Continuity and change in the Mediterranean medical tradition: Ruta spp. (rutaceae) in Hippocratic medicine and present practices

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Abstract

Ethnopharmacological relevance: Ruta is a genus of Rutaceae family. It features mainly shrubby plants, native to the Mediterranean region and present in traditional medicine of this region since Antiquity. The three most diffused species Ruta chalepensis L., Ruta graveolens L., and Ruta montana (L.) L., are morphologically poorly differentiated and were probably interchangeably used during Antiquity.
Aim of the study: Hippocratic and contemporary medical applications of the Ruta genus in the Mediterranean were compared to check if they result from a continuity of use from the ancient times to nowadays.
Results: Ruta spp. was mainly employed in medical preparations by Hippocratic physicians as an abortifacient and emmenagogue. In addition to gynaecological conditions, in several treatises of the Corpus Hippocraticum Ruta spp. were also recommended as a specific remedy against pulmonary diseases. Ruta spp. leaves and also roots and seeds, were administered for internal use by Hippocratic physicians after having been soaked in wine or mixed with honey or its derivatives. Contemporary traditional uses of Ruta spp. have been assessed in detail in the whole Mediterranean area.
Conclusion: Nowadays, Ruta spp. is used to treat different conditions but, as a general rule, the external uses are preferred as the toxicity of the plant is widely acknowledged.

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Keywords: Corpus Hippocraticum; Ethnobotany; Traditional plant use; Medicinal plants

1. Introduction

In his recent synthesis on traditional uses of plants in Italy, the ethnobotanist Paolo Maria Guarrera lists 100+ uses for the following species of Ruta: Ruta angustifolia Pers., Ruta chalepensis L., Ruta corsica DC., and Ruta graveolens L. (Guarrera, 2006). All these species are shrubs, whose bluish-green leaves emit a powerful odour and have a bitter taste. Ruta spp. is among the most-used genera in contemporary Italian traditional medicine, economic botany, and folk life. Such possible intensive use is not specific to Italy, but is also documented for other geographical areas of the Mediterranean (Boulos, 1983; Aliotta et al., 1995; San Miguel, 2003) and other continents (Penso, 1983). Significantly, the Ruta genus (family Rutaceae) was already abundantly used in the most ancient systematic record of medical practice of the Mediterranean world, the so-called Corpus Hippocraticum, that is, the collection of 62 treatises written between the 5th century BCE and the 2nd century CE that were attributed at a certain point of time to Hippocrates (b. 465 – d. between 375 and 350 BCE). In this paper, we compare the Hippocratic and contemporary medical applications of the Ruta genus in the Mediterranean basin in order to verify possible similarities and, should they be numerous and significant enough, to check if they result from a continuity of use from the ancient times to nowadays.
2. Materials and methods

Outlines of Ruta spp. in ancient literature

The first therapeutic indications of Ruta spp. (called pēganon; see below for the discussion of the identification) in ancient Greek medical literature can be found in nine Hippocratic treatises, none of which is by Hippocrates himself. The treatises are listed below (English and most commonly used Latin titles) in their plausible chronological order with some information on their origin and contents (Jouanna, 1992) and with references to their original text (Greek) and translation (English or French):

- **Diseases III (De morbis III)** (Hippocrates vol. VI, translator Potter, 1988): this work contains the description of a certain number of diseases ordered from head to toe (a capite ad calcem). Data are from the so-called School of Cnidus and are usually dated to the middle or end of the 5th century BCE.
- **Diseases II (De morbis II)** (Hippocrates vol. V, translator Potter, 1988): the medical information in this treatise, similar to that in Diseases III and arranged in the same way, probably dates back to mid-5th century BCE, even though the work itself might have been written later. It is generally believed that the material at the origin of the work comes from the so-called School of Cnidus.
- **Nature of women (De natura muliebri)** (Hippocrates vol. VII, translator Littre, 1851): as for the previous treatise, the information contained in this work is of the mid-5th century BCE, although the work itself was written sometime later. The title does not correspond to the contents, but to a first section that was added later. The main part of the work is made of descriptions of diseases, mainly of the womb, as in the previous two.
- **Diseases of women I-II (De morbis mulierum I-II)** (Hippocrates vol. VIII, translator Littre, 1853): this is a collection of mid-5th century BCE data.
- **Sterile women (De sterilitate mulierum)** (Hippocrates vol. VIII, translator Littre, 1853): the data in this treatise are of the same period and origin as those of the previous, that is, mid-5th century and the supposed School of Cnidus. However, such data have been reorganized and rewritten (possibly several times), perhaps in the 4th century. Both deal with the diseases of women from menarche to pregnancy, childbirth and sterility. They also include lists of remedies.
- **Internal affections (De affectionibus interioribus)** (Hippocrates vol. VI, translator Potter, 1988): this work probably comes from the so-called School of Cnidus and might be attributed to the years 400-390 BCE. It is a series of reports on clinical cases ordered without strict head to toe regularity.
- **Ulcers (De vulneribus)** (Hippocrates vol. VIII, translator Potter, 1995): a 5th/4th century BCE work, this treatise deals with certain wounds, including ulcers. In the second part, it lists medicines for their treatment.
- **Regimen (Regimen)** Hippocrates et al. (1931)(Hippocrates vol. IV, translator Jones, 1931): though similar in contents to the Hippocratic treatises from the supposed School of Kos, this is a rather independent work, traditionally dated to the 5th or the 4th century BCE.
- **Affections (De affectionibus)** (Hippocrates vol. V, translator Potter, 1988): this work, which can probably be dated to the 380s BCE, somewhat resembles other Hippocratic treatises from the Cnidian School, although it also differs substantially from Cnidus teaching.

Data collected from these works were complemented by means of additional medical and scientific literature, listed here in chronological order:

- the Problems (Problêmata) (Aristotle, books 1–21, translator Hett, 1978): once attributed to Aristotle himself (384–322 BCE), they are now more correctly attributed to his school, being notebooks in which the teachers and students of the school wrote down both the scientific questions they were interested in and the solutions each of them could bring over time. This explains why some questions have been repeatedly treated, sometimes in contradictory ways.
- **De materia medica** (in Greek peri ulês iatrikês, Greek text by Wellmann, 1906–1914 and English translation by Beck, 2005) by Dioscorides (1st century CE). Often considered as herbal, the work is in fact an encyclopaedia of the natural products from the three reigns (vegetal, mineral, and animal) used at Dioscorides’ time, and known to him, for therapeutic purposes.
- the Natural History (Naturalis Historia) of the encyclopaedist Pliny (23/24-79 CE). In this all-encompassing work made of 38 books (each devoted to a specific topic), Pliny analysed the medicinal uses of plants in books 20–27 (Jones, 1951, 1956).

Finally, medical and therapeutic elements need to be complemented with botanical information. The main source on this point is the work traditionally known as Historia plantarum, but more correctly cited as Enquiry into plants (1916–1926), by the so-called Father of Botany, Theophrastus (387–278 BCE), as well as another work by the same author, De causis plantarum (1976–1990).

As for data on contemporary uses of Ruta spp., they have been collected from modern ethnobotanical literature mentioned in the bibliographical list at the end of the article and summarized in Table 2.

Data on the uses of medicinal plants in the Corpus Hippocraticum have been compiled on the basis of the original Greek text by Alain Touwaide and databased by Emanuela Appetiti (ACCESS database). This material has already permitted a first analysis of the uses of plants in the Corpus Hippocraticum (Aliotta et al., 2003). Additional work is underway by Alain Touwaide. Traditional medical indications of Ruta spp. currently used for therapeutic purposes in Mediterranean area have been collected from the literature listed below and databased by Antonino De Natale (Table 2).
3. Results and discussion

3.1. Identification of péganon as Ruta spp. in ancient texts

An abundant literature has been devoted to the identification of the plants mentioned in ancient literature according to Linnean binomial nomenclature (Touwaide, 1997, 1998; for the Corpus Hippocraticum more specifically, also see Moisan, 1990). The historian of medieval botany and herbalism Jerry Stannard (1961) renewed the question by suggesting to combine philological and phytogeographical data, and to complete these data with the morphological information to be found in Enquiry into plants by Theophrastus, which was written approximately a century after the most ancient treatises of the Corpus Hippocraticum. More recently, an interdisciplinary research conducted by a team associating philology, botany, and pharmacology (Aliotta et al., 2003) concluded that many authors who have worked on the topic since the early 19th century generally agree on the identification of a large majority of the plants mentioned in the Corpus Hippocraticum. Such a conclusion has been confirmed by Buenz et al. (2004), for whom the identification of the plant-based prescriptions in the Corpus Hippocraticum – supposedly totalling 257 items – is uncertain for only 11 plants.

Post-Linnean authors are almost unanimous in considering that the Greek phyonym péganon corresponds to the evergreen shrub Ruta graveolens L. (André, 1985). The plant is not described in any of the treatises of the Corpus Hippocraticum, maybe because it was well known, as its high number of therapeutic uses suggest. The earliest botanical descriptions of it are found in Theophrastus’ Enquiry into plants (HP) and De causis plantarum (CP). Ruta spp. is described sometimes as a typical evergreen undershrub (HP 1.3.1 and 1.9.4) and sometimes as a vegetable (CP 2.5.3, 6.14.7, 6.14.12, 6.20.1). As an undershrub it can assume a tree habit (HP 1.3.4), with dry wood (HP 6.7.3) and fleshy leaves (HP 1.10.4), which can degenerate (HP 1.9.4). Theophrastus also affirms that Ruta spp. was a cultivated pot-herb (HP 7.4.1), although he is ambiguous about the existence of a wild and a cultivated species: while early in HP he affirms that only one species of the plant was known (HP 7.4.1), later on in the same treatise he affirms that the cultivated plant differs somewhat from the wild one, this latter having “leaves and stalks smaller and rougher”, and being “more pungent and stronger in taste” (HP 7.6.1). Similarly in CP, when he analyses the difference in fragrance in cultivated and wild species of Ruta spp., he affirms that fragrance can become too pungent in wild varieties (CP 6.20.1; the text is significant, defining the characteristics of the wild species). He may have grouped a variety of plants under the name péganon as is shown by his comment that “various plants are called Ruta spp.” (HP 1.10.4). Whatever the case, according to Theophrastus, Ruta spp. is propagated through a cutting from a branch (HP 2.1.3 and 7.2.1) or from a detached sucker, as well as from other parts (CP 1.4.2). Seed propagation is also possible, although, according to Theophrastus, some deny it because it is slow (HP 7.2.1). The plant dislikes dung (HP 7.5.1) and benefits from saline water as is shown by the fact that it improves when watered with it (CP 2.5.3). To paraphrase the Greek text, ashes are applied to its roots to protect them from worms and decomposition (CP 3.1.7.1), and the plant gets hard and dry, but, when it has grown up again after being cut down, it is larger, finer, and juicier (CP 3.19.2). When growing “in a fig tree”, it is of the best quality as fig juice feeds Ruta spp. and provides a remedy to Ruta spp. if necessary as it is hot (CP 5.6.10). The fragrance of the plant is analysed in some detail in CP. It is defined as dry, pungent, and astringent, and considered to occur not in the fruit, but in the other parts of the plant (CP 6.14.7). Such fragrance becomes worse when dryness goes too far, and is too pungent and harsh (CP 6.14.12). In such case, it is as pungent and untempered as to become disagreeable (CP 6.16.7).

In the Problems from Aristotle’s school, Ruta spp. is mainly mentioned as a cultivated and edible plant, often associated with figs and eaten at the beginning of meals, since it was thought valuable against evil-eye (Aristotle, books 1-21, translator Hett, 1978).

Dioscorides in De Materia Medica (3.45) does not add any new element to Theophrastus’ description. However, he more clearly affirms the existence of a wild species which he considers harsher than the cultivated species and unfit to eat, just like the species growing in mountains. Also he explicitly mentions that the cultivated species growing close to fig trees is more edible.

Pliny gives some information in Naturalis Historia, particularly on the cultivation of Ruta spp. For him, indeed, it is sown in spring and after the autumn equinox (19.156), grows both from seeds and cuttings (19.121), and blossoms in a bunch (19.100).

In spite of this good general correspondence between the characteristics of Ruta spp. in Theophrastus and those of Ruta graveolens L., it cannot be excluded that other members of the genus Ruta could have been collected and used by Hippocratic physicians time for the same medicinal purposes as Ruta graveolens L. The centre of diversity for Ruta spp. covers indeed the entire Mediterranean area, with some species endemic only to Corsica and the Canary Islands, and others with a larger distribution not necessarily limited to the Mediterranean area but extending to Africa, Asia, and the American continent. The species with the widest diffusion are Ruta chalepensis L. (including Ruta angustifolia Pers.) and Ruta graveolens L., the latter also being frequently cultivated. Ruta montana (L.) is also widespread in the Mediterranean area, mainly in dry and rocky habitats (Tutin et al., 1968). The taxonomy of Ruta spp. is based on the floral morphology, and species limits are not currently well known, but are the object of a continuing study of species boundaries and biogeographic patterns (Salvo and Conti, in press). Ruta graveolens L., Ruta chalepensis L. (included the variety angustifolia) and Ruta montana (L.) might have been confused (or associated) by the physicians of the Corpus Hippocraticum, particularly because the flower of the three species is neither described nor mentioned as a descriptor in ancient medical texts, and all three species have partially overlapping geographical distribution patterns.
<table>
<thead>
<tr>
<th>Medical use</th>
<th>Preparation</th>
<th>Other herbs in the same medicine</th>
<th>Identification of the plants</th>
<th>Hippocratic medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess (potion)</td>
<td>Rue, smoke, and lettuce with pounded barley flour applied, mixed in wine.</td>
<td>(1) Mentha sp. (2) Mentha spicata L. (3) Cuminum cyminum L. (4) Elelisfakon origanon (1)</td>
<td>Med. III 70</td>
<td></td>
</tr>
<tr>
<td>Angina (throat)</td>
<td>(1) Rue, (2) origanon, (3) addax, and (4) thymbra, macerated with wine and</td>
<td>(1) Mentha sp. (2) origanon (3) addax, and (4) thymbra, macerated with wine and diluted with</td>
<td>Med. III 49</td>
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<td></td>
<td>added, and whole seeds macerated in wine.</td>
<td>water and thymbra, seseli, added with water and diluted with water.</td>
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<td></td>
</tr>
<tr>
<td>Conception (to</td>
<td>Rue, origanon, and thymbra, macerated with powdered kuparittos or</td>
<td>(1) Mentha sp. (2) origanon (3) addax, and (4) thymbra, macerated with water and diluted with</td>
<td>Med. III 45</td>
<td></td>
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<tr>
<td>help to conceive</td>
<td>conglomeratus lapathon wood, drunken in wine.</td>
<td>water and thymbra, seseli, added with water and diluted with water.</td>
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</tr>
<tr>
<td>Delivery of placenta</td>
<td>(1) Rue, (2) origanon, (3) addax, and (4) thymbra, macerated with</td>
<td>(1) Mentha sp. (2) origanon (3) addax, and (4) thymbra, macerated with water and diluted with</td>
<td>Med. III 44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>added, and whole seeds macerated in wine.</td>
<td>water and thymbra, seseli, added with water and diluted with water.</td>
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<tr>
<td>Delivery of placenta</td>
<td>Rue, origanon, and thymbra, macerated with powdered kuparittos or</td>
<td>(1) Mentha sp. (2) origanon (3) addax, and (4) thymbra, macerated with water and diluted with</td>
<td>Med. III 84</td>
<td></td>
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<tr>
<td></td>
<td>conglomeratus lapathon wood, drunken in wine.</td>
<td>water and thymbra, seseli, added with water and diluted with water.</td>
<td></td>
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</tr>
<tr>
<td>Delivery of placenta</td>
<td>Rue, origanon, and thymbra, macerated with powdered kuparittos or</td>
<td>(1) Mentha sp. (2) origanon (3) addax, and (4) thymbra, macerated with water and diluted with</td>
<td>Med. III 84</td>
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<td></td>
<td>conglomeratus lapathon wood, drunken in wine.</td>
<td>water and thymbra, seseli, added with water and diluted with water.</td>
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<td></td>
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</table>
3.2. Therapeutic uses of *Ruta* spp. in the Corpus Hippocraticum

3.2.1. Therapeutic indications

The several therapeutic uses of *péganon* in the Hippocratic treatises listed above are presented in Table 1 and can be summarized as follows. *Ruta* spp. was prescribed to treat pulmonary diseases (*Morb. III*, 15 and *Morb. II* 47 and 64), included phthisis (*Aff. Int.*, 12; *Morb. II*, 50), which might correspond at least in part to modern tuberculosis (*Stannard, 1961*). *Ruta* spp. draughts were also used as a gargle against throat angina (*Morb II*, 26), and to reduce a swelling of the spleen, which might be one of the symptoms of malaria (*Aff. Int.*, 30). *Ruta* spp. is also included among the herbs employed externally to cure wounds (*Valn.*, 11).

The major number of therapeutic uses of *Ruta* spp. is in the field of gynaecology. *Ruta* spp. was mainly used for the treatment of various ailments of the womb, which are not necessarily well identified. *Usteria*, for example, which does not correspond by any means to the process described by this term in modern neuropsychiatry, was considered to be a move of the uterus within the female body. In so doing, it could disturb respiration, provoking the so-called *uterine suffocation*, as well as other vital functions. It seems reasonable to consider that the term was a generic one to designate any kind of uterine condition (*Potter, 1990*). *Ruta* spp. was also prescribed for menses disturbance, be it their regulation, amenorrhoea or excess. It was administered both as an abortive and to help conception. It was prescribed to treat all the possible disturbances during pregnancy, during the delivery, to expel the placenta, and against puerperal fever.

The use of *Ruta* spp. for different, and sometimes opposite, gynaecological conditions might result from the fact that the *Corpus Hippocraticum* is a collection of treatises from different times, locations, and also methodological approaches to pharmacological treatment of disease. There were mainly two ways to treat disease: by administering medicines counteracting disease mechanisms according to the principle *contraria contrariis* (principle of contrary) or by imitating disease mechanisms according to *similia similibus* (principle of similarity). In both cases, medicines were credited with the role of restoring the right balance of the physiological components of the body, which, in the specific case of the Hippocratic system(s) were the four humours: blood, phlegm, yellow bile and black bile. As *Ruta* spp. was credited with hot and dry properties, it could be used either to treat inflammations (heat against heat; principle of similarity) or to reduce any excess of fluids in the body (heat against moisture and cold; principle of contrary).

It might be worth mentioning that the name *péganon* has been interpreted by philologists as deriving from a Greek root of which the verb *pégnumi* is another derivative (*André, 1985*). Yet the root and, hence, the verb derived from it, mean to flow or to make flow, something that might refer to the use of *Ruta* spp. as an abortifacient. If so, the very name of the plant might have been produced on the basis of its use according to the principle of contrary (*contraria contrariis*). The heat with which *Ruta* spp. was credited was applied to provoke an elimination...
<table>
<thead>
<tr>
<th>Country</th>
<th>Species</th>
<th>Uses</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>R. c.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Infusion</td>
</tr>
<tr>
<td></td>
<td>R. g.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Decoction</td>
</tr>
<tr>
<td></td>
<td>R. m.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Cataplasmata</td>
</tr>
<tr>
<td></td>
<td>R. c.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Tincture</td>
</tr>
<tr>
<td></td>
<td>R. g.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Tincture</td>
</tr>
<tr>
<td></td>
<td>R. m.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Tincture</td>
</tr>
<tr>
<td>Greece</td>
<td>R. c.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Infusion</td>
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<td></td>
<td>R. g.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Decoction</td>
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<td></td>
<td>R. m.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Cataplasmata</td>
</tr>
<tr>
<td>Ireland</td>
<td>R. c.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Infusion</td>
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<td></td>
<td>R. g.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Decoction</td>
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<td></td>
<td>R. m.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Cataplasmata</td>
</tr>
<tr>
<td>Italy</td>
<td>R. c.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Infusion</td>
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<tr>
<td></td>
<td>R. g.</td>
<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
<td>Decoction</td>
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<td>Abortive; genito-urinary system disorders (prostate); mental disorders (anti-convulsive); poisoning</td>
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</tbody>
</table>

Note: The table provides a summary of modern phytotherapeutic uses of Ruta spp. in the Mediterranean area (countries are in alphabetical order). The uses are indicated by specific conditions and the corresponding preparations used. The table includes references for each use and preparation method.
(1) Abortive; (2) anti-helmintic; (3) antispasmodic; (4) digestive; (5) respiratory; (6) anti-rheumatic; (7) skin affection; (8) injuries and wounds; (9) antidote for poisoning; (10) cold; (11) anti-acne; (12) mild laxative; (13) tonic

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local, 4. local: respiratory) Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

Leaves, tips

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

R. c.

Leaves

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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R. g.

Flowers

R. g.

Anchovy

R. g.

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

R. c.

Leaves

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

R. c.

Leaves

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

R. c.

Leaves

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

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Carras (1994)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Flowers

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Anchovy

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Carras (1994)

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

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Carras (1994)

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

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Carras (1994)

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Leaves

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Flowers

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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R. c.

Leaves

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Flowers

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Anchovy

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Carras (1994)

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Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

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Carras (1994)

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

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Carras (1994)

R. g.

Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Leaves

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Flowers

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Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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R. c.

Leaves

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Flowers

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Carras (1994)

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Trotter (1915)

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Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

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Flowers

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Anchovy

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Leaves

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Flowers

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Carras (1994)

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Trotter (1915)

R. g.

Pain killer (1. analgesic, 2. anti-rheumatic, 3. local: respiratory)

R. g.

R. c.

Leaves

R. g.

Flowers

R. g.

Anchovy

R. g.

Carras (1994)

R. g.

Trotter (1915)
<table>
<thead>
<tr>
<th>Country</th>
<th>Medicinal uses</th>
<th>Preparation</th>
<th>Species</th>
<th>Part(s) used</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>(1) Abrasive, radiopharmaceuticals; (2) abortive; (3) anti-inflammatory; (4) antispasmodic; (5) astringent; (6) corticosteroid; (7) diuretic; (8) expectorant; (9) fibrotic; (10) haemostatic; (11) hypoglycaemic; (12) hypotensive; (13) inulin; (14) nutritive; (15) oxytocic; (16) stimulant; (17) vermifuge</td>
<td>Infusion</td>
<td>R. c., R. g., R. m.</td>
<td>Aerial parts, lard</td>
<td>Loz et al. (2002)</td>
</tr>
<tr>
<td>Portugal</td>
<td>Internal desease (malignant/lupus); diarrhoea, against intestinal pain</td>
<td>Direct use, Topical</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>Vázquez et al. (1997)</td>
</tr>
<tr>
<td>Morocco</td>
<td>Ear affection (pain); (1) Ear infection (pain); (2) allergy</td>
<td>Oil, fumigations, infusions, drinkable decoctions, injections, sometimes in association with Cannabis sativa L.</td>
<td>R. c., R. g.</td>
<td>Aerial parts</td>
<td>Merzouki et al. (2000)</td>
</tr>
<tr>
<td>Palestine</td>
<td>Pain killer (stomach, intestine, teeth, blood, veins, haemorrhoids); (7) digestive, eye affections, genito-urinary system disorders, injuries and wounds; mental psychiatric, epilepsy; (2) headaches; (3) toothache; (4) rheumatic affections; (5) respiratory system affection; (6) diuretics, for the treatment of male and female genitalia; (7) head swimming; (8) head aches; (9) eye affections, injuries and wounds; (10) digestive; (11) wounds; (12) injuries and wounds; (13) respiratory system affection; (14) anti-inflammatory</td>
<td>Infusion</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>Loz et al. (2002)</td>
</tr>
<tr>
<td>Near East</td>
<td>Circulatory system affection (hypertension); (2) anti-inflammatory; (3) astringent; (4) antispasmodic; (5) anti-rheumatic; (6) anthelmintic; (7) diuretic; (8) expectorant; (9) fibrotic; (10) hypoglycaemic; (11) hypotensive; (12) inulin; (13) nutritive; (14) oxytocic; (15) vermifuge</td>
<td>Infusion</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>Novais et al. (2004)</td>
</tr>
<tr>
<td>Near East</td>
<td>Abortive, circulatory system affection (vasoregulator); (2) anti-inflammatory; (3) astringent; (4) antispasmodic; (5) anti-rheumatic; (6) anthelmintic; (7) diuretic; (8) expectorant; (9) fibrotic; (10) hypoglycaemic; (11) hypotensive; (12) inulin; (13) nutritive; (14) oxytocic; (15) vermifuge</td>
<td>Infusion</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>Bonet and Valles (2007)</td>
</tr>
<tr>
<td>Near East</td>
<td>Abortive, circulatory system affection (vasoregulator); (2) anti-inflammatory; (3) astringent; (4) antispasmodic; (5) anti-rheumatic; (6) anthelmintic; (7) diuretic; (8) expectorant; (9) fibrotic; (10) hypoglycaemic; (11) hypotensive; (12) inulin; (13) nutritive; (14) oxytocic; (15) vermifuge</td>
<td>Infusion</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>San Miguel (2003)</td>
</tr>
<tr>
<td>Near East</td>
<td>Abortive, circulatory system affection (vasoregulator); (2) anti-inflammatory; (3) astringent; (4) antispasmodic; (5) anti-rheumatic; (6) anthelmintic; (7) diuretic; (8) expectorant; (9) fibrotic; (10) hypoglycaemic; (11) hypotensive; (12) inulin; (13) nutritive; (14) oxytocic; (15) vermifuge</td>
<td>Infusion</td>
<td>R. c.</td>
<td>Aerial parts</td>
<td>Bonet et al. (1999)</td>
</tr>
</tbody>
</table>

**Note:** The table continues with similar information for other countries and medicinal uses, preparation methods, and species parts used, along with references for each entry.
Species: (R.) Ruta spp., (R. c.) Ruta chalepensis L., (R. g.) Ruta graveolens L., (R. m.) Ruta montana L.

**Table 1.**

<table>
<thead>
<tr>
<th>Species</th>
<th>Therapeutic Indications</th>
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</thead>
<tbody>
<tr>
<td><strong>R. c.</strong></td>
<td>Leaves</td>
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<tr>
<td><strong>R. g.</strong></td>
<td>Leaves, (2) flowers</td>
</tr>
<tr>
<td><strong>R. c. and R. g.</strong></td>
<td>Leaves, seeds</td>
</tr>
</tbody>
</table>

3.2.2. Preparations

Ruta spp., was used entirely the fresh plant or parts, especially the leaves, also its seeds, and, less frequently, its roots (Table 1). For internal use, have been soaked in wine or mixed with honey or its derivatives, dried, or dry, perfumed, mixed with water or pure. Wine use was not limited to an excipient, as it was also credited with therapeutic properties and was frequently prescribed in the cure of different diseases. In the Hippocratic pharmacopoeia, wine was used purgatively as airmixtures of vinegar and honey, and like, was an astringent, a mixture of vinegar and honey-like. It was used pure or in such derivatives, as a mixture of vinegar and honey.

3.2.3. Preparations

As for the excipients for internal administration, wine was among the most used in Hippocratic pharmacotherapy. Several varieties are mentioned, ranging from (a) red-flavored drinks to (b) white ones. Wine was not limited to an excipient, as it was also credited with therapeutic properties and was frequently prescribed in the cure of different diseases. In the Hippocratic pharmacopoeia, wine was used purgatively as a mixture of vinegar and honey-like, it was used pure or in such derivatives, as a mixture of vinegar and honey.

3.2.4. Preparations

As for the excipients for internal administration, wine was among the most used in Hippocratic pharmacotherapy. Several varieties are mentioned, ranging from (a) red-flavored drinks to (b) white ones. Wine was not limited to an excipient, as it was also credited with therapeutic properties and was frequently prescribed in the cure of different diseases. In the Hippocratic pharmacopoeia, wine was used purgatively as a mixture of vinegar and honey-like, it was used pure or in such derivatives, as a mixture of vinegar and honey.

3.2.5. Preparations

As for the excipients for internal administration, wine was among the most used in Hippocratic pharmacotherapy. Several varieties are mentioned, ranging from (a) red-flavored drinks to (b) white ones. Wine was not limited to an excipient, as it was also credited with therapeutic properties and was frequently prescribed in the cure of different diseases. In the Hippocratic pharmacopoeia, wine was used purgatively as a mixture of vinegar and honey-like, it was used pure or in such derivatives, as a mixture of vinegar and honey.

3.2.6. Preparations

As for the excipients for internal administration, wine was among the most used in Hippocratic pharmacotherapy. Several varieties are mentioned, ranging from (a) red-flavored drinks to (b) white ones. Wine was not limited to an excipient, as it was also credited with therapeutic properties and was frequently prescribed in the cure of different diseases. In the Hippocratic pharmacopoeia, wine was used purgatively as a mixture of vinegar and honey-like, it was used pure or in such derivatives, as a mixture of vinegar and honey.
### Table 3
Comparison between hippocratic and modern therapeutic uses of rue

<table>
<thead>
<tr>
<th>Condition</th>
<th>Algeria</th>
<th>Bulgaria</th>
<th>Cyprus</th>
<th>Greece</th>
<th>Israel</th>
<th>Italy</th>
<th>Jordan</th>
<th>Libya</th>
<th>Morocco</th>
<th>Near East</th>
<th>Palestine</th>
<th>Spain</th>
<th>Tunisia</th>
<th>Turkey</th>
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3.3. Contemporary traditional uses of Ruta spp.

Available documentation on contemporary traditional uses of Ruta spp. in the Mediterranean basin varies from region to region. For Spain and Italy and, to a lesser extent, Turkey, a conspicuous corpus of ethnopharmacological data is documented, whereas information is scanty and often vague for the rest of contemporary Mediterranean world. However, some common features in the therapeutic uses of Ruta spp. can be evidenced.

Leaves are the most frequently used part of the plant, but it is also common to administer the entire aerial parts. Flowers and roots only are used in few unrelated locations, while they are used in association with the leaves for the same conditions elsewhere. Use of seeds has been reported prevalently in Turkey (Akalin and Ertuğ, 2002–2003).

Therapeutic indications cover a wide range of medical conditions affecting almost all parts of human body, even though in many cases they are general and do not refer to any specific part of the body. This is particularly evident for the countries with no recent detailed ethnopharmacological study such as Algeria, Morocco, and Tunisia. In addition, the indications for Eastern Europe (Bulgaria, Cyprus, and Greece) are far from being precise in the current state of research. Focusing on Spain, Italy, and Turkey, it is possible to have a clearer idea of the actual medicinal uses of the plant, although the resulting picture is not homogeneous. In Spain, Ruta spp. is mainly prescribed to cure menstrual disorders and as abortifacients, and also against digestive disorders (San Miguel, 2003). Anthelmintic and vermifuge are by far the most common properties throughout Italy, including Sicily and Sardinia. Anti-inflammatory and analgesic properties are second to the previous. A survey carried out among herbalists in 40 provinces of Turkey has revealed that the plant is mainly prescribed as a laxative (Akalin and Ertuğ, 2002–2003), whereas field investigation evidenced that therapeutic indications vary from region to region, and include a wide array of diseases (Table 2).

The most frequent type of preparation for internal use is infusions and/or decoctions of Ruta spp. leaves, whereas for external use direct application of fresh leaves or juice is the standard type of administration. Oleolites made by faying Ruta spp. leaves in olive oil are frequent in Spain and Italy. They are recommended against rheumatisms. A similar preparation is used in Turkey to prepare a cataplasm against severe cough and croup (Akalin and Ertuğ, 2002–2003).

Ruta spp. is frequently used with other herbs. Complex recipes are rarely described. In Italy and Spain Ruta spp. is most frequently associated with members of Origanum, Mentha, Nepeta or Thymus genera, and also garlic (Allium sp. pl.). Of the two cases of plants being mixed with Ruta spp. in Turkey, one includes Nigella seeds (Akalin and Ertuğ, 2002–2003). Nigella, particularly Nigella sativa L., is frequently used in folk recipes in the Near East against numerous conditions, mainly involving the vascular and respiratory systems (Aliotta et al., 2003).

The comparison between the Corpus Hippocraticum and modern Mediterranean ethnopharmacology (Table 3) evidences differences not only in the uses, something that led the early-20th century German pharmacognost Rudolf Schmid (1919) to omit Ruta spp. from among the plants of antiquity still used at that time, but also, and perhaps more significantly, in the ways of preparing medicines made of Ruta spp.

In the Corpus Hippocraticum, Ruta spp. was macerated in, and administered with wine, or mixed with hydromel. In other cases, Ruta spp. was pounded, mixed into wine, and immediately drunk (Table 1). Although hot water extracts (both as decoctions and infusions) were used by Hippocratic practitioners, there is no mention of these preparations for Ruta spp. By contrast, both infusions and decoctions represent the most diffused way of preparing higher medicinal plants, including Ruta spp., in modern Mediterranean ethnopharmacognosy. It is well known that the choice of a solvent influences the chemical composition of the extract, both quantitatively and qualitatively. Although none of the extractants is ideal, wine, considered as a diluted ethanolic solvent, should ensure high rates of extraction of non-polar and polar substances, also at ambient temperature. On the other hand, water extracts, which are carried out at high temperature (>90 °C), could damage thermo-labile compounds (Eloff, 1998). Administering Ruta spp. leaves after maceration in wine might ensure the preservation of the major chemical constituents of the plant.

4. Conclusions

Ruta spp. has been constantly present in the Western therapeutic from Hippocratic medicine on. Not only did Dioscorides and Galen (On the mixtures and properties of simple medicines) mention it in their major works on materia medica, but also late antique manuals of therapeutics such as the Medicines from Vegetables and Fruits by Gargilius Martialis (d. 260 CE) and the Pseudo Apuleius, which was written sometimes in the 4th century CE and circulated widely in the pre-1100 Western world, devoted each a paragraph to the plant. The more typically Western recipe book known as the Lorscher Book of Medicines, used sometimes around 800 BC in the Abbey of Lorsch in Carolinian Germany, included it in several prescriptions. In the Arabic world, Ruta spp. is present in the major syntheses on materia medica by al Biruni (973–1048 CE), al Ghafiqi (d. ca. 1160 CE) and ibn al Baytar (ca. 1204–1248), as well as in other therapeutic works as those of ibn Butlan (d. 1063 CE [?]) and his contemporary ibn Ridwan (ca 980–1060 CE). After the translation of Arabic medicine into Latin from the late-11th to the 13th century, Arabic pharmacological knowledge was available in the West. Ruta spp. appeared in the many versions of the Tacuinum Sanitatis, an adaptation of ibn Butlan’s work, as well as in the so-called Circa Instans and Book on Simple Medicines from the Salerno school, which were among the most diffused and influential works on medicinal plants in the Late Middle Ages. With the rediscovery of Greek scientific texts in the Renaissance, the information to be found in Dioscorides’ De materia medica was again available and abundantly commented on, particularly by Pietro Andrea Mattioli (1501–1577), whose repeated new editions of his commented translation of Dioscorides’ treatise contributed to popularize the traditional Greek uses of plants, including Ruta spp. New 16th-century herbals such as the History of Plants (1542) by Leonhart Fuchs (1501–1566), rooted
in ancient science, expanded on it, and integrated local uses of plants into traditional knowledge, among others Ruta spp. At the turn of the 19th–20th centuries, Georg Dragendorf included it in his manual entitled Die Heilpflanzen der verschiedenen Völker und Zeiten. Ihre Anwendung, wesentlich Bestandtheile und Geschichte. Ein Handbuch für Äzte, Apotheker, Botaniker und Droguisten (Stuttgart, 1898), which was a sort of summary of traditional uses.

The medicinal uses of Ruta species in the Corpus Hippocraticum were preserved at least in part over time. Nevertheless, during the centuries, Ruta spp. was prevalently administered against eye affections and different kinds of aches, and as an antidote against poisons and venomous bites by various animals. Also, the plant got an increasingly growing symbolic value. Thanks to its numerous little leaves, it was used to sprinkle the Holy Water and to bless people in the Roman rites of the Catholic Church. Known for this reason as Herb of grace (Cleene and Lejeune, 2003), Ruta spp. was among the first plants introduced by Europeans in the New World. Heinrich et al. (2006) have suggested that this religious role contributed to promote the therapeutic uses of Ruta spp. in Latin America.

The ethnopharmacology of Ruta spp. in the Mediterranean area does not seem to have been influenced by the symbology and ritual uses of the plant. Ruta spp. was considered by Hippocratic physicians as a remedy mainly suitable for women diseases and, secondarily, as an effective pharmakon in the cure of pulmonary affections. Although these indications have remained alive in circum-Mediterranean countries through the centuries, there is now a greater awareness of the potential toxicity of the plant. Current recommended therapeutic indications of Ruta spp. are no longer related to the gynaecological sphere, with the exception of the use as an abortifacient. Ruta spp. is still used internally in the treatment of pulmonary diseases, and externally as an antihelminitic and antirheumatic (something that constitutes the most frequent uses of the plant). Often it is treated at high temperature before being administered. These current indications seem to suggest that a shift towards a safer application occurred at a certain point in time. If so, this evolution might have been among the factors that contributed to eliminate many of the Hippocratic uses.

References


Salvo, G., Conti, E. Investigating the monophyly and biogeographic history of *Ruta* (Rutaceae) with chloroplast DNA sequence data. Annual Meeting of Botanical Society of America, California State University Chico – Sistematics section, abstract no. 181, in press.


