Bionos

Testing Efficacy

UPDATED BIBLIOGRAPHIC REVIEW OF THE POSSIBLE FUNCTIONAL EFFECTS OF DIFFERENT GRAPEFRUIT NUTRIENTS (*C. paradisi*)

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FINAL REPORT

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UPDATED BIBLIOGRAPHIC REVIEW OF THE POSSIBLE FUNCTIONAL EFFECTS OF DIFFERENT GRAPEFRUIT NUTRIENTS (*C. paradisi*)

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Executive Summary.

In its brief history, grapefruit has been considered to be a fruit with a large number of functional properties beneficial to the organism for its rich chemical composition. However, many of these effects have been assumed to be true as a result of tradition rather than because of specific studies performed on the matter.

The aim of this report is to conduct a bibliographic review on the scientific evidence regarding the functionality and biological effectiveness of the different extracts obtainable from grapefruit as raw material, as well as its most important elements due to their concentration or activity.

Studies have focused on the effects produced by the **juice** or extracts obtained from grapefruit's **skin** and **seed**, or by the most abundant chemical compounds in it, mainly D-limonene and naringenin.

For the **skin** extract, as well as its essential oil, several studies show its potential as an **antibacterial, antifungal** and **insecticidal** agent.

Regarding the **seed**, its **antioxidant potential** has been demonstrated when consumed entirely, while its glycerine extract also has **antibacterial** activity. Its methanolic extract has shown to have **beneficial properties for the cardiovascular system**, as well as for the **treatment of diabetes**, while other types of seed extracts would help in the **prevention of gastric and liver damage**.

As for the **juice**, several studies have established **beneficial effects for the cardiovascular system**, as well as for the **treatment of diabetes** and **prevention of gastric lesions**, having also confirmed its popularly attributed effects as a **dietary agent**, since it is capable of reducing fat and cholesterol levels, as well as producing an effective weight loss.

Regarding the **D-limonene**, its **antidiabetic potential** has been demonstrated, in addition to being beneficial for **gastric function** and having a great potential to **improve nutrient absorption** in the intestine. Furthermore, it has been demonstrated to have **analgesic and anxiolytic properties**. Additionally, preliminary studies suggest its possible use as an **anticancer** for the treatment of different types of cancer, an effect

shared with **bergamottin**, also present in grapefruit.

Other studies show evidence on the effects provided by **naringenin**, proving its activity as an **antioxidant and antidepressant agent**, as well as its **beneficial effects on the cardiovascular system**.

Finally, studies performed with different **furanocoumarins** present in grapefruit show their capacity to **increase bone density** by stimulating osteoblast differentiation and function.

Besides its medical uses, this revision goes through other applications such as those in the **food industry**, thanks to the **antifungal** effects for food preservation, or those of the **cosmetic industry** for which several applications are described to **strengthen the skin**, or to prevent the effect of **acne, dandruff** or **impetigo** among other functions.

On the other hand, many other compounds present in the grapefruit juice could present difficulties for their absorption in the intestine and demonstrate the expected physiological effect due to the matrix and the environment where they are found. In addition, it is important to highlight the effect of interactions with the consumption of medicines due to its possible implications on human health.

In this sense, future studies should focus their effort on modifying oral administration systems and conducting clinical trials that demonstrate safety and efficacy in groups of human individuals, improving the payload of nutrients, its *in vivo* stability, its bioavailability, and efficacy in biological functionality.

1 Title.

Updated bibliographic review of the possible functional effects of different grapefruit nutrients (*C. Paradisi*).

2 Introduction.

Citrus x paradisi (hereinafter *Citrus paradisi* or *C. paradisi*) is an evergreen tree with edible fleshy fruits of the Rutaceae family. Its fruit, the grapefruit, is a citrus fruit whose pulp is usually consumed whole or in the form of juice, to which vegetable glycerine is usually added to reduce its acidity and bitterness. In addition, medicinal properties are attributed to both the skin and the seed extracts, these being by-products of the production of grapefruit juice.

Grapefruit is commonly ingested for weight loss. In food and beverages, grapefruit is consumed as a fruit and juice and is used as a flavouring component. It is also applied to treat asthma, high cholesterol levels, cancer, and many other conditions but, as of yet, there is not enough scientific evidence to support these uses from the medical community.

In the manufacturing industry, grapefruit oil and grapefruit seed extract are used as a fragrance component in soaps and cosmetics, and at home it is used to clean fruits, vegetables, meats, surfaces and kitchen utensils, dishes, etc.

In agriculture, grapefruit seed extract is used to kill bacteria and fungi, stop mould growth, neutralize parasites in animal feed, preserve food, and disinfect water.

It is important to remember that the interactions between medications and grapefruit juice are well documented, so it is advisable to consult a doctor before consuming it along with any medication[1].

The aim of this systematic review is to provide an overview of scientific papers and an in-depth analysis of the latest research related to *C. paradisi* as a valuable and important plant species in pharmacy, cosmetology and the food industry.

3 The genus *Citrus*.

The genus *Citrus* is one of the most important taxonomic subunits of the Rutaceae family. The fruits produced by the species belonging to this genus are colloquially called 'citrus'. Citrus fruits are commonly known for their valuable nutritional, pharmaceutical, and cosmetic properties. The *Citrus* genus includes perennials, shrubs, or trees (3-15 m tall). Its leaves are leathery, ovoid or elliptical in shape. Some of them have spikes. The flowers grow individually in the axils of the leaves. Each flower has five petals, white or reddish. The fruit is a hesperidium berry. Species belonging to the genus *Citrus* are found naturally in warm areas with a temperate climate, mainly in the Mediterranean region. They are usually sensitive to frost[2].

There are several species of the *Citrus* genus that are widely known, among which are *Citrus limon* (L.) Burm. f. (Latin synonyms: *C.* × *limonia, C. limonum*) (lemon), *Citrus aurantium* ssp. *Aurantium* (bitter orange), *Citrus sinensis* (Chinese orange), *Citrus reticulata* (mandarin), *Citrus x paradisi* (grapefruit), *Citrus bergamia* (bergamot orange), *Citrus medica* (citron), among others.

The botanical classification of the species of the *Citrus* genus is very complex due to the frequent formation of hybrids and the introduction of numerous crops through cross pollination. Hybrids are produced to obtain fruits with valuable organoleptic and industrial properties, including seedless fruit, high juiciness, and new flavours. Advanced molecular techniques are often necessary to identify older varieties, hybrids and crops.

One of the oldest still preserved botanical sources describing species of the genus *Citrus* is the "Monograph on Wên-chou oranges" by Han Yanzhi of 1178[3,4]. Other historical works describing citrus species are "Nürnbergische Hesperides" from 1708 and "Traité du Citrus" from 1811. Historically, one of the best-known classifications of citrus species is "Histoire Naturelle des Orangers" from 1818. American botanist Walter Tennyson Swingle (1871-1952) had a particularly significant impact on the current taxonomy of the *Citrus* genus. He is the author of

up to 95 botanical names for species of the *Citrus* genus. Currently, the systematics of the species of the *Citrus* genus are based on studies of molecular markers and other DNA analysis technologies that continue to provide new information to this day[5].

3.1 Botanical characteristics and presence of *C. paradisi.*

Grapefruit is the result of a natural cross between sweet grapefruit (*Citrus maxima* Burm) with a sweet orange (*Citrus sinensis*), a process that took place on the island of Barbados during the 18th century[6,7]. *C. paradisi* is a eukaryotic plant that belongs to the Magnoliophyta division, Magnoliopsida class, Rosidae subclass, Sapindales order, Rutaceae family, and Citroideae subfamily. Two other species in the genus have been described: *C. limon* and *C. aurantifolia*[8,9]. In addition, there are different varieties of such species, depending on the size, shape and colour of leaves, flowers and fruits[10]. In particular, colour is a factor that has been related to the presence of lycopene[11].

C. paradisi, like many other prolific citrus species, gives rise to numerous varieties, both pure (Table 1), and hybrids (Table 2)[12].

Name	Origin	Characteristics
Citrus × paradisi **'Star Ruby'** (Citrus × paradisi 'Sunrise')	Texas, USA	It is the grapefruit with more intense coloration. Seedless fruit, very thin peel with high juice content, with a sweeter flavour and less bitter than the Marsh variety.
Citrus × paradisi **'Rio Red'**	Texas, USA	Medium sized fruit with hardly any seeds. Smooth thin peel. It is yellow with reddish tones. Its pulp has an intense red colour. Less bitter than other varieties and a lot sweeter.
Citrus × paradisi '**Marsh**' (Citrus × paradisi 'Marsh seedless')	Florida, USA	The pulp of the fruit has small vesicles and a light coloration. The peel is harder than in the rest of varieties and has high sweet juice content, slightly sour at the beginning of the harvest. Seedless fruits with a weight of about 260 g.
Citrus × paradisi '**Macfadyen**' (Citrus maxima var. racemosa Osbeck)	Barbados	Big fruits with a pale-yellow peel. It has few seeds, and its pulp is slightly bitter.
Citrus × paradisi '**Duncan**'	Florida, USA	Quite large fruit, flattened on its poles. Tender Pulp with high juice content. Variety mainly intended for the juice industry.
Citrus × paradisi '**Melogold**' (Citrus maxima 'Siamese Sweet' × (Citrus × paradisi '4n Marsh'))	California, USA	Extremely big fruits, with a yellowish green granular peel and a pale-yellow pulp with bittersweet flavour.
Citrus × paradisi '**Oroblanco**' (Citrus maxima 'Siamese Sweet' x Citrus paradisi '4n Marsh' Citrus maxima 'Sweetie')	California, USA	Round or oval shaped fruit with thicker peel than other varieties. It lacks the bitterness associated with grapefruit and is quite sweet, even when the outer peel is still green, but the white membranes separating the pulp segments are bitter.

Name	Origin	Characteristics
Citrus × paradisi **'Jaffa Sweetie'** ((Citrus × paradisi) × Citrus maxima)	Florida, USA	Fruit larger than other varieties and generally round, with a thick peel that varies from pale green to yellow when ripe. It ripens early, but it holds up well on the tree and has an average weight of 500 g. Pale-yellow pulp, practically seedless, considerably sweeter than other varieties and divided into segments, but the white membranes that separate the fleshy segments are bitter.
Citrus × paradisi **'Foster'**	Florida, USA	Medium-large fruit, flattened to spherical; short basal grooves, radiant; indistinguishable areolar ring; with many seeds. Its colour varies from pale to light yellow or pinkish. Rind of medium thickness and smooth surface. Suede of primary skin colour, but pink in favourable conditions; tender and juicy pulp texture; good taste. Medium-early ripe.
Citrus × paradisi **'Henderson'**	Texas, USA	The largest tree and more resistant to the frosts than other varieties. Bigger fruits.
Citrus × paradisi **'Marsh Pink** ' (Citrus × paradisi **'Thompson'**)	Florida, USA	It was the first pigmented seedless variety and arose through spontaneous mutation of the Marsh variety. Its fruits resemble the aforementioned variety, although it differs in the colour of the pulp, slightly pink, which tends to vanish with time.
Citrus × paradisi **'Ray Ruby'**	Texas, USA	Medium-sized fruit with hardly any seeds. Very smooth, fine, and thin skin, yellow with reddish hues. Pulp of an intense red colour, less bitter and sweeter that other varieties.
Citrus × paradisi **'Redblush'** (Citrus × paradisi 'Ruby Red' Citrus × paradisi 'Ruby Sweet')	Texas, USA	The tree is very similar to the Marsh's grapefruit one, as are the characteristics of the fruit, but it is smaller and has a higher ripe index. The fruits are coloured pink in some areas of the peel. The pulp membranes and the walls of the vesicles that contain juice are also pinkish.
Citrus × paradisi 'S**hambar**'	California, USA	Fruit with few or no seeds, yellow in colder climates and pinkish in mild climates.
Citrus × paradisi **'Flame'**	Florida, USA	Fruit with a very red pulp and no seeds.

Table 1. Pure varieties of *C. paradisi*.

The plant is an evergreen, 5-6 m tall tree with oval, alternate and finely dented 7-15 cm long leaves, as well as white flowers[13,14]. The fruit is about 15 cm in diameter, externally protected by the peel, which is formed by a thick epidermis, followed by the flavedo, a structure that can have pigments and oily sacks, and by the albedo, which can store flavonoids and participate in the transport of water, nutrients and gases[15]. Protected by the skin we can find 11 to 14 segments (carpels), each of which is surrounded by a membrane and contains the juice sacs, as well as the seeds[16,17].

Citrus paradisi is a plant well known for its high nutritional value[18,19]. It is distributed throughout the tropical and subtropical regions of the world, at a variable altitude ranging from 0 to 1800 m[20,21], and at a temperature of 13 ° to 35 ° C[22]. According to the USDA and data from the Foreign Agricultural Service[9], in the period 2015-2016, the countries and the region with the highest grapefruit production were China, the USA,

Mexico, South Africa, Turkey, Israel and the European Union.

Name	Origin	Characteristics
Citrus × paradisi '**Chironja** '	Puerto Rico	Large fruit with few seeds, with thin, smooth, moderately adherent peel. Yellowish-orange pulp. The fruits appear on the tree individually instead of in bunches .
Citrus × paradisi **'New Zealand Grapefruit** ' (Poorman Orange)	China or Australia	Fruit with seeds, orange pulp with low acidity. It requires less heat than other varieties to ripen.
Citrus × paradisi **'Rex Union'**	South Africa	Round shaped and slightly flattened at the ends, approximately 7 to 9 centimetres in diameter, light to dark orange with a partial or full red blush. Moderately thick peel, with a slightly rough and grainy texture and occasional stretch marks. Light orange pulp with few seeds.
Citrus × paradisi **'Smooth Flat Seville '** (Citrus × paradisi 'Smooth Seville')	Australia	Fruit with seeds, slightly rough. Both the skin and the pulp are reddish orange. It requires less heat than other varieties to ripen.
Citrus × paradisi '**Triumph** '	Florida, USA	It lacks the bitterness of a typical grapefruit and has a strong sweet orange flavour. Medium sized fruits, pale-yellow and with seeds, slightly flattened both on the top and the bottom.
Citrus × paradisi '**Cocktail**' (Citrus maxima 'Siamese Sweet' × Citrus reticulata 'Frua')	Riverside, California, USA	Fruits in bunches, of medium-large size, thin, smooth and yellow peel. Granulated pulp, orange-yellow colour, low acidity.

Table 2. Hybrids of *C. paradisi*.

4 Chemical composition of *C. paradisi*.

The chemical composition of the *C. paradisi* fruit has been widely studied. It has been determined, not only for the whole fruit, but also separately for the skin, seed, and pulp.

The **epicarp** is made up of a large number of compounds that can be classified into 7 main groups: terpenes, sesquiterpenes, hydrocarbons, alcohols, aldehydes, esters, oxides, and a variety of other compounds (Table 3). As shown in the table, terpenes are the most prevalent compounds, along with limonene, myrcene, citral, and terpin making up 80% of it, approximately.

COMPOUND	QUANTITY (%)
Terpenes	
(E) -caryophyllene	0.1
Neral	0.4
Citral	1.22
Trans-p-2,8-mentadien-1-ol	0.63
δ-3-carene	0.01
p-cymene	0.01
p-cymene	0.17
Limonene and D-limonene	75.07
Myrcene and β-myrcene	5.32
(E) and (Z) -β-ocimene	0.31
α and β-phellandrene	1.212
α and β-pinene	1.26
Sabinene	0.5
α and γ-terpinene	1.58
Terpinolene	0.02
α-thujene	t
Sesquiterpenes	
Trans-α-bergamottin	t
γ-gurjunene	0.6
β-bisabolene	0.41
δ and γ-cadinene	0.102
Caryophyllene, α and β	3.91
Valencene	3.36
Nerolidol	0.32
α-sinensal	0.19
Santolina epoxide	0.42
α and β-cubebene	0.1
β-elemene	0.02
α and β-farnesene	0.097
(E) -β-farnesene	0.06
Germacrene A, C and D	0.86
α-humulene	0.08
α-muurolene	0.01
α-selinene	t

COMPOUND	QUANTITY (%)
Alcohols	
α-bisabolol carveol	0.05
Cis, trans, E and Z-carveol	3.5
Citronellol	1.78
4-carvon mentenol	0.88
Decanol	t
2,7-dimetil-2,6-octadienol	0.01
Elemol	0.2
Farnesol	0.12
Geranial	0.4
Geraniol y γ-eudesmol	0.31
Geraniol	
Germacren D-4-ol	0.005
Hexadecanol	0.01
Isopulegol	0.06
Linalol	0.27
α-muurolol	0.2
Nerol	0.02
Nerolidol	0.01
Nonanol	0.03
1 and Octanol	0.24
Cis-sabinene hydrate	0.01
Trans-sabinene hydrate	0.03
4-terpinenol	0.17
α-terpineol	0.3
Aldehydes	
Citronellal	0.13
Decanal	0.61
(E, E) and (E, Z) -2,4-decadienal	0.06
Dodecanal	0.02
2-dodecenal	0.21
2-undecenal	0.01
Hexanal	0.44
(E) -2-hexanal	t
Nonanal and n-nonanal	0.26
Octanal	1.14
2-octen-4-ol	0.01
Perillaldehyde	0.01
β-sinensal	0.02
Esters	
Carvyl acetate	0.66
Oleate and methyl palmitate	0.50
Phthalate	0.54
Cis-carvyl acetate	0.04
Citronellyl acetate	0.01
Decyl acetate	0.03
Butyrate and geranyl acetate	0.07
Linalyl acetate	0.06
Limonen-10-yl acetate	0.02
(E) -2-hexenyl butyrate	t
Hexyl butyrate	t
P-mentha-1,8-dienyl acetate	0.006
N-methyl methyl anthranilate	t
Neryl acetate	0.02
Nonyl acetate	0.03
Octyl acetate	0.10
α-terpinyl acetate	0.01

COMPOUND	QUANTITY (%)
Oxides	
β-caryophyllene oxide	0.56
Cis-linalool oxide	0.31
Limonene oxide	0.28
Cis-limonene oxide	0.09
Trans-limonene oxide	0.1
Limonene dioxide	0.18
Linalool oxide	0.02
Trans-linalool oxide	0.23
Furanocoumarins (µg/g)	
6´, 7´-dihydroxybergamottin	118.01
Bergamottin	13.81
Others	
Bicyclopentan-2-ene	0.01
Carvone and D-carvone	0.64
Nonane	0.20
Tridecane	0.26
Tetradecane	0.47
4-vinyl guaiacol	0.33
Isophorone	1.29
α-panasinsen	0.39
Isopinocampone	0.013
1,8-cineole dodecanoic acid	0.02
Hexadecane	0.01
Hexadecanoic acid	0.11
Methylheptenone	0.07
Nootkatone	0.84
Octadecane	0.02
Octanoic acid	0.02
Pentadecane	0.05
Perillene	0.005
Tetradecanoic acid	0.03
Naringin	4319 ppm

t = traces (value below the quantifiable limit in each case)

Table 3. Chemical composition of the skin of *Citrus paradisi*. (Adapted from Cristóbal-Luna et al 2018[23])

Although Table 3 shows the complete composition of grapefruit skin, the essential oil obtained from it is more commonly used among its wide applications. The chemical composition of this oil has been determined through gas chromatography (Table 4), D-limonene being the main substance present in it, with an abundance of more than 92%.

COMPOUND	QUANTITY (%)
Monoterpenes	
α-Pinene	0.2 – 0.6
Sabinene	0.1 – 0.6
β -Pinene	0.05 – 0.2
Myrcene	1.5 – 2.5
Limonene[a]	92 – 96
Aliphatic aldehyde	
n-Octanal	0.2 – 0.8
n-Nonanal	0.04 – 0.1
n-Decanal	0.1 – 0.6
Neral	0.02 – 0.04
Sesquiterpenes	
β -Caryophyllene	0.2 – 0.5
Nootkatone	0.01 – 0.8

[a] According to the current knowledge on this oil and the result of various physical tests performed on this International Standard, it can be ascertained that this component is predominantly D-limonene.

Table 4. Chemical composition of the essential oil from *Citrus paradisi* skin, obtained through mechanical pressing according to the ISO 3053:2004(E).

Regarding the seed composition, fewer reports are found. However, it has been described as having a high content of essential oil, reaching 36.5%, as well as 13.5% humidity, 8.5% fibre and 4.1% that consists of a complex mixture of lipids, alcohols, fatty acids, tocopherol, flavonoids, polyphenols and limonoid aglycones (Table 5). Interestingly, compounds such as flavonoids and polyphenols are known to favour seed development by protecting them from predators[24].

The pulp is a complex mixture with various components with a high nutritional value and can contribute to human health improvement. A recent investigation revealed that, although the chemical composition is similar both in the manually obtained juice and in the industrially processed beverage, there are differences in the amount of the components; for example, in the latter case the researchers found higher levels of narirutin, naringin, hesperidin, neohesperidin, didymin, poncerin, limonin, ascorbic and citric acid, whilst a higher level of dihydroxybergamottin was determined in the manually obtained juice[25].

COMPOUND	QUANTITY
	Physicochemical characteristics (%)
Oil content	36.54
Protein content	3.90
Fibre content	8.50
Ashes content	5.03
Humidity	13.5
Total lipids	30.07
	Lipid fractions in seed oils (%)
Polar lipids	8.3
Monoglyceride	3.76
Sterols	3.22
l, 2 and 1,3-diglycerides	6.83
Free fatty acids	6.04
Triglyceride	60.74
Sterol esters	4.91
Wax esters	2.15
Hydrocarbons	2.04
	Alcohols (%)
Alcohols	2.01
	Fatty acid composition (g / 100g) of seed oils
Palmitic	32.17
Palmitoleic acid	0.20
Stearic	3.64
Oleic	21.93
Cis-vaccenic acid	1.51
Linoleic acid	36.10
Arachidic acid	0.29
Linolenic	4.36
Total saturated fatty acids	36.10
Total unsaturated fatty acids	64.10
Toral essential fatty acid	40.46
	Tocopherol (mg / 100 g) from seed oils
α, γ and δ	43.249
	Seed flavanones (mg / 100 g)
Naringin	267.7
	Limonoid aglycones (mg / 100 g)
Limonin	188.5

Table 5. Chemical composition of *Citrus paradisi* seeds (Adapted from Cristóbal-Luna et al 2018[23]).

Table 6 shows the main juice constituents and their variable amounts according to different authors. Among these compounds, the high concentration of flavonoids stands out, which include naringin and naringenin, as well as phenolic compounds, carotenes, and different types of acids.

COMPOUND	QUANTITY
Acids	
Citric	0.42 - 0.95 (g/100 mL)
Malico	0.03 - 0.23 (g/100 mL)
Succinic	0.06 - 0.86 (g/100 mL)
Ascorbic	13.44 - 16.76 (mg/100 mL)
Flavonoids	
Naringin	26.25 ± 0.39 (mg/100 mL)
Narirutin	2.36 - 15.12 (mg/100 mL)
Hesperidin	2.29 - 7.17 (mg/100 mL)
Neohesperidin	2.2 - 9.69 (mg/100 mL)
Didymin	0.09 - 1.38 (mg/100 mL)
Poncirin	2.33 - 16.82 (mg/100 mL)
Narirutin 4´-glycoside	1.03 ± 0.2 (mg/L)
Eriocitrin	34.2 ± 1.06 (mg/L)
Neoeriocitrin	14.0 ± 0.28 (mg/L)
Melitidin	3.71 ± 0.34 (mg/L)
Vicenin-2	0.95 ± 0.11 (mg/L)
Quercetin 3-O-rutinoside	1.20 ± 0.12 (mg/L)
Unknown	3.24 ± 0.13 (mg/L)
Limonoids	
Limonin	0.09 - 2.45 (mg/100 mL)
Furanocoumarins	
Dihydroxybergamottin	0.1 - 0.38 (mg/100 mL)
5-methoxy-7 gernoxycoumarin	0.07 - 0.26 (mg/100 mL)
Bergamottin	0.2-1 (µg/mL)
6´, 7´-dihydroxybergamottin	0.5-3 (µg/mL)
Paradisin A	0.06-0.08 (µg/mL)
Polysaccharides	
Hemicellulose	6 - 7.4[a]
Sugars	
Glucose	3.6 (g/100 g)
Fructose	3.4 (g/100 g)
Sucrose	0.3 (g/100 g)
Lipids	
Total	75 - 86 (mg/100mL)
Fatty acids	
Palmitic	21.7 - 23.7 (%)
Palmitoleic	3.1 - 4.3 (%)
Oleic	23.4 - 24.4 (%)
Linoleic	33.5 - 35.5 (%)
Linolenic	8.2 - 9.4 (%)
Others	5.8 - 7.2 (%)
Carotenoids	
α-carotene	8 - 5 (µg/100 g)
β-Carotene	14 - 603 (µg/100 g)
β-cryptoxanthin	12 (µg/100 g)
Lutein + zeaxanthin	13 (µg/100 g)
Vitamin C *	
L-ascorbic acid	21.3 (mg/100 g)
Dehydroascorbic acid	2.3 (mg/100 g)
Total	23.6 (mg/100 g)

* L-ascorbic acid is the main bioactive form of vitamin C; dehydroascorbic acid corresponds to the oxidized form of vitamin C; the total corresponds to the total concentration of vitamin C.

[a] The values show the percentage of several fractions in the alcohol insoluble solids of C. paradisi

Table 6. Main compounds determined in the juice of the pulp of *Citrus paradisi* (Adapted from Cristóbal-Luna et al 2018[23])

5 Biomedical properties of *C. paradisi.*

The large number of phytonutrients present in *Citrus paradisi* has promoted the development of research to determine its biological and biomedical properties, since the use of plants or their by-products is a strategy with a lower ecological impact than the use of synthetic chemicals.

One of the main chemical groups in *C. paradisi* with bioactive properties are furanocoumarins (Table 7), with multiple proven biological effects.

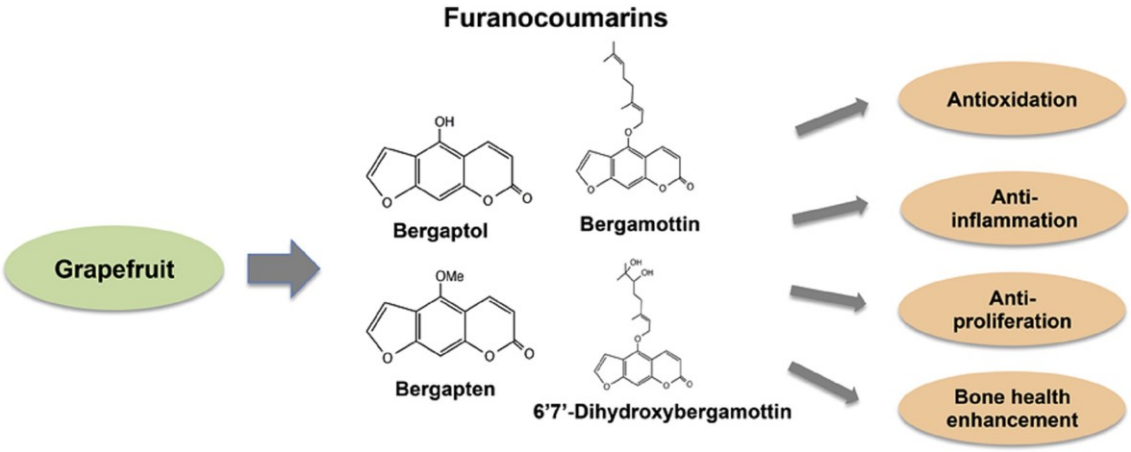

Table 7. Principal effects of *C. paradisi* furanocoumarins[26].

The potential biomedical properties of grapefruit have been classified by the Natural Medicines Comprehensive Database[27] based on its scientific evidence. In this sense, grapefruit has been classified as possibly effective for its use as a slimming agent, but it has been determined that there is not enough evidence to support its efficacy for the rest of the effects attributed to it. Below, the scientific evidence for the different properties can be found.

5.1 Antimicrobial activity.

Regarding the pomegranate's **skin**, it was found that its **essential oil** obtained by hydrodistillation has **antibacterial and antifungal effects** like those observed with ciprofloxacin[28,29]. The authors of these studies demonstrated that several microorganisms were significantly eliminated with 40 mg / mL of the essential oil, including *Bacillus cereus*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella*

pneumoniae, *Pseudococcus sp*, *Salmonella thyphimurium*, *Shigella flexneri*, *Staphylococcus aureus*, *Aspergillus niger*, *Candida albicans* and *Penicillium chrysogenum*. Other authors obtained the oil by cold pressing the peel and confirmed its antifungal potential for some of the microorganisms aforementioned using concentrations between 0.27 and 0.94%[30].

Regarding the **seed**, some *in vitro* studies have established its **antimicrobial capacity**. Sung *et al*. (1990) determined that 500 ppm of a glycerine extract completely inhibited the growth of *Salmonella typhi*[31] cultures. The seed antibacterial effect was determined in four patients with urinary infection[32]. In the study, the authors recorded the infection's remission with the ingestion of 6 seeds every 8 h for two weeks.

5.2 Insecticidal activity.

Regarding their insecticidal potential, it was determined that **essential oils** obtained in an ether extract from *C. paradisi* **skin** applied on pieces of paper were lethal for 95% of the eggs and larvae of *Anastrepha fraterculus* and *Ceratitis capitata*[33]. Furthermore, it was demonstrated that the essential oil of *C. paradisi* skin obtained through steam distillation completely inhibits the viability of *Aedes aegypti* eggs at 400 ppm and inhibits their larval development at 100 ppm[34]. Moreover, there is evidence that the oil is a powerful larvicide against *Anopheles stephensi* at 80 ppm[35]. These data clearly reflect the potential of these oils to be used as **insecticides**. In another study, the authors determined an 89.6% decrease in *Eimeria*-induced coccidiosis contamination with 5 mg/kg of *C. paradisi* ethanolic skin extract administered for 30 days, compared to an efficacy of 99.6 % with the reference drug toltrazuril (20 mg/kg) after 15 days of treatment[36].

5.3 Antioxidant activity.

Without a doubt, one of the most relevant properties of *C. paradisi* is its antioxidant activity.

In one of the studies performed in this regard, methanolic extracts of the fruit **skin** obtained at high temperatures were tested[37]. Through different tests, it was concluded that the **antioxidant power** increased correlatively with the extraction temperature,

consistent with the increase in the phenolic acid fraction not associated with the ester or glucoside fractions.

In relation to the antioxidant potential of the *C. paradisi* **seed**, a study described an **inhibitory effect on lipid peroxidation and a buffer against free radicals** by means of 5-lipoxygenase, 1,1-diphenyl 2-picrylhydrazil (DPPH) and luminol/xanthine/xanthine oxidase tests, respectively. The test was performed on glyceric extracts dissolved in water or alcohol, showing a greater antioxidant capacity in the first case[38].

On the other hand, *in vitro* studies performed on primary mouse splenocytes, RAW 274.6 macrophages and BV2 microglia cells demonstrated the **antioxidant potential of naringenin**, a compound present in grapefruit **juice**. In addition, these studies showed how naringenin was able to inhibit nitrite production and the expression of inducible nitric oxide synthase and cyclooxygenase-2 in a dose-dependent manner[39].

5.4 Effects on the cardiovascular system.

Regarding the antihyperglycemic and antihyperlipidemic potential of *C. paradisi* **seed**, Adeneye (2008) demonstrated that a methanolic extract daily administered orally to healthy rats for 30 days (100-600 mg/kg/day) decreased glucose levels and various lipid parameters, as well as body mass, atherogenicity, and coronary risk, suggesting a **preventive effect against cardiovascular disease**[40].

Furthermore, the administration of *C. paradisi* pulp juice as a food supplement has been shown to produce a reduction in systolic and diastolic blood pressure in both normotensive and hypertensive subjects. The study revealed reductions between 10 mmHg and 55 mmHg41[41]. Additionally, an interesting effect was found in the ethanolic extract of the skin applied to the isolated and perfused heart of a dog (*ex vivo*), as well as to the normal dog's heart (*in vivo*). In both models, the authors observed a significant decrease in mean coronary resistance and blood pressure[41].

The effect of grapefruit components has also been tested in models of important cardiovascular diseases in the western world, such as **myocardial infarctions**. Naringenin administration in an animal model of ischemia-reperfusion in myocardial tissue has shown improvements in cardiac function and a **reduction in infarction and**

cell death in myocardial tissue compared to untreated animals[42].

5.5 Antidiabetic effect.

An investigation performed in diabetic rats confirmed the **antihyperglycemic and antihyperlipidemic effect** of the methanolic extract of *C. paradisi* seeds, mediated by the presence of alkaloids, flavonoids, glycosides, tannins and saponins in variable concentrations[43].

Regarding its effect on the metabolic syndrome, Fujioka (2006) observed a **decrease in insulin resistance and weight** in obese patients[44], and Mallick and Khan (2015) determined a **decrease in the blood glucose level** and an **increase in plasma insulin** in Wistar rats, which were administered 0.5 ml/kg of grapefruit juice for six weeks[45].

The protective effect against diabetes of compounds present in grapefruit has been contrasted in animal models of diabetes induced by streptozotocin. Pure **D-limonene** administration resulted in a **decrease in blood glucose**, the proportion of glycated haemoglobin, the activity of gluconeogenic enzymes, as well as an increase in the activity of glycokinase and the amount of liver glycogen, compared to untreated diabetic individuals[46].

5.6 Effects on the digestive system.

A study performed in rats observed a **50% reduction in gastric lesions** through a 30-minute pre-treatment with *C. paradisi* seed extract of 25 to 36 mg/kg prior to ethanol administration. Additionally, an improvement in gastric blood flow, prostaglandin E2 generation and antioxidant activity were also observed[47].

In a rat colitis model, grapefruit **juice** was found to **decrease gastric lesions and diarrhoea**, and promote an increase in glutathione content, probably due to its antioxidant and anti-inflammatory properties[48].

Regarding acute **pancreatic damage** induced in rats through ischemia/reperfusion (IR), the researchers detected a dose-dependent **decrease** in damage by oral administration of a commercial *C. paradisi* **seed** extract (50-500 µL) 30

minutes before inducing damage[49]. The authors attributed the beneficial effect to improved blood flow and antioxidant capacity. Another report on the toxicity of the methanolic extract of *C. paradisi* seed in rats found that the oral LD50 corresponded to 2000 mg/kg. The authors also observed that an oral administration of the extract (100-600 mg/kg/day) for 30 days produced a dose-dependent increase in various values of hematic biometry; however, an inverse effect was also determined for neutrophils and monocytes[50]. Juice from *C. paradisi* pulp has been reported to have various pharmacological activities.

Various studies have shown that **D-limonene**, present in *C. paradisi* skin, increases **gastric motility** and causes a **reduction of nausea**, **stomach acids neutralization** and **relief of gastric reflux**[51]. On the other hand, *in vitro* studies support that limonene application on human intestinal cells favours the **barrier function of the intestinal epithelium**, an aspect of great relevance for the regulation of nutrient passage into the bloodstream and for the action of immune system components[52].

5.7 Dietary applications.

Regarding its application in diets, in a three-week treatment with overweight patients who ingested grapefruit **juice** three times a day, a **significant decrease in total cholesterol** and low-density lipoprotein levels is observed[53].

Other studies have shown that **D-limonene** is beneficial in **reversing dyslipidemia and hyperglycemia** *in vivo*. In animal models, its administration promotes a decrease in LDL cholesterol, prevents lipid accumulation and regulates blood sugar level. In addition, its antioxidant activity enhances these effects. Moreover, dietary supplementation with D-limonene would restore the liver and pancreas pathological alteration, thus being able to help in obesity prevention[51].

5.8 Interactions with drug consumption.

Another point that deserves special attention due to its possible implications on human health is the **modification of plasma concentration of numerous drugs** with the concomitant consumption of grapefruit **juice**. There are two main causes for this effect: intestinal enzymes **inhibition**, mainly **CYP3A4**, but also others such as CYP1A2,

CYP2C9, CYP2C19 and CYP2D6, which is a process able to alter the metabolism of the drug involved[54–56]. Some examples of drugs related to this mechanism include compounds such as docetaxel, amiodarone, tolvaptan, colchicine, atorvastatin, imatinib, S-ketamine and cortisone acetate[57], as well as some nervous system modulators such as diazepam, triazolam, midazolam and carbamazepine, among others[58].

The second cause that can alter the drug pharmacokinetics refers to the **alteration of specific molecular transporters**, such as the organic anion transporter polypeptide 2B1 (OATP2B1), the multi-resistant sulfotransferases 1 and 3 proteins, and the P glycoprotein transporter[59]. The pharmacokinetic changes induced in this way by grapefruit juice can be observed in most dihydropyridine calcium channel blockers, although with variable increases in the area under the plasma concentration-time curve[60]. Likewise, drugs such as felodipine, nicardipine, lacidipine, amlodipine, verapamil, nitrodipine, pranidipine, nimodipine and nisoldipine are included in this group[58]. In addition to these, there are hydroxymethylglutaryl coenzyme A (HMGCoA) reductase inhibitors, immunosuppressive agents, HIV protease inhibitors, phosphodiesterase type 5 inhibitors, antihistamines, anthelmintics, and anti-inflammatory agents[52,61–65].

Regarding the clinical implications of ingesting grapefruit juice along with the mentioned medications, in addition to presenting moderate effects, several **severe clinical conditions** have been reported, including hypotension, nephrotoxicity, bone marrow suppression, cardiac arrhythmia or gastrointestinal bleeding[66]. Considering these possible health damages, the authors have tried to solve or reduce the problem using **heat treatments of the juice**, **UV irradiation** or **furanocoumarins elimination** through the use of edible mushrooms incorporated into the juice and sterilized in an autoclave[26,67].

5.9 Anticancer activity.

Among the compounds present in grapefruit, **bergamottin** has been reported to have anticancer activity against many types of cancer, so it may be a suitable candidate for the development of new agents for cancer prevention and treatment[68].

On the other hand, **D-limonene** has a well-established chemopreventive activity against many types of cancer. Evidence from a phase I clinical trial demonstrated a partial response in a breast cancer patient and a stable disease for more than six months in three patients with colorectal cancer[69].

5.10 Activity in the nervous system.

Different studies have shown that **D-limonene** present in grapefruit skin, administered by inhalation in mice, has a significant **calming and anxiolytic effect** by activating serotonin and dopamine receptors. Furthermore, D-limonene has an **analgesic effect** similar to that of indomethacin and hyoscine, two well-known and characterized analgesics[70].

Likewise, through behavioural models of depression in mice, the **antidepressant potential** of **naringenin** has been demonstrated through the central serotonergic and noradrenergic systems[39].

5.11 Activity in the skeletal system.

Osteoblasts are cells with a crucial role in bone creation, maintenance, and mineralization. Studies performed in rats have shown how treatment with *C. paradisi* **furanocoumarins** increases the osteoblast proliferation and differentiation, as well as promotes bone formation, this treatment with furanocoumarins being related to **higher bone density**. Furanocoumarins are hence good candidates to be used in the osteoporosis treatment[26].

Activity	**Mechanism of action**
Antimicrobial activity	Antibacterial activity against *Bacillus cereus*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudococcus sp*, *Salmonella thyphimurium*, *Shigella flexneri* and *Staphylococcus aureus*[28,29]. Antifungal activity against *Aspergillus niger*, *Candida albicans* and *Penicillium chrysogenum*[28–30].
Insecticidal activity	Insecticidal activity against the eggs and larve of *Anastrepha fraterculus*, *Ceratitis capitata*, *Aedes aegypti* and the larvae of *Anopheles stephensi*[33–35]. Anticoccidial activity against *Eimeria sp*[36].
Antioxidant effect	Effect demonstrated by total phenol content (TPC), 2,2'-azino-bis(3-etilbenzothiazoline-6-sulfonic) (ABTS) and ferric reducing antioxidant power test (FRAP)[37].
Effects on the cardiovascular system	decreases the average coronary resistance and the blood pressure in the dog's heart both *in vivo* and *ex vivo* [41].
Antidiabetic effect	The administration of pure D-limonene resulted in a decrease in blood glucose, proportion of glycated haemoglobin, the activity of gluconeogenic enzymes, as well as the increase in the activity of glucokinase and the amount of hepatic glycogen, against diabetic individuals in the absence of treatment in animal models of streptozotocin induced diabetes[46].
Effects on the digestive system	Increase by D-limonene of gastric motility and reduction of nausea, neutralization of stomach acids and relief of gastric reflux [51]. Improvement of the barrier function of the intestinal epithelium *in vitro* [52].
Dietary applications	Administration of D-limonene in animal models helps to reverse dyslipidemia and hyperglycaemia, promoting a decrease in cholesterol LDL, preventing, the accumulation of lipids and regulating the level of sugar in blood[51]. Dietary supplementation with D-limonene contributes to the restoration of liver and pancreas pathological alteration [51].
Anticarcinogen activity	Chemopreventive activity demonstrated for D-limonene[69].
Activity in the nervous system	Calming and anxiolytic effect through the activation of serotonin and dopamine receptors by D-limonene [70].

Table 8. Biological activity of *C. paradisi* essential oils, confirmed by scientific research.

Activity	Action mechanisms
Antioxidant effect	Inhibition of nitrite production and inducible nitric oxide synthase and cyclooxygenase-2 expression by naringenin. Demonstrated effects on mouse primary splenocytes, RAW 274.6 macrophages and BV2 microglia cells[39].
Effects on the cardiovascular system	The whole juice induced a reduction in the systolic and diastolic blood pressure in both normotensive and hypertensive subjects[41]. The administration of naringenin improves cardiac function and reduces episodes of infarction and cell death in myocardial tissue in an animal model of ischemia reperfusion in myocardial tissue[42].
Antidiabetic effect	The whole juice induced a decrease in insulin resistance and in weight in obese patients[44]. The whole juice induced a decrease in blood glucose level and an increase in plasma insulin in Wistar rats[46].
Effects on the digestive system	The whole juice induced a decrease in gastric lesions and diarrhoea, and an increase in glutathione content in a model of colitis in rats [48].
Dietary applications	The daily ingestion of grapefruit juice induced a significant decrease in total cholesterol and low-density lipoprotein levels in obese patients[53].
Interactions with drug consumption	Inhibition of intestinal enzymes, mainly CYP3A4, but also others such as CYP1A2, CYP2C9, CYP2C19 and CYP2D6[54–56,58]. Alteration of specific molecular transporters, such as organic anion transporter polypeptide 2B1 (OATP2B1), multiresistant proteins sulfotransferases 1 and 3, the glycoprotein transporter P59[59], la most dihydropyridine calcium channel blockers[52,58,60–65]. Induction of hypotension, nephrotoxicity, bone marrow suppression, cardiac arrhythmia or gastrointestinal bleeding by furanocoumarins present in the juice[66].
Anticarcinogen activity	Anticarcinogen activity reported for bergamottin[68].
Activity in the nervous system	Antidepressant effect of naringenin through the central serotonergic and noradrenergic system[39].
Activity in bone tissue	Furanocoumarins increase the proliferation and differentiation of osteoblasts, as well as promote bone formation [26].

Table 9. Biological activity of *C. paradisi* pulp extract, confirmed by scientific research.

6 *C. paradisi* in the pharmaceutical industry.

One of the great problems of modern medicine is the emergence of multi-resistant pathogens, which has created the need to search for **new antimicrobial compounds** that effectively fight disease-causing microorganisms in plants, animals, and humans.

This review has gone through the antimicrobial and antifungal potential of extracts obtained from different *C. paradisi* parts, as well as their potential use as an **antiparasitic and insecticide**. The application of these extracts, as well as pure compounds isolated from them, therefore appears as a potential alternative to obtaining antimicrobials and antiparasitics by chemical synthesis methods.

On the other hand, the **potential adverse effects** that the consumption of grapefruit along with certain drugs have been reported. The chemical composition of grapefruit varies according to the species, the growing conditions and the process used to extract the juice, so before consuming it, it is advisable to consult a doctor if you are taking any medication.

7 *C. paradisi* in the food industry.

Food contamination by fungi causes great losses to the food industry. The **antifungal** effects of different grapefruit parts shown in this review can be considered for the development of products that favour **food preservation**. For example, grapefruit essential oil has been described as an excellent growth inhibitor of *Penicillium chrysogenum* and *P. verrucosum*[28,29,71].

A viable alternative to improve food preservation and extend its shelf life is the production of edible films or covers and active packaging. Proposals have been designed where it is possible to obtain **biodegradable active films** made with *C. paradisi* seed extract, for which their high potential to be used in active food packaging applications with powerful antimicrobial activity has been demonstrated[72].

8 *C. paradisi* in the cosmetic industry.

The potential irritant and sensitizing effect of the vegetable oil obtained from *C.*

paradisi seeds has been studied, and it is considered suitable for use in lotions, oils, baby powders and creams, other baby products, hair conditioner, others make-up preparations, toothpastes, bath soaps and detergents, beard softeners, face, neck, body and hand cleansers, moisturizers, night creams, other skin care preparations, tanning gels, creams, and liquids. Although this study is based on FDA regulations, its conclusions are applicable to the current cosmetic European Union regulations, except for **furocoumarins**, for which their use in cosmetics is prohibited, except for the normal content in **natural essences and in sunscreen and tanning products**, whose content should be **less than 1 mg/kg**[73].

The use of grapefruit in the cosmetic industry has spread because it helps eliminate impurities and helps strengthen the skin, providing **luminosity and vitality**. The antimicrobial potential of different grapefruit extracts makes it especially beneficial for people prone to **dandruff, acne, impetigo** (bacterial skin infection) or **skin rashes**. Furthermore, it should be noted that grapefruit is very rich in vitamin C, which stimulates the **collagen production**[74], and in lycopene, which **combats the harmful effects of free radicals**[75]. Grapefruit essential oil is also incorporated, along with that of other citrus fruits, as **scent** for different formulations.

According to the CosIng[76] database (Cosmetic Ingredients Database), *C. paradisi* can be used in eighteen different ways, including oil and water extracts obtained from various organs. The most common activities defined by CosIng for the raw material of this species are keeping the skin in good condition, improving the odour of cosmetic products, and masking the odour of other ingredients in cosmetic preparations. The approved forms of raw materials and their possible effects, as well as their use as correctors, are summarized in Table 10.

The form	Activity
C. paradisi fruit extract	skin conditioning
C. paradisi fruit water	fragrance
C. paradisi juice	perfuming, skin conditioning
C. paradisi juice extract	antioxidant, skin conditioning, emollient
C. paradisi peel extract	perfuming, skin conditioning
C. paradisi peel oil	fragrance, perfuming
C. paradisi peel water	fragrance, skin conditioning
C. paradisi seed extract	fragrance, perfuming
C. paradisi seed oil	perfuming, skin conditioning

Table 10. Uses of *C. paradisi* in cosmetic products according to CosIng.

9 *C. paradisi* in the environmental and energy industries.

The most recent applications on the use of citrus derived solid waste are developed in the environmental and energy area. A study investigated the **biosorption** kinetics (capture on the biomass surface) of lead ions in cross-linked pectin obtained from citrus peels[77], since these natural adsorbents are low-cost and useful in these processes, concluding that lead has a higher affinity to biosorption in pectin than by chelation[78,79].

Currently, the design of new technologies has made it possible to obtain **renewable energy sources** from the anaerobic biodegradation of solid citrus waste. The feasibility of producing biogas from the effluents of the citrus industry has been proven, in which the anaerobic digestion in two stages resulted in a high production and yield of biogas and methane[80].

10 Bioavailavility of nutrients from *C. paradisi*.

The bioavailability of bioactive compounds depends mainly on their chemical structure, the effects of the matrix and their interactions. Food processing can be used to stabilize and produce products with a longer shelf life, but it can also be used to increase bioavailability. Bioactivity studies involve *in vivo* experiments in humans, although *in vitro* methods are useful for determining stability under gastrointestinal conditions. Most dynamic digestion models do not simulate the entire human gastrointestinal tract, but only the upper part. The most complex dynamic systems comprise two compartments, simulating the stomach and the small intestine. Other

models include static *in vitro* reproduction of the oral cavity and saliva coupled to a computer-controlled dynamic gastrointestinal model with controlled conditions (temperature, enzyme secretion, pH, and peristaltic movements)[81].

So far, different formulation approaches, including absorption enhancers, structural transformation (eg, prodrugs, glycosylation), or pharmaceutical technologies (eg, carrier complexes, nanotechnology, cocrystals), have been developed to circumvent the low bioavailability of active flavonoids problem in *C. paradisi* juice by **improving their solubility** and increasing the dissolution rate, **increasing their mucosal permeation**, **preventing their degradation** or metabolism in the gastrointestinal tract and their delivery directly to the physiological tract. As expected, by using these strategies, the pharmacokinetic behaviour of several flavonoids has been greatly improved, which is beneficial to improve their biological activity and subsequent clinical application[82].

Another study related to Vitamin C bioavailability, showed that Vitamin C **encapsulation** in new types of liposomes causes an increase in the bioavailability of vitamin C at physiological level, without compromising its potency at cellular level. The clinical study was performed by comparing it with the oral intake of free Vitamin C[83].

11 Conclusions.

The review presented shows that *C. paradisi* and especially its fruit, grapefruit, is a very versatile food for the prevention and treatment of various pathological conditions, although its use as a medicine has not yet been approved due to the lack of a greater number of essays about it. The studies included in this review are focused on the effects produced by the juice or extracts obtained from the skin and seed of grapefruit, or by the most abundant chemical compounds in it, mainly D-limonene and naringenin.

For the **skin** extract obtained, as well as its essential oil, several studies show its potential as an an**tibacterial, antifungal,** and **insecticidal** agent.

As for the **seed**, its **antioxidant potential** has been demonstrated when consumed in its entirety, while its glycerine extract additionally has **antibacterial** activity. Its methanolic extract has shown to have bene**ficial properties for the cardiovascular system**, as well as for the **treatment of diabetes**, while other types of seed extracts would help prevent gastric and liver damage.

As for the **juice**, various studies have established be**neficial effects for the cardiovascular system**, as well as for **diabetes treatment** and **prevention of gastric lesions**, having also confirmed its popularly attributed effects as a **dietary agent**, since it is capable of reducing fat and cholesterol levels, as well as of producing an effective decrease in weight.

For **D-limonene**, its **antidiabetic potential** has been demonstrated, in addition to being beneficial for **gastric function** and having great potential to **improve the absorption of nutrients** in the intestine. Moreover, it has proven to have **analgesic and anxiolytic properties**. Preliminary studies also suggest its potential use as a treatment for different types of cancer due to its **anticancer** effect, shared with bergamottin, a compound that is also present in grapefruit.

Other studies provide evidence on the effects of **naringenin**, demonstrating its **antioxidant activity** and its effect as an **antidepressant agent**, as well as its **beneficial effects on the cardiovascular system**.

Finally, studies performed with different **furanocoumarins** present in grapefruit show their ability to **increase bone density** by stimulating osteoblast function and differentiation.

In addition to its medical uses, this review has shown other applications that are currently being carried out with by-products from the grapefruit industry, with applications as diverse as its introduction in active packaging or as a biofuel in the energy industry.

12 References and notes

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