Digital Journal of
El Hombre y su Ambiente Department
ISSN: 2007-5782

Vol. 1 (15): 20-28. January to June 2018

Biological compounds activity obtained from lime *Citrus limetta* Risso.

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ABSTRACT

Lime *Citrus limetta* Risso, is produced in Mexico and other tropical countries. In traditional medicine it has been awarded various healing properties, which some of them are presented in this paper, to verify the above mentioned. In addition, the techniques applied to the study and the parts of the plant used are reviewed. The compounds that have been isolated from the lime are presented as flavones, flavonoids and phenols and the effect they produce on man. The biological activities that have been observed to have *C. limetta* are: anti-inflammatory, hypoglycemic, hypocholesterolemic, antithrombotic, antimicrobial, antihypertensive and diuretic.

Key words: Lima, *Citrus limetta*, diuretic, hypoglycemic, anti-inflammatory, antimicrobial, antihypertensive.

RESUMEN

La lima *Citrus limetta* Risso, se produce en México y en otros países de clima tropical. En la medicina tradicional se le ha adjudicado diversas propiedades curativas, motivo por el cual en este trabajo se presentan algunas de ellas, para verificar lo antes dicho. Además, se revisan las técnicas aplicadas para el estudio y las partes de la planta utilizada. Se presentan los compuestos que se han aislado de la lima como flavonas, flavonoides y fenoles y el efecto que producen en el hombre. Las actividades biológicas que se han observado en *C. limetta* son: antiinflamatoria, hipoglucemiante, hipocolemia, antitrombótica, antimicrobiana, antihipertensiva y diurética.

Palabras clave: Lima, *Citrus limetta*, diurético, hipoglucemiante, antiinflamatorio, antimicrobiano, antihipertensivo.

INTRODUCTION

Citrus limetta Risso or Persina lime, belongs to the family Rutaceae. Is native from Asia, inhabits in warm, semi-warm and temperate climates, between 200 and 2000 meters above sea level. Is cultured in familiar orchards. Is associated to perturbed vegetation tropical sub-perennial and evergreen forests (Argueta et al. 1994). It is cultivated in Mexico, India, China, Vietnam, Indonesia and Thailand, among other countries. It receives different names, in Iran it is called “limusiri”, in the south of India it is known as “tami”, in France as “bergamot” and in Nepal as “mausam”.

Lime tree is small, it has very sharp thorns; the leaves are slightly wavy and the support that joins them with the stem is slightly winged. The flower it produces are white and have many stamens. Fruits can measure up to 6 cm length and are yellowish green color, they have a protuberance at the tip, their pulp is abundant and is consumed fresh (Luna 1991, Argueta et al. 1994).

C. limetta belongs to the family of citric fruits like: orange, grapefruit, tangerine and lemon. Its flavor is sweet, so it is pleasant for consumption. Possess minerals like calcium, phosphorus, potassium, and iron, in addition to vitamins such as riboflavin, thiamine, niacin and ascorbic acid and has low calories content (Vargas et al., 2016). It also has polyphenolic compounds that has been used as functional foods or supplements. Flavonoids that it produces have antioxidant properties, so they are used to prevent degenerative diseases.

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

Digital Journal of
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ISSN: 2007-5782

Vol. 1 (15): 20-28. January to June 2018

In this work it was made a review of the scientific literature about biological activity of *C. limetta*, because in traditional medicine various therapeutic properties have been assigned to it as anti-inflammatory, antimicrobial and anticancer, among others. The uses mentioned before, the phytochemical compounds responsible for the activity and the pharmacology of these were reviewed.

MATERIAL AND METHODS

To determine the evidence of the studies of *C. limetta* biological activity, it was reviewed the system called Zummon to consult the scientific articles published from 2005 to 2017. It was analyzed the methodology of the articles to know: the used part of the plant, the type of extract used in each study and the applied technique. Only original sources were consulted.

RESULTS AND DISCUSSION

By making the bibliography review it was found that 50% correspond to research about lime peel, 16% to lime juice, 20% to lime leaves, 10% to lime seed, and 3% to lime bagasse (only one manuscript).

Colecio-Juárez et al. (2005), studied the compounds from lime peel, isolating fructose, glucose, and vitamin C. Their concentration changes with respect fruit maturity stage. The citrus contains phenolic compounds mainly flavonoids, like flavones glycosylated (hesperidin and naringin) and flavones (diamine and rutin) like polymixiid (sinensetin) (Perez-Nájera et al. 2013).

To make lime chemical compounds extraction it was used fresh or dry material which chemical structure were not modified. It was used several techniques like: petroleum ether extract or with hexane (Kumar et al. 2013), or with methanol or ethyl acetate (Rodriguez et al. 2014), or by distillation of steam trawl (Javed et al. 2013), or by gas chromatography or mass spectrophotometry (Ahmed et al. 2016), or by fine extraction method to volatile samples called: solid micro-extraction (Rowshan et al. 2013).

The employed technique used by extraction is important because this way it can be isolated compounds with different concentrations. Colecio-Juarez et al. (2012), used mass chromatography and spectrophotometry techniques to identify 46 compounds from essential oils from *C. limetta* from which aldehydes like limonene, linalool, sabinene, and bergamol, were founded in higher concentrations.

The compounds which were founded in lime peel did not stay in the same concentration, they change with respect fruit maturity, as was mentioned by Colecio-Juarez et al. (2012), when they split in four stages fruit maturity for their research. They found that some substances like δ-limonene increase their concentration from 66.8 (first stage) to 77.7% (maturity stage). Others, show contrary effect like β-pinene with 8.63% (first stage) and 6.68% at maturity stage, 29% below. Other compounds like linalool and bergamol show the same behavior. Some compounds vanished like undecanal, neral and α-terpineol that only shows in the first maturity stage. These may be due that initial stages of plants maturity most protect their self against predators, so they have high number of glands that produce essential oils and these decrease with maturity (Table 1).

On the other hand, Rowshan et al. (2013), studied volatiles compounds from lime leaves, founded highest concentrations of sabinene (4.4%), limonene (40.8%), (E) -β-ocimene (4,1%), linalool (23.2%) and citronella (23.2%), with 23 total active substances. It is important to point that diverse compounds only can be found in leaves like: α-phellandrene, δ-3-carene, p-cymene, 1,8, cineole, β-ocimene, limonene oxide, citronella, among others. This is important because it exists a difference among isolated compounds from lime peel and leaves producing different effect on biological activities.

Lime juice also was research object to determine flavonoids. From lime juice it were obtained eight: vicenin (0.37 mg L^{-1}, lucenin (0.75 mg L^{-1}), eriocitrin (2.10 mg L^{-1}), scoparin (0.10 mg L^{-1}), orientin-4-metl ether (0.10 mg L^{-1}), rhoifolin (0.15 mg L^{-1}), diosmin 0.39 mg L^{-1}) and hesperidin (4.29 mg L^{-1}), the last one was founded in highest

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

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ISSN: 2007-5782

Vol. 1 (15): 20-28. January to June 2018

Table 1. Compounds obtained from *Citrus limetta* and their biological activity.

Study country	Medical use	Plant component	Preparation	Obtained compound	Bibliography
Bangladesh		Peel	Ethanolic extract	Mix compounds	Sayeed et al. (2013)
Cuba	Antileishmania	Leaves	Hydro alcoholic extract	Polar mix compounds	García et al. (2008)
India	Hypoglycemic	Peel	Methanolic extract	Alkaloids, steroids, flavonoids, tannins, glucosides	Kundussen et al. (2011)
	Antimycotic, anticancer, antimicrobial and antioxidant	Peel	Aqueous extract and hexanoic extract	β-pinene, δ-limonene, linalool, sabinol	Colecio-Juárez et al. (2012)
	Insecticide	Peel	Petroleum ether extract and hexanoic extract	Terpenes, flavonoids, petroleum ether alkaloids	Kumar et al. (2012)
	Antioxidant, help to capillary circulation, limb pain decreases	Peel	Ether extract	Hesperidin	Kumar et al. (2013)
	Insecticide	Peel	Distillation	Mix compounds of essential oils	Chandell et al. (2016)
	Not studied	Peel and juice	Diverse extract and isolated compounds	129 compounds were isolated	Khan et al. (2016)
	Antioxidant	Flower and juice	Micro extraction in solid base to volatile samples	23essential compounds from leaves and 18 from flowers	Rowhan et al. (2013)
Italy	Antioxidants, anti-inflammatory, atherosclerosis (hypocholesterolemic), platelet antiaggregating and antibiotic	Seeds and peel	Proximal analysis with HPLC	Narirutin, hesperidin, dydim, eriocitrin, diosmin, and hesperidin	Tripoli et al. (2007)
	Antioxidant	Juice	Elucidate (dilution)	Vicenin-z, lucenin, eriocitrin, scoparin, orientin, rhoifolin, orientin, dismine, hesperidin	Barreca et al. (2011)

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

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ISSN: 2007-5782

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Tabla 1. Compuestos obtenidos (Continuación…)

Country study	Medical use	Plant component	Preparation	Obtained compound	Bibliography
Mexico	Antioxidant	Juice	Steam trawl	Citric acid, ascorbic acid, glucose, fructose	Colecio-Juárez et al. (2005)
	Antihypertensive	Leaves	Aqueous extract	Polar mix compounds	Pérez et al. (2010); Esquivel et al. (2010); Talha et al. (2011)
	Antihypertensive	Leaves	Aqueous extract	Mix compounds	Cano (2011)
	Bronchitis, stomach spasm, fever	Leaves	Aqueous infusion	Mix compounds	Alonso-Castro et al. (2012)
	Antioxidant	Peel and juice	Methanolic extract, hexane extract and acetone extract	Phenolics compounds and flavonoids	Pérez-Nájera et al. (2013)
	Antioxidant	Peel	Methanolic extract and ethyl acetate extract	Flavone C, o-glucosides, vicennia, lucenin, flavanone-o-glucosides, derivatives of limo citrine-glucosides, limocitrol-glucosides and abscisic glycoside acid	Rodríguez et al. (2014)
	Diuretic	Peel	Aqueous extract	Polar mix compounds	Vargas et al. (2016)
	Antimicrobial	Juice, seeds and bagasse	Methanolic extract	Total flavonoids, hesperidin, ascorbic acid and phenols	Damián-Reyna et al. (2017)
	Hypoglycemic	Peel	Minced peel	No determined	Flores-Fernández et al. (2017)
Mexico-Nigeria	Hypoglycemic, antioxidant	Peel	Aqueous extract	Polyphenols	Padilla-Camberos et al. (2014)
Pakistan	Antioxidant	Seeds	Seeds oil	Saturated fatty acids: palmitic, stearic, arachidonic. Unsaturated fatty acids: oleic, linoleic, linolenic. Other compounds: α-tocopherol, γ-tocopherol, δ-tocopherol	Farooq et al. (2008)
	Antimicrobial and antioxidant	Peel	Aqueous distillation	Limonene y camphene	Javed et al. (2013)
Peru	Antimicrobial (*Staphylococcus aureus*)	Leaves	Ethanolic extract	Polar mix compounds	Bussman et al. (2010)

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

proportion (Barreca et al. 2011).

In other research, it was analyzed flavonoids concentration in lime bagasse, and was observed a low concentration (1.69 mg g^{-1}) in comparison with lime juice (63.24 mg g^{-1} (Damián-Reina et al. 2017).

Farooq et al. (2008), studied oil seeds and isolated saturated fatty acids like palmitic acid (26.49 g $100g^{-1}$) and unsaturated fatty acids like oleic acid (23.69 g $100g^{-1}$) and linoleic acid (39.81 g $100g^{-1}$), it must be said that these oils are not the only ones, but they have the highest concentrations.

Another important molecule in seed were tocopherol or vitamin E, with three distinct types: α, β y δ with concentration of 26.40, 58.03, 17.27 mg kg^{-1} respectively. This vitamin E was used as referent in other studies to prove antioxidant activity of some compounds. This suggested that some part of lime antioxidant activity obey to this molecule with respect to other compounds. Also, this isoprenoid was considered as dietetic importance.

Biological activity

Toxicity

C. limetta fruit is not toxic as demonstrated by results obtained by Vargas et al. (2006), where it was applied aqueous extract in oral way to two mice groups. To first group it was added 600 mg dose per mice kilogram, and second group 1,500 mg dose per mice kilogram for 10 days. At the end of experiment none mice showed allergic reaction, mortality, and not other alteration type sign.

Antihypertensive

Hypertension disease is present in metabolic syndrome (diabetes, hypertension, and hypercholesterolemia), that's why it is important to find a natural product that helps eradicate this health problem, above all rural population of low income who comes to alternative medicine like herbs or naturalist doctors. In Morelos State, El Vigia city community consume daily lime peel tea to control this health problem.

To check antihypertensive properties, Cano (2011), made a clinic study with 159 patients from Queretaro State. The sample was divided in two groups. One of them was administered twice a day the aqueous extract of *C. limetta* leaves (10 mg), and the other was applied chlortalidone like positive control, for six weeks. At final experiment, the two groups showed normal data of blood pressure. The aqueous extract was safe, tolerable, effective for hypertense patients phase 1.

Diuretic

One study to prove diuretic activity was made by Vargas et al. (2016), with mice batch divided in four groups: group 1 was supplied with sodium chloride; group 2 (positive control) 20 mg per mice kilogram of furosemide, and group 3 and 4 aqueous extract with a dose of 600 and 1,500 mg per mice kilogram respectively. At final experiment was evaluated diuretic activity and were observed that two doses were effective. That's why it is suggested that diuresis of *C. limetta* has the action mechanisms to decrease blood pressure.

Antioxidant

The antioxidant breaks the chain reaction of free radicals as result of their capacity to transfer phenolic hydrogen to proroxilo free radical from polyunsaturated fatty acid peroxidized.

C. limetta is important because it has antioxidant activity, prevent degenerative diseases like cancer, because contain flavonoids phenolic acids and other types of phenolic compounds like 6-8-di-glucosamide, 6-c-b-glucosamide, erythrosine, diosmin-hesperidin, and narirutin. That's why it is recommended like potent antioxidant compared with orange and grapefruit. There are diverse studies where this activity was demonstrated (Colecio et al. 2005, Tripoli et al. 2007, Farooq et al. 2008, Barreca et al. 2011, Kumar et al. 2013, Pérez-Nájera et al. 2013, Rodríguez et al. 2014 and Abdullah et al. 2016).

Anti-inflammatory

These compounds help to inhibit the answer of responsible enzymes to inflammatory conditions. Flavonoids show this effect and can active the responsible cells of immune response like

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

lymphocyte T and B (Tripoli et al. 2007).

Hypoglycemic

An actual degenerative disease is diabetes, that's why many peoples go with medical alternative doctors like herbs to obtain natural remedies to control their hyperglycemia. Kundussen et al. (2011), studied the hypoglycemic effect of lime peel on Wistar mice bioassay, and founded a significant effect in blood glucose levels in animal's diabetes induced with streptotozina with a decrease of 30% of glycemia levels with respect to control experiment. These authors concluded that this effect was due to hesperidin and naringin present at *C. limetta* peel.

On the other hand, Flores-Fernández et al. (2017), evaluated the postprandial effect (after eating) of minced lime peel applied to a model with Wistar male mice. It was oral applied to experimental animals with maltose solution (3 kg per mice kilogram), divided in three groups: group 1 negative control, group 2 hydrated lime peel, and group 3 applied acarbose drug (positive control). Blood samples were taken from mice tails, before and after 30 minutes substances were applied. Glucose levels were taken and was founded that lime extract delay glucose absorption through jejunum and ileum walls, as same to positive control. This can be explained because peel fiber can help to avoid sugar absorption by gut, and in this way can have hypoglycemic effect.

Another study using colorimetric technique, was made by Padilla-Camberos et al. (2014), which studied the aqueous extract effect of *C. limetta* peel on α-glucosidase and α-amylase inhibition. They obtain a dose-dependent correlation between inhibition an extract concentration. These authors suggest that response was due polyphenols presents in aqueous extract.

Antitussive

In a survey made in the community of Aqismón region from San Luis Potosí State, México, the respondents commented that they consume *C. limetta* leaves tea to treat cough, colds, and temperature, among others with satisfactory results (Alonso-Castro et al. 2012).

Hypocholesterolemia

Tripoli et al. (2007), made studies with compounds obtained from *C. limetta* seeds and peel: hesperidin, naringin, and flavones which were applied to hamster group with hypocholesterolemia induced with fat diet. The results showed decrease levels of cholesterol with respect control experiment, at same as low density lipoproteins (LDL), very low-density lipoproteins (VLDL), and triglycerides. Moreover, it was reported that it exists an inverse relationship between cholesterol concentration and the flavonoids ingest.

Platelet Aggregation

Blood clots formation can produce circulation problems in the organism, so it is interesting the platelet antiaggregating effect that some compounds of *C. limetta* have such as nobiletin and tangerine (Tripoli et al. 2007). Actually, some authors study the possible action mechanism of this effect.

Antimicrobial

Bacteria's can produce diverse infections to a healthy organism, so it is desirable to find foods that have antimicrobial effect to avoid this problem. Therefore, some investigators have studied effect of lime peel (ethanolic extract) on a culture of Staphylococcus *aureus* finding positive results, by inhibit its reproduction. This is important because this bacterium can be found in wounds, respiratory tract and postpartum infections (Bussman et al. 2010). Regarding to it, Colecio-Juárez et al (2012) found that the essential oil in lime peel has sabinene that is a compound that has antimicrobial and antioxidant properties.

On the other hand, Javedet al (2013) studied the effect of essential oil of *C. limetta* peel on various species of bacteria and fungus as: *Aspergilus niger, A. flavus, A. fumigatus, A. ficuum, Candida utilis, Penicillium digitatum, Staphylococcus aureus, Bacillus subtilis, B. cereus, Lactobacillus acidophilus*, finding that in every case there was growth inhibition mainly in *Aspergillus niger*, *Bacillus subtilis* and *Bacillus cereus* with a growth percentage of 26.2%, 21%, 27 % respectively at 96

Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018

hours. The investigators concluded that this effect is due to terpenes concentration that act as antimicrobial (Javed et al. 2013).

Anti-malaria

Leishmaniasis comprises a group of infectious diseases caused by genus *Leishmania* currently this disease prevails in 88 tropical countries around the world and there are around 1.5 and 2 millions of new cases per year. Because the drugs used to cure the infection are expensive and the treatment is long, plant extracts are tested to obtain drugs that help eliminate the infection. By proving the hydroalcoholic extract from the leaves of *C. limetta* it was obtained a growth inhibition in *Leishmania* populations of 37% in comparison with other extracts of other plants (García et al. 2008).

Insecticide

It is known that there are plants that act on insects affecting its survival, so it was tested the essential oil of 18 plants, *C. limetta* among them, on a bioassay of the insect of the *Rhizopertha dominica* species, it was found that at a dose of 0.2 and 0.1% there was an inhibition of 100% (Geetanily et al. 2016). Another study was made by Kumar et al. (2012), which applied extracts of hexane and petroleum ether on the insect that produces dengue, *Aedes aegypti*, obtaining positive results. These investigators concluded that phytochemicals such as flavonoids and terpenes that are found in lime peel and are responsible of the produced effect.

CONCLUSIONS

Even though scientific literature is scarce, it can be said that even though *C. limetta* is a crop plant, that is used in food industry, it has not been used properly so it would be desirable ro be used for the obtaining of compounds for pharmaceutic industry and therefore produce medicines of low cost for the persons that have a disease mentioned before.

It is also important that people consume this fruit, to prevent degenerative diseases and maintain health, because it is rich in phenols, flavones and flavonoids, in all parts of the lime both in the juice and in the husk, leaves and seeds

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Receive: 01st November 2017 Accepted: 10nd December 2017 Published: 30th June 2018