucose reabsorption as evidenced by the increased glycosuria. The inhibition of sodium-glucose symporters located in the proximal renal tubule should be involved in the mechanism of action. However, other mechanisms could explain these results, such as the stimulation of glucose uptake by muscle or adipose tissues, correction of insulin resistance, inhibition of endogenous glucose production, and a rise in glucogenogenesis (Maghrani et al. 2003). The same results have been found with the intravenous administration of a decoction of the whole plant (Maghrani et al. 2005b). In addition, orally administrated aqueous extract exhibits lipid (cholesterol and triglycerids) and body-weight lowering activities in both normal and severe hyperglycemic rats (Maghrani et al. 2004); this fact links with an interesting application of the extract in atherosclerosis and cardiac disease.

These results are not in accordance with those of Algandaby et al. (2010), who orally administrated a methanolic extract of *R. raetam* fruit. Results showed a significant extract capacity to reduce blood glucose levels. However, in this case, an increase in serum insulin levels was detected. Furthermore, *in vitro* studies demonstrated that the extract was capable of inhibiting glucose absorption by rat isolated intestine. No effect was detected *in vitro* over gluconeogenesis or glycogenolysis or on skeletal muscle glucose uptake (Algandaby et al. 2010).

The antidiabetic effect of these extracts is attributed to quinolizidine alkaloids such as methylcytisine, lupanine and sparteine (Abdel Halim et al. 1997), but also to flavonoids such as chrysin and, mainly, quercetin (Lukačínová et al. 2008). The antioxidant ability of flavonoids as free radical scavengers or metal chelators could help to preserve β-cells from ROS deleterious effects in islet of Langerhans. On the other hand, alkaloids block ATP-sensitive potassium channels present in β-cells, with subsequent insulin release. Differences in the mechanisms of action between alkaloids and flavonoids should explain the discrepancies between the aforementioned studies, since they use different extraction procedures.

It should also be borne in mind that *Retama* spp. is rich in pinitol (González-Mauraza et al. 2016). This compound has been reported to possess insulin-like properties since it is able to regulate the insulin-mediated glucose uptake in liver through translocation and activation of the PI3K/Akt signalling pathway (Gao et al. 2015).

Effect on the nervous system

The methanol extract of aerial parts of *R. raetam* affects ambulatory and non-ambulatory movements in a dose-dependent way: no effect is detected with a dose of 125 mg kg^{-1} body weight; an increment-only ambulatory movement is detected with a dose of 250 mg kg^{-1} body weight; and a decrease in both movements is detected in mice after treatment with a dose of 375 mg kg^{-1} body weight. These results could be explained by the fact that certain alkaloids, in small doses, stimulateliver the brain, as does, for example cytisine, although in high doses, it can cause the inhibition of locomotor activity. In addition, high concentrations of methylcytisine produce a sedative effect (Al-Tubuly et al. 2011). Depending on the dose, the extract is anxiolytic at lower doses, has no effect at moderate doses, and is anxiogenic at higher doses, whereby an activity pattern similar to that triggered by nicotine is presented, which points to alkaloids as the metabolites responsible for the extract effect over central nervous system. Finally, different doses affect the onset of sleep and sleep duration in different ways (Al-Tubuly et al. 2011).

Effect on bone metabolism

A methanol:water (7:3) extract of *R. raetam* seeds had demonstrated efficacy in the protection and treatment of osteoporosis. This extract, probably due to phenolic compounds such as genistein, improved bone-tissue architecture in the form of regularity of inner and outer bone-tissue surfaces. With the increase in *R. raetam* treatment, the number and activity of the osteocytes also rise, as does the bone-tissue regeneration, due to an improved imbalance between bone formation and resorption. Omara et al. (2009a) concluded that this plant could be useful in the prevention of bone loss in postmenopausal women as an alternative to hormone replacement therapy.

Hepatoprotective effect

Aqueous seed extract of *R. raetam* is also active as a hepatoprotective agent in reducing histopathological alterations induced by CCl_4 in the liver. This extract could also reverse increased pathological serum levels of aspartate and alanine aminotransferases and alkaline phosphatase (Omara et al. 2009b). Korien et al. (2010) found similar results for formalin - induced liver, blood and kidney toxicity. This study is particularly interesting since the effects of formalin in rats are similar to those of several environmental pollutants in humans. The capability of the extract to increase diuresis, to decrease serum cholesterol and the hyperglucemia caused by formalin, its antioxidant and chelating activities, as well as its ability to restore serum levels of liver enzymes, and to reverse histopathological alterations, make this extract a promising treatment of environmental toxicity in humans (Koriem et al. 2010).

CONCLUSION

Retama spp. is a plant that grows almost exclusively in the Mediterranean Basin. Its ability to grow on dry soil and to withstand extreme temperatures facilitates its cultivation. Throughout history, these species have been used in traditional medicine by several cultures from the Mediterranean area and many of these activities have been demonstrated to be in use today. Their hypoglycemic effect and their antioxidant capacity are worthy of note, as is their diuretic activity associated with blood-pressure-lowering bioactivity. For this reason, these plants, especially *R. raetam*, the most commonly studied species, represent a major source of active principles. In this regard, the presence at *Retama* spp. of high concentrations of pinitol, quinolizidine alkaloids and isoflavones should be highlighted. These compounds are responsible for the majority of the pharmacological activities of the plant. However, the existence of toxic effects of the plant, such as respiratory failure and depression of the central nervous system, has been detected (Schmid et al. 2006). Repeated administration of the methanolic extract of *R. raetam* has a low nephrotoxic subacute toxicity potential, while it might have hepatotoxic, nephrotoxic, and mutagenic effects at higher doses (Algandaby 2015). Certain flavonoids have been pointed out as being responsible for the poisoning of livestock by ingestion of *R. raetam* (El Bahri et al. 1999). For this reason, toxicological research is needed to study the adverse effects of these plants before they can be recommended for clinical use. In addition, certain molecular and cellular mechanisms of action must first be thoroughly investigated and elucidated.

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Table 1. Species of the *Retama* genus. Synonyms and worldwide distribution (GBIF 2017; Greuter et al. 1989; Sequeira et al. 2011; The Plant List 2017)

Retama species (Accepted names)	Synonyms	Country
R. monosperma (L.) Boiss.	*Genista monosperma* (L.) Lam.; *Lygos monosperma* (L.) Heywood; *Retama monosperma* subsp. *monosperma*; *Retama rhodorhizoides* Webb & Berthel.; *Spartium monospermum* L.	Spain, Portugal, Morocco, Algeria, Egypt
R. raetam (Forsk.) Webb.	*Genista monosperma; Genista raetam* Forssk.; *Lygos raetam (*Forssk.) Heywood; *Retama duriaei* (Spach) Webb; *Retama raetam* subsp. *Raetam; Retama raetum* (Forssk.) Webb]	Morocco, Algeria, Tunisia, Libya, Egypt, Sicily, Jordan, Israel, Lebanon, Palestina
Retama raetam subsp. *gussonei* (Webb) Greuter	*Lygos raetam* subsp. *gussonei* (Webb) Heyw. *Retama gussonei* Webb *Retama gussonii* Webb	Sicily
R. sphaerocarpa Boiss.	*Lygos sphaerocarpa* (L.) Heywood	Spain, Portugal, Morocco, Algeria, Tunisia
R. dasycarpa Coss.		SW Morocco

Table 2: Ethnopharmacological uses of *Retama* spp. Species, common name, part of the plant that is used in each case, preparation, via of administration and Country. NS: not specified.

Species	Common name	Plant part	Traditional use	Preparation	Administration and application area	Country/Province	References
R. monosperma (L.) Boiss	Retam, Rtem	Cladodes	Emetic	Powdered and mixed with honey	Oral	Morocco	Bellakhdar 1997
		Cladodes	Purgative,Vermifuge	Decoction	Rectal washings	Morocco	Bellakhdar 1997
	Tillugwît, îllugwî, Allugû, Talggût (ber	Cladodes	Prevention of hydrophobia (rabies)	Decoction	Oral	Algeria	Helmstädter 2016
R. raetam (Forsk.) Webb.	R'tam, Retam, Rataym,	Cladodes	Emetic	Powdered and mixed with honey	Oral	Morocco	Bellakhdar 1997
		Cladodes	Purgative,Vermifuge	Decoction	Rectal washings	Morocco	Bellakhdar et al. 1991; Bellakhdar 1997
		Cladodes	Healing in circumcisions Antiseptic and sedative in local wound care, wound and skin ulcers, vulnerary	Powered	Cataplasm	Morocco (Tissint)	Bellakhdar et al. 1991; Bellakhdar 1997
		Cladodes	Antipruritic and Scabies	Decoction	Liniments	Morocco (Marrakech)	Bellakhdar et al. 1991; Bellakhdar 1997
		Cladodes, Flowers	Abortive	Infusion	Oral	Morocco	Abouri et al. 2012; Bellakhdar 1997
		Roots	Abortive	Decoction	Vaginal washings	Morocco (Sahara)	Bellakhdar 1997
	Rtem	Roots	Diphtheria	NS	NS	Morocco (Sahara)	Mouhajir 2002
		Cladodes, Flowers	Skin disease	Decoction	External use	Morocco (Taounate, Tata)	Bellakhdar et al. 1991; El-Hilaly et al. 2003; Abouri et al. 2012
		Cladodes	Rheumatism	Infusion	Oral	Morocco (Tata)	Abouri et al. 2012
		Cladodes	Scorpion bite, wounds he	Cataplasm	External use	Morocco (Tata)	Abouri et al. 2012
	Retam	Cladodes	Rheumatism, Scorpion sting, Skin wounds	NS	NS	Algeria (Ouargla)	Ould El Hadj et al. 2003
		Cladodes	Healing in skin diseases, inflamed eyes, diarrhea, fever	NS		Algeria (Ouanougha)	Rebbas et al. 2012
		Cladodes	Treat stomachache	Infusion	Oral	Algeria	Rebbas et al. 2012
		Cladodes	Skin wounds, back pain	Powdered and mixed with olive oil	External use	Algeria	Rebbas et al. 2012
		Fruits, seeds	Diabetes	Decoction, Infusion	Oral	Algeria (Ouargla)	Telli et al. 2016
		Cladodes	Eczema	Decoction	External use	Algeriaç (M'Sila)	Boudjelal et al. 2013
	Rtam	Cladodes	Scabies	NS	Poultice	Tunisia	Viegi and Ghedira 2014
	Ratam	NS	Diabetes, sinusitis	NS	NS	Libya (Al-Jabal Al-Akhder)	El-Mokasabi 2014
	رتيم	Cladodes	Aching joints, back pain and skin bruise	Decoction	Bath	Israel	Said et al. 2002

	Retem	Cladodes	Fractures and burns	Decoction	Poultice	Jordan	Hudaib et al. 2008
	Retem	Cladodes	Joint aches	Decoction	Bath	Lebanon	El Beyrouthy et al. 2008
	Ratame	Cladodes, seeds	Antiinflammatory, treat inflamed eyes and sore throat, antirheumatic, treat infertility, treat paralysis	NS	Poultice	Palestine	Ali-Shtayeh et al. 1998
		Cladodes, seeds	Analgesic, treat stomachache	NS	Oral	Palestine	Ali-Shtayeh et al. 1998
	Ratam, rotem hamidbar	Cladodes	Hepatitis, jaundice	Infusion	Internal use	Yemen	Hehmeyer and Schönig 2012
	Ratam, Ratama	Cladodes,Flowers	Syphilis, women infertility	Decoction	External use	Middle –East	Yaniv and Dudai 2014
R. sphaerocarpa Boiss.	R'tam, Retam, Algu	Cladodes	Emetic	Powdered and mixed with honey	Oral	Morocco	Bellakhdar 1997
		Cladodes	Purgative,Vermifuge	Decoction	Rectal washings	Morocco	Bellakhdar 1997
	Rtem	Root	Diabetes	Decoction	Internal use	Morocco (Errachidia)	Tahraoui et al. 2007
	Rtem	Roots	Diphtheria	NS	NS	Morocco (Sahara)	Mouhajir 2002
		NS	To cure rabies	NS	NS	Algeria	Louaar et al. 2005
	Retama de flor amarilla	Cladodes	Joint aches,	Crushed with salt, vinegar or ash	Poultice	Spain	Benitez Cruz 2007
		Fruits	Diarrhoea	Fresh ingested	Oral	Spain	Benitez et al. 2010
		Flowers	Liver disease	Infusion	Oral	Spain	Benitez Cruz 2007; Benitez et al. 2010
		Cladodes	Fever	Infusion/Decoction	Oral	Spain	Benitez Cruz 2007; Benitez et al. 2010
		Flowers	Contusion, pain	Cataplasm	Topic	Spain	Benitez et al. 2010
		Cladodes	Luxation	No preparation	Topic	Spain	Benitez et al. 2010
		Flowers	Healing wounds skin	Crushed with water	Poultice	Spain	Benitez Cruz 2007
		Cladodes, Flowers	rheumatism, warts, Healing, Diabetes	Decoction	Oral and external use	Spain	Benitez Cruz 2007
R. dasycarpa Coss.	Algu	Seeds	Urological, nephrological disease		Oral	Morocco (Atlas Mountains)	Teixidor-Toneu et al. 2016

Table 3. Phytochemical composition of different parts of each *Retama* species

Phytochemical clasiffication	Part of plant	Plant species	References
MINERALS			
Al, Ba, Cd, Cu, Fe, Mg, Pb,Zn, Mn, Ca, K, Na, P	Cladodes, Seeds	*R. monosperma*	El Hamdani and Fdil. 2015
ALKANES			
Pentacosane	Flowers, cladodes	*R. monosperma*	Derhali et al. 2016
Hexacosane	Flowers, cladodes	*R. monosperma*	Derhali et al. 2016
Heptacosane	Flowers, cladodes	*R. monosperma*	Derhali et al. 2016
ACIDS			
Hexadecanoic acid	Flowers	*R. monosperma*	Derhali et al. 2016
ALDEHYDES			
Nonanal (Pelargonaldehyde)	Flowers	*R. raetam*	Edziri et al. 2010
Octanal (Caprylic aldehyde)	Flowers	*R. raetam*	Edziri et al. 2010
Dodecanal (Lauraldehyde)	Flowers	*R. raetam*	Edziri et al. 2010
Undecanal	Flowers	*R. raetam*	Edziri et al. 2010
ALCOHOLS			
Hexadecan-1-ol	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
Octadec-9-en-1-ol	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
Octadec-1-ol	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
Eicosan-1-ol	Cladodes	*R. sphaerocarpa*	Touati et al. 2015
Docosan-1-ol	Cladodes	*R. sphaerocarpa*	Touati et al. 2015
Tetracosan-1-ol	Cladodes	*R. sphaerocarpa*	Touati et al. 2015
Octacosan-1-ol	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
CYCLITOLS			
Pinitol	Cladodes	*R. monosperma, R. sphaerocarpa, R. raetam*	Gonzalez Mauraza et al. 2016
Quinic acid	Cladodes	*R. sphaerocarpa*	Touati et al. 2017
POLYSACCHARIDES			
Galactomannans	Seeds	*R. raetam*	Ishurd et al. 2004
Xilo-gluco-4-*O*-methyl-α-D-glucopyranosyluronic acid	Seeds	*R. raetam*	Wu et al. 2006
FATTY ACIDS			
Saturated			
Lauric acid	Cladodes, seeds	*R. monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Myristic acid	Cladodes, Seeds	*R. monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al, 2015
Pentadecanoic acid	Cladodes, Seeds	*R. monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Margaric acid	Cladodes, Seeds	*R. monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Stearic acid	Cladodes, Seeds, Flowers	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al.

			2015; Derhali et al. 2016
Arachidic acid	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Heneicosanoic acid	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
Behenic acid	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Tricosanoic acid	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Lignoceric acid	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Pentacosanoic acid	Cladodes	*R. monosperma*	El Hamdani and Fdil. 2015
Palmitic acid	Cladodes, Seeds	*R. monosperma*	El Hamdani and Fdil. 2015
Unsaturated			
Palmitoleic acid (omega 7)	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Oleic acid (omega 9)	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Elaidic acid (omega 9)	Cladodes, Seeds	*R. sphaerocarpa*	Touati et al. 2015
Linolelaidic acid (omega 6)	Cladodes, Seeds	*R .monosperma; R. sphaerocarpa*	El Hamdani and Fdil. 2015; Touati et al. 2015
Linoleic acid (omega 6)	Cladodes, Seeds	*R. monosperma*	El Hamdani and Fdil. 2015
Linolenic acid(omega-3)	Cladodes, Seeds	*R. monosperma*	El Hamdani and Fdil. 2015
PHENOLIC COMPOUNDS			
Phenolic Alcohols			
Resorcinol	Cladodes	*R.raetam*	Mariem et al. 2014
Tyrosol	Cladodes	*R. sphaerocarpa*	Touati et al. 2015
Phenolic Acids			
Hydroxybenzoic acids			
Gallic acid	Cladodes, seeds	*R. raetam*	Mariem et al. 2014
Protocatechuic acid	Cladodes	*R.raetam*	Mariem et al. 2014
Ferulic acid	Cladodes	*R. sphaerocarpa*	Touati et al. 2017
Homoprotocatechuic acid	Cladodes	*R.raetam*	Mariem et al. 2014
Salycilic acid	Cladodes	*R .raetam*	Mariem et al. 2014
p-Hydroxybenzoic acid	Cladodes	*R .raetam*	Mariem et al. 2014
Vainillic acid	Cladodes	*R.raetam*	Mariem et al. 2014
Gentisic acid	Cladodes	*R .raetam*	Mariem et al. 2014
Syringic acid	Cladodes	*R. raetam*	Mariem et al. 2014
Piscidic acid	Stems	*R. sphaerocarpa*	Touati et al. 2017
Hydroxycinnamic acids			
trans-Cinnamic acid	Cladodes	*R .raetam*	Mariem et al. 2014
Caffeic acid	Cladodes	*R .raetam*	Mariem et al. 2014

Ferulic acid	Cladodes	*R. raetam; R. sphaerocarpa*	Mariem et al. 2014; Touati et al. 2015
p-Coumaric acid	Cladodes; seeds	*R. raetam; R. sphaerocarpa;*	Djeddi et al. 2013; Mariem et al. 2014; Touati et al. 2017
o-Coumaric acid	Cladodes	*R .raetam*	Mariem et al. 2014
Phenylpropanoids			
Chlorogenic acid	Cladodes	*R .raetam*	Mariem et al. 2014
Rosmarinic acid	Cladodes	*R .raetam*	Mariem et al. 2014
Flavonoids			
Flavonols			
Quercetin	Cladodes, Seeds	*R. raetam; R. sphaerocarpa*	El Sherbeiny et al. 1978; Touati et al. 2017
Quercetin 3,7-di-*O*-β-glucoside.		*R. sphaerocarpa*	Louaar et al. 2005
Rhamnazin (Quercetin 3',7-dimethylether)	Cladodes	*R. sphaerocarpa*	Lopez-Lázaro et al. 1999
Rhamnazin-3-*O*-β-glucopyranosyl-(1→5)-*α*-arabinofuranoside	Cladodes	*R. sphaerocarpa*	Martín-Cordero et al. 1999
Rhamnazin 3-*O*-β-D-glucopyranosyl-(1-->5)-[β-D-apiofuranosyl(1-->2)]-α-L-arabinofuranoside (Retamatrioside)	Cladodes	*R. sphaerocarpa*	Martín-Cordero et al. 2000a
Kaempferol	Cladodes , Seeds	*R. raetam*	El Sherbeiny et al. 1978; Djeddi et al. 2013; Mariem et al. 2014
Kaempferol-7-glucoside	Seeds	*R.raetam*	El Sherbeiny et al. 1978
Isorhamnetin	Cladodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Morin	Cladodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Galangin	Cladodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Flavononols			
Taxifolin	Cladodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Flavones			
Luteolin	Cladodes, seeds	*R.raetam, R.sphaerocarpa*	Abdalla and Saleh 1983; Djeddi et al. 2013; Mariem et al. 201; Touati et al. 2017
Luteolin-di-*O*-rhamnoside	Claodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Luteolin 4'-*O*-neohesperidoside	Cladodes	*R.raetam*	Kassem et al. 2000
Orientin (Lutexin, Luteolin 8-*C*-glucoside)	Cladodes	*R.raetam, R.sphaerocarpa*	Abdalla and Saleh 1983; Touati et al. 2017
Orientin-4'-glucoside	Cladodes	*R.raetam*	Abdalla and Saleh 1983
Apigenin	Cladodes, Seeds	*R.raetam; R.sphaerocarpa*	El Sherbeiny et al. 1978; Mariem et al. 2014; Touati et al. 2017

Apigenin 8-C-glucoside (vitexin)	Cladodes	*R.sphaerocarpa*	Louaar et al. 2005
Apigenin-7-glucoside	Cladodes	*R.raetam*	Abdalla and Saleh 1983
Apigenin 6,8-di-*C*-glucoside (vicenin-2)	Cladodes, seeds	*R.raetam; R.sphaerocarpa*	Louaar et al. 2005; El Sherbeiny et al. 1978; Abdalla and Saleh 1983
Chrysoeriol (3'-Methoxyapigenin)	Cladodes	*R.raetam*	Abdalla and Saleh 1983
Scutellarein (6-Hydroxyapigenin)	Cladodes	*R.raetam*	Djeddi et al. 2013
Prenylated flavones			
Licoflavone C	Cladodes	*R.raetam*	Xu et al. 2015
Isoprenylated flavones			
Ephedroidin	Cladodes	*R.raetam*	Kassen et al. 2000; Xu et al. 2015
Furanoflavones			
Retamasins A	Cladodes	*R.raetam*	Xu et al. 2015
Retamasins B	Cladodes	*R.raetam*	Xu et al. 2015
Atalantoflavone	Cladodes	*R.raetam*	Xu et al. 2015
5,4'-dihydroxy-(3",4"-dihydro-3", 4"-dihydroxy)-2",2"-dimethylpyrano-(5",6":7,8)-flavone	Cladodes	*R.raetam*	Kassen et al. 2000
Flavanones			
Naringenin	Cladodes, Seeds	*R. raetam, R. sphaerocarpa;*	El Sherbeiny et al. 1978; Mariem et al. 2014; Touati et al. 2017
Isoflavones			
Genistein	Cladodes, Seeds	*R. monosperma, R. raetam*	Harborne 1969; El Sherbeiny et al. 1978; Djeddi et al. 2013
6-Hydroxygenistein	Cladodes	*R. raetam*	Djeddi et al. 2013
Genistin (Genistein-7-glucoside)	Cladodes	*R. sphaerocarpa*	Lopez-Lázaro et al. 1998; Louaar et al. 2005
5-methoxy-Genistein	Cladodes	*R.monosperma, R.raetam*	Harborne 1969
Genistein 8-*C*-glucoside	Cladodes	*R.sphaerocarpa*	Louaar et al. 2007
Genistein-7-*O*-xylosyl- 8-*C*-glucoside	Cladodes	*R.sphaerocarpa*	Akkal et al. 2010
Daidzein	Cladodes, Seeds	*R.monosperma, R.raetam*	Harborne 1969; El Sherbeiny et al. 1978; Abdalla and Saleh 1983
Daidzein-7-glucoside (Daidzin)	Cladodes	*R.sphaerocarpa*	Lopez-Lázaro et al. 1998
6′-methoxypseudobaptegenin	Cladodes	*R.sphaerocarpa*	Louaar et al. 2007
6′-methoxypseudobaptigenin 7-*O*-β-glucoside	Cladodes	*R.sphaerocarpa*	Lopez-Lázaro et al. 1998
Biochanin A	Cladodes	*R. raetam*	Djeddi et al. 2013
Pratensein (3'-hydroxy-biochanin A)	Cladodes	*R. raetam*	Djeddi et al. 2013
3'-*O*-Methylorobol	Cladodes	*R. raetam*	Djeddi et al. 2013

Calycosin	Cladodes, seeds	*R.sphaerocarpa*	Touati et al. 2017
Puerarin	Cladodes	*R.sphaerocarpa*	Touati et al. 2017
Furanoisoflavones			
Derrone	Cladodes	*R.raetam*	Xu et al. 2015
5”-Hydroxy-Derrone	Cladodes	*R. raetam*	Xu et al. 2015
Dihydrochalcones			
Phloretin	Cladodes, seeds	*R. sphaerocarpa*	Touati et al. 2017
Aurones			
6,4’-dihydroxyaurone (Hispidol)	Seeds	*R .raetam*	El Sherbeiny et al. 1978
Hispidol-6-glucoside	Seeds	*R. raetam*	El Sherbeiny et al. 1978
TERPENOIDS			
Monoterpenes			
Oxygenated Monoterpenes			
β-Linalool	Flowers	*R. raetam*	Edziri et al. 2010; Awen et al. 2011
α-Terpineol	Flowers	*R. raetam*	Edziri et al. 2010; Awen et al. 2011
cis-linalool oxide	Flowers	*R. raetam*	Awen et al. 2011
Ethyl linalool	Flowers	*R. raetam*	Awen et al. 2011
Linalyl acetate	Flowers	*R. raetam*	Edziri et al. 2010
2-Decen-1-ol	Flowers	*R. raetam*	Awen et al. 2011
Isobornyl thiocyano acetate	Flowers	*R. raetam*	Awen et al. 2011
Geraniol	Flowers	*R. raetam*	Edziri et al. 2010
Geraniol formate	Flowers	*R. raetam*	Awen et al. 2011
Geranyl acetate	Flowers	*R. raetam*	Edziri et al. 2010
Citronellal	Flowers	*R. raetam*	Edziri et al. 2010
Neral (Citral)	Flowers	*R. raetam*	Edziri et al. 2010
Nerol	Flowers	*R. raetam*	Edziri et al. 2010
Geranial	Flowers	*R. raetam*	Edziri et al. 2010
Geraniol			Edziri et al. 2010
Non-oxygenated Monoterpenes			
cis-β-Ocimene	Flowers	*R. raetam*	Awen et al. 2011
Limonene	Flowers	*R. raetam*	Awen et al. 2011
Terpinolene	Flowers	*R. raetam*	Edziri et al. 2010; Awen et al. 2011
α-Pinene	Flowers	*R. raetam*	Edziri et al. 2010
β-Pinene	Flowers	*R. raetam*	Edziri et al. 2010
α-Thujene	Flowers	*R. raetam*	Edziri et al. 2010
Camphene	Flowers	*R. raetam*	Edziri et al. 2010
Sabinene	Flowers	*R. raetam; R.monosperma*	Edziri et al. 2010; Derhali et al. 2016
Myrcene	Flowers	*R. raetam*	Edziri et al. 2010
α-Terpinene	Flowers	*R. raetam*	Edziri et al. 2010
Limonene	Flowers	*R. raetam*	Edziri et al. 2010
p-Cymene	Flowers	*R. raetam*	Edziri et al. 2010
γ-Elemene	Flowers	*R. raetam*	Edziri et al. 2010
Santolinatriene	Flowers	*R.monosperma*	Derhali et al. 2016
Sesquiterpenes			
Nerolidol acetate	Flowers	*R. raetam*	Awen et al. 2011
α-Humelene (α-Caryophyllene)	Flowers	*R. raetam*	Edziri et al. 2010
β-Caryophyllene	Flowers	*R. raetam; R.monosperma*	Edziri et al. 2010; Derhali et al. 2016
Farnesol	Flowers	*R. raetam*	Edziri et al. 2010

Diterpenes			
Carnosic acid	Cladodes	*R. raetam*	Mariem et al. 2014
Phytol	Cladodes	*R.monosperma*	Derhali et al. 2016
Triterpenes			
β-Amyrin	Caldodes	*R.sphaerocarpa*	Touati et al. 2015
NOR-ISOPRENOIDS			
β-Damascenone	Flowers, cladodes	*R.monosperma*	Derhali et al. 2016
β-Damascone	Flowers, cladodes	*R.monosperma*	Derhali et al. 2016
Theaspirane A	Flowers, cladodes	*R.monosperma*	Derhali et al. 2016
Theaspirane B	Flowers, cladodes	*R.monosperma*	Derhali et al. 2016
β-Ionone	Flowers	*R.monosperma*	Derhali et al. 2016
β-Damascenone	Flowers, cladodes	*R.monosperma*	Derhali et al. 2016
β-Sitosterol	Cladodes, Seeds	*R.monosperma, R.sphaerocarpa, R.raetam*	El Sherbeiny et al. 1978; Belayachi et al. 2014 ; Touati et al. 2015
Stigmasterol	Cladodes, seeds	*R.monosperma, R.sphaerocarpa*	Belayachi et al. 2014; Touati et al. 2015
Campesterol	Cladodes,seeds	*R.monosperma, R.sphaerocarpa*	Belayachi et al. 2014; Touati et al. 2015
ALKALOIDS			
Bipyperydine			
Ammodendrine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996
N-Formylammodendrine	Cladodes	*R.monosperma*	El-Shazly et al. 1996
Dehydroammodendrine	Cladodes	*R.monosperma*	El-Shazly et al. 1996
Quinolizidine			*El-Shazly Et Al. 1996*
Epilupinine	Cladodes	*R.sphaerocarpa*	El-Shazly et al. 1996
Sparteine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996
A-Isosparteine	Cladodes	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996
β-Isosparteine	Cladodes, fruits, flowers, roots	*R.monosperma, R.raetam*	El-Shazly et al. 1996
11,12-Dehydrosparteine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	El-Shazly et al. 1996
17-Oxosparteine	Stems, flowers	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996
Lupanine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996

α-Isolupanine	Cladodes	*R.monosperma, R.sphaerocarpa*	El-Shazly et al. 1996
5,6-Dehydrolupamine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996
12α-Hydroxylupanine	Cladodes	*R.sphaerocarpa, R.raetam*	El-Shazly et al. 1996 Abdel-Halim et al. 1992
6 α-Hydroxylupanine	Cladodes	*R.raetam*	Abdel-Halim 1995
Retamine	Cladodes, fruits, flowers, roots	*R.monosperma, R.sphaerocarpa, R.raetam*	Martín-Cordero et al. 1991; El-Shazly et al. 1996

Table 4. Main biological activities of *Retama* spp. Species, part of the plant that was analysed, extract tytpe, test system and effects are summarized.

Activity	Extracts	Test Systems	Effects	Study	Dosage	Species	Plant part	References
Analgesic								
	Isolated flavonoids (3-methylorobol, Biochamin A)	Acetic acid induced writhing behavior in mice	86.2% and 75.23 % inhibition	*In vivo*	1 mg kg^{-1}	*R. raetam*	*Aerial parts*	Djeddi et al. 2013
Anti-anxiety								
	MeOHE	Elevated plus-maze test in mice model	The extract enhances ambulatory movement at a dosage of 250 mg kg^{-1}, but decrease it at higher doses. Anxiolytic at lowest doses and anxiogenic athighest doses	*In vivo*	125, 250 and 375 mg kg^{-1}	*R. raetam*	Aerial parts	Al-Tubuly et al. 2011
Antihypertensive/Diuretic								
	AE	Normotensive and hypertensive animal model. Oral administration	Lowered systolic blood pressure in spontaneous hypertensive rats by 26.5 mmHg from 7 days (increased Na^+,K^+,and Cl^- excretion). Enhancement of glomerular filtration rate	*In vivo*	20 mg kg^{-1} body weight day^{-1} p.o. for 3 weeks	*R. raetam*	Leaves	Eddouks et al. 2007
	AE	Wistar rats (urinary excretion, clearance of creatinine, plasma osmolality). Intravenously administration.	Elevation of Glomerular filtration rate, a significant decrease of osmolarity and a significant diuretic effect in normal rats. Reduction of blood pressure	*In vivo*	5 mg kg^{-1} body weight. h i.v.	*R. raetam*	Aerial parts	Maghrani et al. 2005
Anti-inflammatory								
	MeOHF EtOAcF	Monocytes from healthy human donors	Inhibition 80-100% against the activation of TNF-α signalling	*In vitro*	10 µg ml^{-1}	*R. sphaerocarpa*	Cladodes	Bremmer et al. 2009
	AE	Wistar rats (Extension of colon lesion) (Colonic weight length ratio)	This extract significantly attenuated the extend and severity of the colonic injury against control TNBS. 0.18 and 0.19 mg cm^{-1} at 9 and 18 mg kg^{-1} respectively against the negative control TNBS (0,26 mg cm^{-1})	*In vivo*	9 and 18 mg kg^{-1} p.o.	*R. monosperma*	Cladodes	González-Mauraza et al. 2014
	HEtOHE	%-Lipoxygenase enzyme inhibition assay	IC_{50}: 0.421 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
Antimicrobial								
	EtOAcE	*Bacillus subtilis, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecium, Staphylococcus aureus (*MSSA*), and Staphylococcus aureus (*MRSA*)*	MICs : 0.256–1.25 mg ml^{-1}	*In vitro*	0,1 µg ml^{-1} up to 2mg ml^{-1}	*R. raetam*	Flowers	Edziri et al. 2008
	MeOHE	*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*	An Inhibition zone diameter at 14-19 mm	*In vitro*	150 µg ml^{-1} disc	*R. raetam*	Leaves	Alghazeer et al. 2012
	EtOAcF	*Bacillus cereus* ATCC 14579, *Escherichia coli* ATCC 85218	An Inhibition zone diameter equal to 12mm	*In vitro*	300 µg ml^{-1}	*R. raetam*	Cladodes	Mariem et al. 2014
	Essential oil	*Staphylococcus aureus* ATTC 27950, *Streptococcus faecalis* ATCC 29212	MICs: 2.5 and 0.625mg ml^{-1} respectively	*In vitro*	0.625-5 mg ml^{-1}	*R. raetam*	Flowers	Edziri et al. 2010
	Essential oil	*Staphylococcus aureus*, *Streptococcus pyogenes*	MICs: 250 and 375 µg ml^{-1} for isolated compunds 3-6 mg ml^{-1} essential oil	*In vitro*	Up to 6 mg ml^{-1}	*R. raetam*	Flowers	Awen et al. 2011
	Flavonoids isolated from EtOAcE (licoflavone	*Escherichia coli* *Pseudomonas aeruginosa* *Candida sp*	MICs: 7.81-15.62 81 µg ml^{-1} for bacteria 7.81 µg ml^{-1} for fungi	*In vitro*	0.125 µg ml^{-1} up to 250 µg ml^{-1}	*R. raetam*	Flowers	Edziri et al. 2012

	C and darrone)							
	HMeOHE	*Staphylococcus aureus ATCC 25923, L. innocua CLIP 74915, Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 2785*	Inhibition zone diameter *S. aureus*: 11.17 mm (cladodes); *P. aeruginosa*: 10.23 mm	*In vitro*	20 µl at 3mg ml^{-1} per disk ml^{-1}	*R. sphaerocarpa*	Cladodes	Touati et al. 2016
	EtOAcE	*Bacillus subtilis, Enterococcus faecium, Enterococcus fecalis, Streptococcus agalactiae, Streptococcus pyogenes, Corynebacterium spp, Staphylococcus aureus* (MSSA), and *Staphylococcus aureus* (MRSA), *Acinetobacter beumannii, Erratia marcescens, Escherichia coli, Klebsiella pneumonia, Candida albicans, C. glabrata, C. parapsilosis, C. kreusei*	MIC less than 1mg ml^{-1} for Gram-positive bacteria, especially *MSSA, MRSA and Streptococcus* spp. Low antifungal activity	*In vitro*	1 µg ml^{-1} up to 10 mg ml^{-1}	*R. raetam*	Aerial parts	Edziri et al. 2007
	Acid-base alkaloids purification from a MeOHE extract	*Aspergillus niger, Candida albicans, Candida tropicalis*	An Inhibition zone diameter at 125 µg ml^{-1} 10.1, 9.66 and 8.10 mm respectively for stems; 9.66; 9.33; 7,01 mm for leaves	*In vitro*	31,25 µg ml^{-1} up to 500 µg ml^{-1}	*R. monosperma*	Stem Leaves Flowers Seeds	El Hadmani et al. 2016
Anti-osteoporosis								
	HMeOHE	Dexamethasone induced osteoporosis in rats	Increase in alkaline phosphatase activity Amelioration of the imbalance between bone resorption and formation	*In vivo*	30 mg kg^{-1}, 3 months	*R. raetam*	Seeds	Omara et al., 2009
Antioxidant								
	AE	DPPH, Hydrogen peroxide scavenging activity	Low free radical scavenging activity, good hydrogen peroxide scavenging activity flowers: 54 %; stems 53 %)	*In vitro*	100-1000 mg L^{-1}	*R. raetam*	Roots Stems Flowers Fruits	Djeddi et al. 2013
	HEtOHE	Indometacin administred reduced significantly SOD, CAT, GST	SOD, CAT, GST increased by the extract	*In vivo*	25 mg kg^{-1}	*R. raetam*	Seeds	El-Toumy et al. 2011
	HMeOHE	Gavage of 7.2 mg kg^{-1} per day of Formalin for two weeks	This extract cancels out the formalin mediated increase in red blood cells count, hemoglobin content, serum glucose, SOD and GPX.	*In vivo*	20 mg $kg^{-1}day^{-1}$ for 3 weeks	*R. raetam*	Seeds	Koriem et al. 2010
	HMeOHE	ABTS, Reduction power, DPPH	ABTS IC_{50}: 125.62 µg ml^{-1}; Reduction power:1.25 mg ml^{-1}; DPPH IC_{50}: 252.03 µg ml^{-1};	*In vitro*		*R. sphaerocarpa*	Cladodes	Touati et al. 2016
	HEtOHE	TBARS	IC_{50}: 1.05 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
	HEtOHE	DPPH	IC_{50}: 0.477 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
	HEtOHE	OH scavenging activity	IC_{50}: 0.144 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
	HEtOHE	Chelating metal ions	IC_{50}: 0.134 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
	HEtOHE	ABTS	IC_{50}: 0.237 mg ml^{-1}	*In vitro*		*R. raetam*	Aerial parts	Miguel et al. 2014
	MeOHE	DPPH test, TAC and Reduction power assay	IC_{50}: 25 µg gallic acid equivalents ml^{-1}; 70.5 mg gallic acid equivalents ml^{-1}; EC_{50}: 78.10 µg ml^{-1} respectively	*In vitro*		*R. raetam*	Seeds	Tlili et al. 2015

	MeOHE	DPPH test	IC_{50}: 40 μg ml^{-1}	*In vitro*	0.03 up to 3.13 mg ml^{-1}	*R. raetam*	Leaves	Alghazeer et al. 2012
	MeOHE	ORAC, TEAC, DPPH, FRAP, Antiglycation capability	7.3 mmol Trolox equivalent g^{-1} extract, 0.4 mmol Trolox equivalent g^{-1} extract, 0.24 mmol Trolox equivalent g^{-1} extract, 0.2 mmol Fe^{2} g^{-1} extract, respectively. IC_{50} of AGEs inhibition: 40.32 μg ml^{-1}	*In vitro*	5 μg ml^{-1} up to 100 μg ml^{-1}	*R. sphaerocarpa*	Fruits	Boussahel et al. 2017
	AE	ORAC, TEAC, DPPH, FRAP, Antiglycation capability	4.03 mmol Trolox equivalent g^{-1} extract, 0.3 mmol Trolox equivalent g^{-1} extract, 0.16 mmol Trolox equivalent g^{-1} extract, 0.7 mmol Fe^{2+} g^{-1} extract, respectively. IC_{50} of AGEs inhibition: 249.86 μg ml^{-1}	*In vitro*	50 μg ml^{-1} up to 400 μg ml^{-1}	*R. sphaerocarpa*	Fruits	Boussahel et al. 2017
	MeOHE	TBA test	IC_{50}: 0.122 %(w/v)	*In vitro*	0.005 % w/v up to 0.5 % w/v	*R. raetam* subsp. *gussonei*	Seeds	Conforti et al. 2004
	MeOHE	TBA test	IC_{50}: 0.59 % (w/v)	*In vitro*	0.005 % w/v up to 0.5 % w/v	*R. raetam* subsp. *gussonei*	Leaves	Conforti et al. 2004
	EtOAcF	DPPH test	EC_{50}: 150 μg ml^{-1}	*In vitro*		*R. monosperma*	Seeds	Belmokhtar and Harche 2014
	EtOAcF	DPPH test	IC_{50}: 166 μg ml^{-1}	*In vitro*	1 μg ml^{-1} up to 100 μg ml^{-1}	*R. sphaerocarpa*	Cladodes	León-González 2012
	EtOAcF	DPPH test	IC_{50}: 400 μg ml^{-1}	*In vitro*	0,1 μg ml^{-1} up to 2mg ml^{-1}	*R. raetam*	Flowers	Edziri et al. 2008
	EtOAcF	DPPH test	IC_{50}: 33.5 μg ml^{-1}	*In vitro*		*R. raetam*	Cladodes	Mariem et al. 2014
	EtOAcF	ABTS assay	EC_{50}: 500 μg ml^{-1}	*In vitro*		*R. raetam*	Cladodes	Mariem et al. 2014
	Essential oil	DPPH test	EC_{50}: 800 μg ml^{-1}	*In vitro*		*R. raetam*	Flowers	Edziri et al. 2010
Antiulcer								
	HEtOHE	Gastroprotective effect of ulcers induced by Indometacin	76% protection compared to Ranitidine (85%)	*In vivo*	25 mg kg^{-1}	*R. raetam*	Seeds	El-Toumy et al. 2011
Antiviral								
	MeOHE	Ability of the extract to inhibit the cytopathic effect of human cytomegalovirus (HCMV) strain AD-169	IC_{50}: 250 μg ml^{-1}	*In vitro*	0,1 μg ml^{-1} up to 2 mg ml^{-1}	*R. raetam*	Flowers	Edziri et al. 2008
Cytotoxic								
	DCMEF	MTT assay: SiHa cervical carcinoma and HeLa cervix carcinoma	IC_{50}: 15 and 21 μg ml^{-1}	*In vitro*	5 up to 80 μg ml^{-1}	*R. monosperma*	Leaves	Merghoub et al. 2011
	DCMEF	Apoptosis induction: annexin V and propidium iodide stain in SiHa and HeLa cell lines	28.34 % early apoptosis in SiHa; 57.68 % in HeLa. Reduction of mitochondrial membrane potential, increase in ROS levels, activation of Caspase 3 and a decrease in Bcl2 expression	*In vitro*	20 μg ml^{-1}	*R. monosperma*	Leaves	Merghoub et al. 2011
	EtOAcE	MTT assay: SiHa cervical carcinoma and HeLa cervix carcinoma	IC_{50}: 28 and 77 μg ml^{-1}	*In vitro*	5 up to 80 μg ml^{-1}	*R. monosperma*	Leaves	Merghoub et al. 2011
	MeOH	SRB assay: large lung carcinoma cell (COR-L23)	IC_{50}:40 μg ml^{-1}	*In vitro*	1,5, 10, 20, 30, 50, 100, 150 μg ml^{-1}	*R. raetam* subsp. *gussonei*	Leaves	Conforti et al. 2004
	MeOH	SRB assay: large lung carcinoma cell (COR-L23)	IC_{50}:150 μg ml^{-1}	*In vitro*	1,5, 10, 20, 30, 50, 100, 150 μg ml^{-1}	*R. raetam* subsp. *gussonei*	Seeds	Conforti et al. 2004

	HE	Cell Titer –Glo Luminiscent assay: Leukemic T-cell lymphoblast (Jurkat cell line)	IC_{50}: 34.44 µg ml^{-1} Cell cycle arrest, activation of Caspase 3, 7, 8, and 9. increase in Fas L level	*In vitro*	0 up to 50 µg ml^{-1}	*R. monosperma*	Leaves	Belayachi et al. 2014
	HEXE	Cell Titer –Glo Luminiscent assay: Lymphocyte cells (Jurkat)	IC_{50}: 34.44 µg ml^{-1}	*In vitro*	1 µg ml^{-1} up to 50 µg ml^{-1}	*R. monosperma*	Leaves	Belayachi et al. 2013
	MeOHE	Cell Titer –Glo Luminiscent assay: Lymphoblast cells (Jeko-1)	IC_{50}: 21.47 µg ml^{-1}	*In vitro*	1 µg ml^{-1} up to 50 µg ml^{-1}	*R. monosperma*	Leaves	Belayachi et al. 2013
	DCMF	Cell Titer –Glo Luminiscent assay: Lymphoblast cells (Jeko-1), Lymphocyte cells (Jurkat)	IC_{50}: 24 .77 µg ml^{-1} ml^{-1} and 9.12 µg ml^{-1} respectively	*In vitro*	1 µg ml^{-1} up to 50 µg ml^{-1}	*R. monosperma*	Leaves	Belayachi et al. 2013
	EtOAcF	Cell Titer –Glo Luminiscent assay: Lymphoblast cells ((Jeko-1), Lymphocyte cells (Jurkat)	IC_{50}: 12.01 µg ml^{-1} and 20.22 µg ml^{-1} respectively	*In vitro*	1 µg ml^{-1} up to 50 µg ml^{-1}	*R. monosperma*	Leaves	Belayachi et al. 2013
	TCMF	SRB assay: human renal adenocarcinoma (TK-10); human breast adenocarcinoma (MCF-7): human melanoma (UACC-62)	IC_{50}: 87 µg ml^{-1} , 76 µg ml^{-1} and 42 µg ml^{-1} respectively	*In vitro*	25 µg ml^{-1} up to 250 µg ml^{-1}	*R. sphaerocarpa*	Aerial parts	López-Lázaro et al. 2000
	EtOAcF	SRB assay: human renal adenocarcinoma (TK-10); human breast adenocarcinoma (MCF-7): human melanoma (UACC-62)	IC_{50}: 49 µg ml^{-1} , 52 µg ml^{-1} and 36 µg ml^{-1} respectively	*In vitro*	25 µg ml^{-1} up to 250 µg ml^{-1}	*R. sphaerocarpa*	Aerial parts	López-Lázaro et al. 2000
	BuOHF	SRB assay: human renal adenocarcinoma (TK-10); human breast adenocarcinoma (MCF-7): human melanoma (UACC-62)	IC_{50}: >250 µg ml^{-1} , 51 µg ml^{-1} and 65 µg ml^{-1} respectively ml^{-1}	*In vitro*	25 µg ml^{-1} up to 250 µg ml^{-1}	*R. sphaerocarpa*	Aerial parts	López-Lázaro et al. 2000
Hypolipidaemic								
	AE	STZ rats	This extract exhibited long term cholesterol and triglycerides lowering activities in normal and streptozotocin	*In vivo*	20 mg kg^{-1}	*R. raetam*	Cladodes	Maghrani et al. 2004
	HMeOHE	Gavage of 7,2 mg kg^{-1} per day of Formalin for two weeks	This extract decrease serum cholesterol levels	*In vivo*	20 mg kg^{-1} day^{-1} for 3 weeks	*R. raetam*	Seeds	Koriem et al. 2010
Hypoglycaemic								

	AE	STZ rats	This extract induced a significant hypoglycaemic effect both in normal an streptozotocin diabetic rats (STZ). This effect was more pronounced in STZ than normal rats. This effect was greater than metformin. No effect in insulin levels	*In vivo*	20 mg kg^{-1}	*R. raetam*	Leaves	Maghrani et al. 2003
	MeOHE	STZ rats	This extract at 250 or 500 mg kg^{-1} significantly lowered blood glucose levels at the 3rd and 1st week of treatment, respectively. Increase of insulin levels. Inhibition of glucose intestine absorption	*In vivo*	100, 250, 500 mg kg^{-1}	*R. raetam*	Fruits	Algandaby et al. 2010
Hepatoprotective								
	AE	Carbon tetrachloride induced liver damage in rats	Reduce histopathological alterations. Restore enzyme serum levels (aspartate and alanine aminotransferase, alkaline phosphatase	*In vivo*	20 and 40 mg kg^{-1} for 2, 3 or 4 weeks	*R. raetam*	Seeds	Omara et al. 2009
	HMeOHE	Liver and kidney toxicity induced bay formalin	Diuresis, Decrease in cholesterol levels, reduce hyperglucemia, antioxidant properties, reverse of histopathological laterations, restore lvier enzimes serum levels	*In vivo*	100 or 20 mg kg^{-1} for 2 weeks	*R. raetam*	Seeds	Koriem et al. 2010

AE: Aquous extract; BuOHF: buthanol fraction; EPE:ether petroleum extract; DCMEF: Dichloromethane fraction; EtOAcE: Ethyl acetate extract; EtOAcF: Ethyl acetate fraction; HEtOHE: H_2O: Ethanol extract; HMeOHE: H_2O: Methanol extract; MeOHE: Methanol extract; MeOHF: Methanol fraction; TCMF: Trichloromethane fraction