Pharmacological properties of citrus and their ancient and medieval uses in the Mediterranean region

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Pharmacological properties of citrus and their ancient and medieval uses in the Mediterranean region

Beatriz Álvarez Arias, Luis Ramón-Laca

Abstract

This paper reviews the pharmacological properties of Mediterranean-grown citrus species (*Citrus* L., Rutaceae), including citron (*Citrus medica* L.), lime (*Citrus* × *auantiifolia* [Christm.] Swingle), lemon (*Citrus* × *limon* [L.] Osbeck), bitter orange (*Citrus* × *aurantium* L.) and pomelo (*Citrus maxima* [Burm.] Merr.), as referred to in ancient, medieval and 16th century sources. The virtues of the species reported in these texts were compared to those known to modern science. A much broader spectrum of pharmacological properties was recorded by these early writers than one might expect. The use of the citron and lemon as antidotes for 'poison and venom' is recorded in the very earliest material. According to modern scientific literature the citron and the bitter orange may possess anti-cancer activity, lime may have an immunomodulatory effect in humans, and the pomelo may be useful for treating circulatory problems. Lemons might even ease hangover symptoms. Research is required to confirm these properties.

Keywords: *Citrus* fruits; Pharmacological properties; Remedies

1. Introduction

Eight taxa belonging to the genus *Citrus* (Rutaceae) have been traditionally cultivated in the Mediterranean region. The citron (*Citrus medica* L.) was probably the only citrus fruit known in ancient times in Europe since the lemon (*Citrus limon* [L.] Osbeck), lime (*Citrus* × *auantiifolia* [Christm.] Swingle), pomelo (*Citrus maxima* [Burm.] Merr.) and bitter orange (*Citrus* × *aurantium* L.) were all introduced into Europe by the Muslims via the Iberian Peninsula and Sicily. The sweet orange (*Citrus* × *aurantium* L.), mandarin (*Citrus reticulata* Blanco) and grapefruit (*Citrus* × *aurantium* Macfad.) arrived in the West between the 15th and 19th centuries as a result of trade with British and Portuguese colonies.

This paper presents ethnobotanical information discovered in ancient and medieval manuscripts during research into the history and origin of Mediterranean-grown citrus fruits. The obvious edible uses of these fruits are not included. The information presented comes from the 5th century B.C. up to the 16th century A.D., meaning these treatises were published well before the advent of modern pharmacology. Current chemical, medical, and pharmacological literature confirms some of the uses reported by these early authors. This work may shed light on the reliability of ancient and medieval, i.e., empirical–pharmacological knowledge.

2. Materials and methods

The citrus taxa studied were taxonomically treated using the synthetic proposal of Mabberley (1997), in which the subgenus *Citrus* comprises four allopatric species: two tropical, *Citrus halimii* B.C. Stone and *Citrus maxima* (pomelo), and two subtropical, *Citrus medica* L. (citron) and *Citrus reticulata* Blanco (mandarin). According to Barrett and Rhodes (1976), the last three species have given rise to all the edible citrus fruits (i.e. to *Citrus* × *auantiifolia* [Christm.]

Swingle [lime], *Citrus* × *limon* [L.] Osbeck [lemon], and *Citrus* × *aurantium* L. [orange]) via natural and deliberate hybridisation.

The search for the historic pharmacological uses of cultivated citrus plants involved the review of agricultural, botanical and medical works by Greek, Roman, Muslim and Medieval European authors. The Greek texts in which information was found included a story by Democritus (5th–4th century B.C.) told in the *Deipnosophists* by Athenaeus (3rd century A.D.), *Enquiry Into Plants* by Theophrastus (4th century B.C.) probably written about 310 B.C. in Babylon, and *De Materia Medica* written between 60 and 79 A.D. by Dioscorides. The Roman texts that provided data were *The Georgics* by Virgil (70–19 B.C.), and *Natural History* by Pliny (23–72 A.D.). Useful works from the Muslim world were by authors who lived from Syria to al-Andalus (i.e., the Iberian Peninsula), including *A Treatise on Foodstuffs* by Abu Marwan (died in 1162), *Umda* recently attributed to Abu l-Khayr (12th century), and *A Treatise of the Dietetic Properties of the Lemon* by a Hebrew physician (Egypt, 12th century). The latter was later translated from the Arabic into Latin by the philosopher Andrea Alpago (1450–1520). The Medieval European source that provided information was *A Description of Palestine* written about 1219–1221 by Jacques de Vitry. The works examined from the 16th century were *Work of Agriculture* by Gabriel Alonso de Herrera (1470–1539), published in 1513, *A Treatise on Citrus* by the Sevillian physician Nicolás Monardes (1508–1588), published in 1540, and The Spanish edition of Dioscorides' *De Materia Medica*, by Andrés de Laguna, published in 1555. The uses of the fruits referred to in the above works were compared to current knowledge on citrus pharmacology. The results are offered in the following paragraphs and summarised in Table 1. The medical terms used are mostly those of Sayre (1917).

3. Results

According to Theophrastus, (1968 pp. 310–313) if the fruit of the citron tree was placed among clothes, it kept them from being eaten by moths. It was also useful when one had drunk 'deadly poison'; administered in wine it acted as an emetic, expelling the toxin. Theophrastus also records citrons being used as breath fresheners; the inner part of the fruit was boiled to form a sauce or the juice of the fruit was squeezed into the mouth. The juice could also be prepared in other media, and then inhaled.

Democritus wrote that this fruit should be stored like some precious heirloom in chests containing one's clothes to keep them from being eaten by moths (Athenaeus, 1969, pp. 357–367). Democritus believed, as did Theophrastus, that the citron, either in solid or liquid form, was an effective antidote against all poisonous agents when taken before food. In his work *Deipnosophists*, Athenaeus included the story of a number of convicted criminals in Egypt whose punishment was to be thrown into a pit of asps. After eating some of a citron belonging to a woman in the street, they remained unharmed by the animals' venom. This story seems to have inspired similar accounts by Dioscorides (1555, p. 102), Pliny (1968, pp. 484–485) Virgil (1986, pp. 124–125) and several 16th century authors, such as Laguna (Dioscorides, 1555, p. 106) and Monardes (Fernández and Ramón-Laca, 2002, pp. 159–160). According to Democritus, the citron was a proven antidote to every kind of poison (if eaten beforehand) since its protectant properties had been recorded on many occasions, even once when someone had taken aconite (*Aconitum* L., Ranunculaceae). Like Theophrastus, Pliny (1968, pp. 12–13) said the fruit had an exceptionally strong scent (also a property of the leaves), which on penetrating stored garments warded off insects. The Parthian grandees cooked the seeds of the fruit with their meat in order to freshen the breath, and both the fruit and the pips were taken in wine to counteract poison (Pliny, 1969, pp. 484–485). The pips were also prescribed for nausea during pregnancy, and the fruit was eaten for 'weakness of the stomach' –although apparently not very easily without the aid of vinegar (Pliny, 1968, pp. 160–161).

Dioscorides (1555, p. 102) wrote that citron pips counteracted poison and relaxed the stomach. When boiled, they improved one's breath, as did the juice. The fruit was useful for bouts of fainting after childbirth. And again, if put in chests with stored garments, it warded off moths.

According to Abu Marwan (1992, p. 76) people sometimes prepared a marmalade with the peel of the citron, mixing it with a pinch of sugar to ensure better preservation. This marmalade, which comforted the stomach, was also made from the leaves. Abu Marwan (1992, p. 76, 121) also believed the peel of the citron to act as a mild antidote for poison, that it perfumed the breath, and that its scent 'comforted the spirit'. The pulp, he wrote, quenched one's thirst, the pips cleaned the stomach, and when applied in a poultice they cleansed and lightened the skin. The syrup made from the peel was thought to be a diuretic and a mild antidote for poison. The oil obtained from the flowers and peel was used as a stomach tonic.

Herrera (1970, p. 76) believed if the leaves of the citron were placed among clothes, they gave off a pleasant odour and kept moths away. He also wrote that the fruit was a remedy against the plague, invigorated the stomach and prevented vomiting. It was also useful as an antidote for poison, especially that of the scorpion or viper, either when drunk or applied externally to the wound.

Laguna wrote that all citrus fruits could be used as antidotes against poison, especially the juice and seeds of the citron and lemon (Dioscorides, 1555, pp. 105–106).

Abu Marwan (1992, p. 91) believed lime pickle improved the appetite, invigorated the stomach and acted as an antidote against poison.

According to a Hebrew physician living in Egypt in the 12th century (Ebenbitar, 1583, pp. 6–11), the peel, pulp and seed of the lemon had different virtues and uses. The peel invigorated the stomach, whetted the appetite, helped one to digest food, provided better breath, improved the smell

Table 1
Ancient and medieval uses of the citrus cultivated in the Mediterranean region

Species	Active ingredients	Properties and uses cited in ancient and medieval sources	Actions recognised in current literature
Citrus medica L.	Peel: essential oil (monoterpene hydrocarbons [limonene], 5–6% citral + dipentene) (Font Quer, 1992, p. 434). Pulp: flavonoid glycosides (hesperidine) (Font Quer, 1992, p. 434), Vitamin C (Ajaiyeoba et al., 2003). Pip: tetranortriterpenoids (limonin, limonol, and nomilinic acid) (Govindachari et al., 2000). Pollen: purine alkaloids (caffeine, theophylline) (Kretschmar and Baumann, 1999)	Leaf: *digestif* (AM), insect repellent (P, H). Fruit: antiemetic (H), antitoxic (T, D, Di, V, P, H, L), insect repellent (T, D, P), remedy against plague (H), stomach tonic (P, H), tonic (D). Peel: *digestif* and tonic (AM). Syrup from peel: antitoxic and diuretic (AM). Essential oil from flower and peel stomachic (AM). Pulp: antitoxic (L), pulmonary sedative (T, Di, P). Pip: antiemetic (Di, P), antitoxic (P, AM, Eb, L), *digestif* (Di), hygienic (AM), purgant (AM), pulmonary sedative (Di, P).	Leaf: remedy against febrile illnesses? (Ajaiyeoba et al., 2003). Peel: aromatic and tonic (Font Quer, 1992). Pulp: remedy against febrile illnesses? (Ajaiyeoba et al., 2003). Pip: anti-cancer activity? (Tian et al., 2001)
Citrus × *auantiifolia* (Christm.) Swingle	Leaf: essential oil (Pertiwi, 1992). Peel: essential oil (sesquiterpene hydrocarbons [α-santalene, γ-curcumene, β-selinene and germacrenes A, B, C, D], monoterpene hydrocarbons (sabinene, γ-pinene, limonene), monoterpene alcohols (linalool, terpinen-4-ol, α-terpineol), γ-terpinene, esters, monoterpene aldehydes, aliphatic aldehydes, pectinesterase (Syamsuhidayat and Hutapea, 1991; Dugo et al., 1997; Limyati and Juniar, 1998; Mondello et al., 1998; Contreras-Esquivel et al., 1999; Feger et al., 2000). Pulp: sucrose, protein components (Echeverría, 1992; Gharagozloo and Ghaderi, 2001). Flavonoids and saponines (Limyati and Juniar, 1998).	Fruit pickle: antitoxic (AM), appetizer (AM), and stomachic (AM).	Leaf: antibacterial (Pertiwi, 1992). Fruit: antimicrobial (Syamsuhidayat and Hutapea, 1991; Limyati and Juniar, 1998; Rodrigues et al., 2000). Pulp: immunomodulatory effect? (Gharagozloo and Ghaderi, 2001).
Citrus × *limon* (L.) Osbeck	Flower: purine alkaloids (caffeine, theobromine, theophylline, paraxanthine) (Kretschmar and Baumann, 1999). Peel: essential oil (2.5% maximum [(+)-limonene, canfen, citral, citronelal, felandren, pinene, terpinol], coumarins (bergamotin, limetin), citroflavonoids (neohesperidosides, rutinosides), Vitamin C, carotenoids, mucilage, calcium oxalate (Arteche García, 1998). Pulp: pectin, sugars, organic acids (ascorbic, citric, malic), citroflavonoids (Arteche García, 1998).	Fruit: *digestif* (L), remedy against plague (Di). Boiled with sugar or honey, fruit *digestif* (L). Peel antitoxic (Eb), appetizer (Eb), cardiac tonic (Eb), *digestif* (Eb, L), elixir (Eb), hygienic (Eb), pulmonary sedative (Eb), removes palate phlegm (Eb), stomachic (Eb). Pulp: antihelmintic (L), antilithic (L), antipyretic (Eb, AJ), appetizer (JV), cholagogue (Eb), cures boils and throat, uvula and tonsil abscesses (Eb), purgant (Eb), remedy against drunkenness (AJ, Eb), stomach anti-inflammatory (Eb), vascular stimulant (Eb). With food, pulp antiemetic (Eb), prevents dizziness (Eb), and tonic (Eb). With wine, pulp remedy against drunkenness (Eb). With bezoar, pulp juice antitoxic (Eb). Pips antitoxic (Eb).	Fruit: analgesic, antianaemic, antiemetic, antiesclerotic, antipyretic, antiseptic, demulcent, moisturizing, remineraliser and vulnerary (Arteche García, 1998). Antitoxic? (Otero et al., 2000a, b). Pulp: antidiarrhoeic, diuretic, intestinal mucosa protector, local haemostatic, vascular stimulant and protectant, vitaminic (Arteche García, 1998). Peel antiseptic, carminative, diuretic, eupeptic, vascular stimulant and protector, vitaminic (Arteche García, 1998).

Table 1 (*Continued*)

Species	Active ingredients	Properties and uses cited in ancient and medieval sources	Actions recognised in current literature
Citrus × *aurantium* L.	Leaf: essential oil (0.2–0.4%) (monoterpene hydrocarbons [limonene], alcohols [linalol, nerol, and methyl antranilate]), flavonoid-glycosides (hesperidine), tetranortriterpenoids (limonin) (Arteche García, 1998; Font Quer, 1992, p. 435; Hou et al., 2000a). Flower: essential oil (0.05–0.5%) (monoterpene hydrocarbons [limonene], alcohols [linalol, nerol, and methyl antranilate]) (Arteche García, 1998). Fruit: flavanone (Hou et al., 2000b). Peel: essential oil (2%) (monoterpene hydrocarbons [limonene {90%}]), bitter (naringoside, neohesperidoside) and non-bitter (hesperidoside, rutoside, and sinensetoside) flavonoids, furanocoumarins, meranzin, nobiletin, tangeretin, flavonoid-glycosides (hesperidin, neohesperidin, naringin, narirutin, rhoifolin), mineral salts, pectin, organic acids (ascorbic, citric, malic) (Tsuchida et al., 1996; Arteche García, 1998).	Distillation from flowers cardiac stimulant (L), digestif (H, L), stomachic (L), and tonic (L). With honey or sugar, flowers cardiac stimulant (L). Peel ingredient of digestion-aiding preserves (L). Pulp: eliminates greenness of jaundice (H). Wood: woodworm repellent (H).	Leaf: anti-cancer activity? (Tian et al., 2001), antispasmodic, sedative, and tranquilliser (Arteche García, 1998). Flower: antispasmodic, sedative, and tranquilliser (Arteche García, 1998). Peel: appetizer, cholagogue, demulcent, eupeptic, reduces cholesterol, tonic, vascular stimulant (Arteche García, 1998).
Citrus × *maxima* (Burm.) Merr.	Flower: purine alkaloids (caffeine, theobromine, theophylline, and paraxantine) (Kretschmar and Baumann, 1999). Peel: flavanone (Hou et al., 2000b), flavonoid-glycosides (naringin), naringenin (Hou et al., 2000a). Coumarin compounds (xanthyletin, xanthoxyletin, and suberosin (Teng et al., 1992a; Teng et al., 1992b).	Pulp: antitoxic (L), appetizer (JV), cardiac stimulant (L), and stomach tonic (L).	Antiplatelet action of coumarin compounds from fruit essence? (Teng et al., 1992a). Essential oil from fruit antibacterial? (Ontengco et al., 1995).

AJ = Abu l-Khayr; AM = Abu Marwan; D = Democritus; Di = Dioscorides; Eb = Ebenbitar; H = Herrera; JV = Jacques de Vitry; L = Laguna; P = Pliny; T = Theophrastus; V = Virgil.

accompanying belching, and strengthened the heart. He also believed it to have bezoaric properties and thus it acted against the effects of consumed or external poisons, that it was useful in personal hygiene, and that it helped remove phlegm adhered to the palate. The juice, he wrote, relieved stomach inflammation, improved the blood and alleviated fevers, cured boils, abscesses of the throat, uvula, and tonsil, and also cleaned the liver and stomach. Mixed with food, it could be employed as a tonic against dizziness and used to prevent vomiting and nausea. Taken after wine, it prevented drunkenness. Combined with a bezoar, he believed it counteracted the effects of all kinds of consumed poisons and could even act against viper and scorpion venoms. The seeds of the lemon and citron were thought to counteract the effect of poisons too. Syrup of lemon was believed to have similar virtues, even when combined with that of other plants such as quince (*Cydonia oblonga* Miller, Rosaceae) or mint (*Mentha* sp., Lamiaceae).

Abu l-Khayr (1990, pp. 443–444) wrote that sweet lemon juice was beneficial for drunkenness and fevers.

According to Jacques de Vitry (Gallesio, 1811, p. 255), both lemon and pomelo juice were served in Palestine in summer with meat and fish, since they were refreshing and whetted the appetite.

The lemon was once thought to cure the plague (Laguna in Dioscorides, 1555, pp. 105–106). Lemon juice could be prepared as a syrup called *acredine citri*, which quenched one's thirst and at the same time fought off fever. Boiled with sugar or honey, lemons were thought act as *digestifs* – the same as citron and lemon peel. Lemon juice, it was believed,

could purge one's face of pimples and other spots. When drunk, it was thought to kill intestinal worms, and to dissolve kidney stones and gravel.

Herrera (1970, p. 178) wrote that a distillation which invigorated the stomach could be made from orange flower. The same was thought to be true of orange flowers prepared with honey or sugar. He also believed orange wood kept woodworm at bay, and that orange juice made the face smooth and eliminated the greenness of jaundice.

Laguna (Dioscorides, 1555, pp. 103,105–106) recorded that *agua de azahar* (orange blossom water) was obtained from the orange flower, which is particularly fragrant. This product was thought to be a tonic for the heart and stomach, and was therefore very useful for treating bouts of fainting after childbirth. The flowers of the bitter orange, when boiled with honey and sugar, are recorded as strengthening the heart and stomach. Preserves that comforted the stomach could be made from the peel.

4. Discussion

Recent studies suggest that both the seeds of the citron and the leaves of the bitter orange might have anti-cancer activity due to their limonin content. Limonoids have been shown to inhibit the growth of oestrogen -negative and -positive receptor human breast cancer cells in culture (Tian et al., 2001). Limonin significantly slows the proliferation of MCF-7 tumour line cells (responsible for breast cancer in vivo). This inhibitory action depends on the dose of limonin used and the duration of exposure. Further work is needed, however, to establish the mechanism underlying this effect, especially with respect to the high concentrations needed to induce apoptosis.

Both the leaves and juice of the citron are commonly employed by the Yoruba people of south-western Nigeria for the treatment of febrile illnesses (Ajaiyeoba et al., 2003), a use not recorded in the ancient literature. Vitamin C is similarly added to remedies in orthodox medical practice. The Malaria Research Group of the University of Ibadan (Nigeria) is currently trying to determine the effectiveness of citron in the treatment of the malaria.

Modern literature has nothing to say about the use of the citron as an insect repellent (or to prevent garments from being eaten by moths). However, according to Paru et al. (1995), squashed lime leaves applied to the skin kept off anopheline and culicine mosquitoes —vectors of malaria— in experiments performed in the Wosera area, Papua New Guinea. They suggest "this low-technology control method may be included in the range of options for householders in order to reduce mosquito nuisance and improve their standard of health".

Govindachari et al. (2000) tested limonin, limonol and nomilinic acids from the citron for their antifungal activity against *Puccinia arachidis*, a groundnut rust pathogen, and showed them to be effective in reducing the emergence of red pustules.

Lime leaves contain an oil which acts against *Staphylococcus aureus* and *Escherichia coli* (Pertiwi, 1992, cited by Limyati and Juniar, 1998). This is not surprising since saponins, flavonoids and the oil from the lime have been recorded as antimicrobial compounds (Syamsuhidayat and Hutapea, 1991; Limyati and Juniar, 1998). In experiments performed in Guinea-Bissau, limes were shown to prevent or reduce food-borne transmission of *Vibrio cholerae*. They may therefore be considered an effective protectant against cholera when added to food (Rodrigues et al., 2000).

The essential oil of the pomelo shows in vitro activity against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922, and was found to have significant potential as a broad-spectrum antibacterial raw material for galenic preparations (Ontengco et al., 1995). From experiments performed in vitro, it is known that concentrated lime juice extract has immunomodulatory effects on activated human mononuclear cells, perhaps due to the proteins it contains (Echeverría, 1992; Gharagozloo and Ghaderi, 2001).

Modern scientific literature confirms the antipyretic and digestive properties of the lemon fruit recognised by the above medieval authors, as well as its virtues in combating nausea and loss of appetite (Arteche García, 1998). It has also been found useful in the treatment of hepatobiliar dyskinesia, oxiurasis, varicose veins, haemorrhoids, phlebitis, and urolithiasis.

No confirmation exists that a preparation of lemon juice and sugar can treat drunkenness, but due to its antiemetic, analgesic, and diuretic properties, the fruit pulp might accelerate the elimination of aldehydes, the compounds responsible for hangovers. The second author tried a solution made of lemon juice, water, salt and sodium bicarbonate which relieved the symptoms of hangover dehydration.

The lemon is used by traditional healers for treating snake bites in north-western Colombia. Otero et al. (2000a,b) showed that the ethanolic extract of ripe lemon fruits was significantly active against the lethal and haemorrhagic effects of *Bothrops atrox* venom when administered to mice. If it could be shown that lemons can act as an antidote against snake venom in humans, this would provide an interesting alternative to the sera currently used.

Due to a lack of current literature on the lime and pomelo, the virtues afforded this fruit by medieval authors could not be confirmed. However, the experiments of Teng et al. (1992a) show that the coumarin compounds in the pomelo—xanthoxyletin and suberosin—inhibit the aggregation by rabbit platelets and their release of ATP. It might therefore be useful in the treatment of problems such as thrombosis. However, confirmation of the inhibition of human platelet aggregation is still required.

The digestive and tonic virtues attributed to the bitter orange by medieval authors are confirmed by the recent literature (Arteche García, 1998).

5. Conclusions

Ancient and medieval sources report a much broader spectrum of pharmacological properties and uses of cultivated citrus species than might be expected from modern scientific literature. As frequently occurs, the more common a plant is, the less well its properties are known. In the absence of synthetic drugs, ancient and medieval physicians had to rely upon the properties of plants, in the same way that healers do nowadays, and they recognised the pharmacological value of cultivated citrus species. The citron, and perhaps other citrus fruits, might be useful as antidotes against certain venoms. Concentrated lime juice may have an immunomodulatory effect in humans. The citron and bitter orange appear to show anti-cancer activity. The coumarin compounds found in the pomelo may be useful for treating circulatory problems such as thrombosis. Due to its antiemetic, analgesic, and diuretic properties, it is likely that lemon pulp can ease the symptoms of hangovers. Further research is needed, however, to confirm these possibilities.

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