

# Myrtle (*Myrtus communis* L.) berries, seeds, leaves, and essential oils: New undiscovered sources of natural compounds with promising health benefits

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## Abstract

Myrtle (*Myrtus communis* L.) is a typical plant of the coasts of Mediterranean area, which grows spontaneously as a shrub or a small tree. Myrtle berries, leaves, seeds, and essential oils are natural sources of several nutrients and bioactive compounds with marked health effects. In the ancient medicine, it has been indeed used for treating several common diseases, including gastrointestinal, urinary, and skin disorders, whereas currently it is widely employed in food, cosmetic, and pharmaceutical industries. This review aims to describe the nutritional and the phytochemical compositions of different parts of myrtle plant, as well as their antioxidant activities. In addition, several *in vitro*, *in vivo*, and *ex vivo* studies are also presented to give a general overview of the potential effects of myrtle on human health. Finally, a critical analysis of the limitations related to the current research on myrtle is given.

## KEYWORDS

antioxidants, bioactive compounds, disease prevention, human health

## 1 | INTRODUCTION

Myrtle (*Myrtus communis* L.) is an aromatic medicinal plant, typical of the coastal areas of the Mediterranean regions, such as North Africa or Southern Europe, but it is also present in South America, Australia, and in some areas of Himalaya (Alipour, Dashti, & Hosseinzadeh, 2014; Jabri, Marzouki, & Sebai, 2018a; Sumbul, Ahmad, Asif, & Akhtar, 2011). It belongs to the Myrtaceae family, which includes about 3,000 species, and grows spontaneously as an evergreen shrub or a small tree. The plant can reach a height of 2.5 m, with a full head deeply covered by branches and small leaves; flowers are starry, scented, and can be white

or pink, whereas berry fruits are edible, small, with a round shape and many seeds inside, generally blue-black, even if some varieties have white-yellow fruits, and ripen in autumn, between October and February (Figure 1). Insects do pollination and birds spread seeds in the environment (Alipour et al., 2014; Petretto et al., 2016).

In ancient medical traditions, different parts of myrtle, in particular berries, leaves, flowers, and essential oils, have been extensively used as a remedy for treating cough, gastrointestinal disorders (i.e., peptic ulcers, diarrhea, and hemorrhoids), urinary diseases (i.e., urethritis), and skin ailments (i.e., reddened skin), as well as for inactivating microorganisms and for the wound healing (Aleksic & Knezevic, 2014;

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**FIGURE 1** Details of myrtle (*Myrtus communis* L.) tree (a), branches (b), leaves, and unripe fruits (c) grown in Italy

Alipour et al., 2014; Sumbul et al., 2011). All these beneficial properties are essentially due the wide range and amount of bioactive compounds, such as polyphenols, flavonoids, anthocyanins, phenolic acids, lignans, tannins, antioxidants, organic acids, fatty acids, and minerals, present in the different parts of the myrtle plants (Aleksic & Knezevic, 2014; Alipour et al., 2014; Sumbul et al., 2011). Currently, it is mainly used in culinary practice and in cosmetic, pharmaceutical, and food products: for example, one of the most known derived product is the famous Sardinian sweet liqueur, called “Mirto di Sardegna,” that is made from the hydroalcoholic infusion of the berries, contains high amount of anthocyanins and tannins, and is recognized as a geographical indication of the island (EC Reg. no. 110/2008).

However, to the best of our knowledge, only few studies have evaluated the nutritional and phytochemical composition of this plant, as well as its health benefits. The aim of this work is to present and summarize the nutritional and phytochemical composition of the different parts of myrtle plant, as well as their antioxidant capacity. The biological effects of myrtle will be also discussed, paying special attention to the most common human diseases.

## 2 | PROXIMAL, NUTRITIONAL, AND PHYTOCHEMICAL COMPOSITION OF MYRTLE

### 2.1 | Proximal and nutritional composition

The proximal composition of myrtle is strongly influenced by several factors, including the plant genotype, the geographical area, the climatic conditions, the cultural practice, the maturation stage, and the maceration period of the fruits (Haciseferoğulları, Özcan, Arslan, & Ünver, 2012; Şan, Yildirim, Polat, & Yildirim, 2015; Tuberoso, Melis, Angioni, Pala, & Cabras, 2007).

Total soluble solid contents of fruits are reported to vary from 15.5% to 24.0%, titratable acidity ranges are between 0.01% and 0.44%, whereas pH values range between 4.39 and 5.64 (Fadda, Palma, d'Aquino, & Mulas, 2016; Haciseferoğulları et al., 2012; Şan et al., 2015). Similarly, the content of berry protein varies between 4.17% and 9.02%, carbohydrates and cellulose values are around 79.78% and 23.49%, ashes between 0.73% and 3.47%, oil concentration between 2.37% and 3.48%, dry matter between 24.28% and 89.73%, and crude fiber around 17.41%, according to the genotype studied (Aydin &

**TABLE 1** Most representative organic acids found in myrtle white and black berry

Organic acid	Concentration		References
	White berry	Black berry	
Ascorbic acid (mg/100 g)	1.43	2.82	Şan et al., 2015
Tannic acid (µg/100 g)	23.63	52.46	Şan et al., 2015
Citric acid (mg/100 g)	120.00	1104.85	Haciseferoğulları et al., 2012; Fadda et al., 2016
Malic acid (%)	0.17	0.30	Haciseferoğulları et al., 2012
Tartaric acid (mg/100 g)	0.29	0.30	Haciseferoğulları et al., 2012

Özcan, 2007; Correddu et al., 2019; Haciseferoğulları et al., 2012). Additionally, the most common organic acids present in myrtle berry are citric, ascorbic, tartaric, tannic, and malic acids, whose concentration is very variable, as shown in Table 1.

Myrtle plant is also a rich source of lipids and fatty acids (Alipour et al., 2014; Sumbul et al., 2011). As reported by Aidi Wannes, Mhamdi, Sriti, and Marzouk (2010), the content of total lipids is about 28.97 mg/g in the whole berry fruits, 4.14 mg/g in pericarp, and 61.26 mg/g in seeds, whereas the concentration of neutral glycerolipids in seeds is 58.45 mg/g, including triacylglycerol (57.47 mg/g), diacylglycerol (0.51 mg/g), free fatty acids (0.32 mg/g), and monoacylglycerol (0.15 mg/g). Polar glycerolipids are only 2.81 mg/g of the total glycerolipids (Aidi Wannes et al., 2010).

Moreover, seeds, berries, and essential oils are particularly rich in fatty acids. The most representative are unsaturated fatty acids, especially linoleic (18:2n6c) and oleic (18:1n9c) acids, whereas palmitic (16:0) and stearic (18:0) acids are the most abundant fatty acids of the saturated fraction (Aidi Wannes et al., 2010; Correddu et al., 2019; Jabri et al., 2017, 2018a; Messaoud & Boussaid, 2011; Şan et al., 2015; Serce, Ercisli, Sengul, Gunduz, & Orhan, 2010; Sumbul et al., 2011). The presence of these polyunsaturated *n*-3 fatty acids is very important because they confer to myrtle its anti-inflammatory potential, because they inhibit the production of eicosanoids from arachidonic acid, as well as the production and expression of proinflammatory cytokines, TNF- $\alpha$ , and several interleukins that promote inflammation (Jabri, Marzouki, & Sebai, 2018b).

## 2.2 | Mineral and terpene contents

The types and the amounts of minerals of myrtle depend on several aspects, such as the plant parts, the genotype, the fruit maturation, the environmental conditions (i.e., soil type, fertility, and humidity), and the plant age (Haciseferoğulları et al., 2012; Özcan, Al Juhaimi, Ahmed, Babiker, & Ghafoor, 2020; Yildirim, Şan, Yildirim, Polat, & Ercişli, 2015). In general, Ca, K, P, Mg, Na, S, and Mn are the most representative minerals, whereas Se and P have been reported in lower concentrations; additionally, leaves and fruits are the myrtle parts with the higher concentrations of minerals compared to the stems (Özcan et al., 2020; Yildirim et al., 2015).

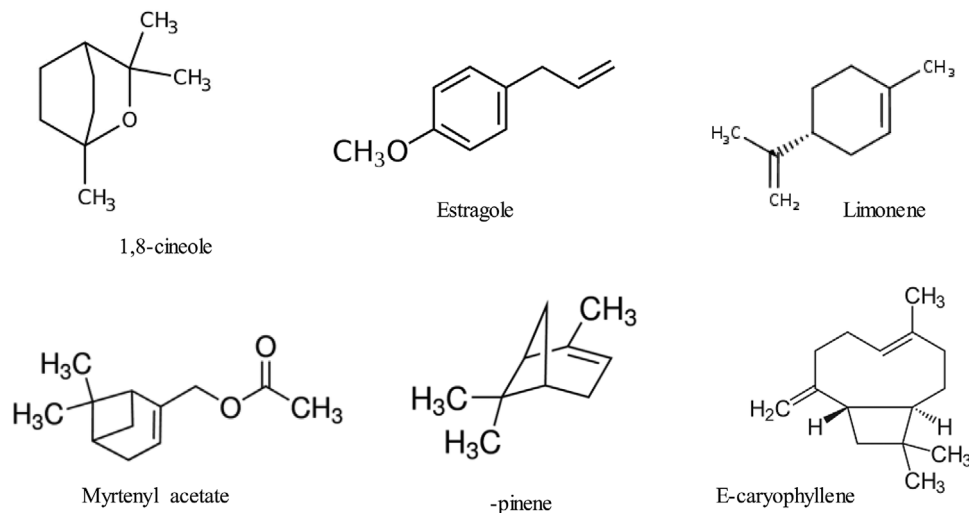
Essential oils derived from myrtle leaves, flowers, and berries have been deeply studied for their chemical composition, which, also in this

case, can be influenced by several factors, including the plant variety, the geographical area, the type of extraction and drying plant parts, the plant developmental and fruit maturation stage, the storage conditions, and the environmental stress (Hennia, Nemmiche, Dandlen, & Miguel, 2019). In general, monoterpenes hydrocarbon, oxygenated monoterpenes, and sesquiterpenoids are the most common classes of compounds found in essential oils extracted from myrtle berries and leaves, with 1,8-cineole,  $\alpha$ -pinene, limonene, geranyl acetate, linalool, estragole,  $\alpha$ -terpinyl acetate, myrtenyl acetate, bergamotene, and E-caryophyllene the most representative ones (Figure 2) (Brada, Tabti, Boutoumi, Wathélet, & Lognay, 2012; Hennia et al., 2019; Kordali, Usanmaz, Cakir, Komaki, & Ercisli, 2016; Mahmoudvand, Ezzatkah, Sharififar, Sharifi, & Dezaki, 2015; Messaoud & Boussaid, 2011; Pereira, Cebola, & Bernardo-Gil, 2009; Petretto et al., 2016; Rahimmalek, Mirzakhani, & Pirbalouti, 2013; Tuberoso et al., 2007; Usai, Marchetti, Culeddu, & Mulas, 2018; Viuda-Martos et al., 2011).

## 2.3 | Phytochemical content of myrtle

Regarding phytochemical composition, fruits and leaves are by far the most studied parts of the myrtle. In both cases, polyphenols are the most representative compounds, extremely important not only for the morphological and physiological functions of the plant, but also essential for human health because of their multiple biological activities (Afrin et al., 2020; Battino et al., 2019; Forbes-Hernandez et al., 2020; Sieniawska, Maciejewska-Turska, Świątek, & Xiao, 2020; Sun et al., 2020).

According to the myrtle ecotypes, the geographical area, and the extraction methods, the amount of total polyphenols, flavonoids, and anthocyanins in berry fruits varies from 14.68 to 138.21 mg gallic acid equivalents (GAE)/g, from 52.03 to 158.94 mg/g, and from 5.355 to 60.252 mg/g, respectively (Amenour, Sendra, Abrini, Pérez-Alvarez, & Fernández-López, 2010; Fadda & Mulas, 2010; González de Peredo et al., 2018, 2019; Messaoud & Boussaid, 2011; Özcan et al., 2020). Specifically, the phytochemical composition of myrtle berries is characterized by the dominant presence of anthocyanins, which confer the purple-dark color to the fruits and contribute to the health effects of myrtle, thanks to their antioxidant, anti-inflammatory, antitumoral, and lipid-lowering effects, among others (Afrin et al., 2020; Battino et al., 2019; Forbes-Hernandez et al., 2020). In myrtle berry, these bioactive compounds are mainly represented by delphinidin 3-O-glucoside,



**FIGURE 2** Most common monoterpenes and sesquiterpenoids found in myrtle-derived essential oils

petunidin 3-O-glucoside, malvidin 3-O-glucoside, and peonidin 3-O-glucoside, followed by cyanidin 3-O-glucoside, delphinidin-pentose, and petunidin-pentose (Maldini et al., 2016; Montoro et al., 2006; Pereira, Cebola, Oliveira, & Gil, 2016, 2017; Sarais et al., 2016; Scorrano et al., 2017; Siracusa et al., 2019) (Figure 3; Snoussi et al., 2012; Tuberoso et al., 2010).

In addition, phenolic acids (i.e., gallic acid and derivatives, caffeic acid, and syringic acid), flavanols (i.e., (-)-epigallocatechin), flavanols (i.e., naringin), flavonols (i.e., myricetin, myricetin 3-O-galactoside, myricetin 3-O-rhamnoside, quercetin 3-glucoside, and quercetin 3-rhamnoside), among others have been identified in berry extracts (Barboni, Cannac, Massi, Perez-Ramirez, & Chiaramonti, 2010; Şan et al., 2015; Sarais et al., 2016; Tuberoso et al., 2010; Viuda-Martos et al., 2011).

Concerning leaves composition, the concentration of total polyphenols and flavonoids varies from 31.25 to 298.63 mg GAE/g and from 129.96 to 376.82 mg/g, respectively, according to the myrtle variety and the methods applied for extraction and analysis (Amenour et al., 2010; Özcan et al., 2020). In particular, lignans (i.e., secoisolariciresinol hexoside), tannins (i.e., eugeniflorin D2, tellimagrandin I and II, and oenothain B), flavonoids (i.e., (+)-catechin, quercetin 3-O-rhamnoside, quercetin-galactoside-gallate, (-)-epigallocatechin, (-)-epigallocatechin 3-O-gallate, myricetin galactoside, myricetin 3-O-rhamnoside, myricetin arabinoside, and kaempferol-O-galloyl-hexoside), phenolic acids (i.e., ellagic acid and derivatives, gallic acid and galloyl derivatives, syringic acid, t-ferulic acid, and caffeic acid), and gallomyrtucommulones (i.e., gallomyrtucommulone A and C) are the main phytochemicals found in myrtle leaf extracts (Babou et al., 2016; Özcan et al., 2020) (Figure 4; Pereira et al., 2016, 2017; Siracusa et al., 2019; Taamalli et al., 2014; Viuda-Martos et al., 2011; Yoshimura, Amakura, Tokuhara, & Yoshida, 2008).

Finally, only few studies have been performed to evaluate the phytochemical composition of myrtle seeds. The concentration of total polyphenols and flavonoids is comprised between 25.25 and 147.56 mg GAE/g dry weight and between 0.75 and 85.06 mg/g dry weight,

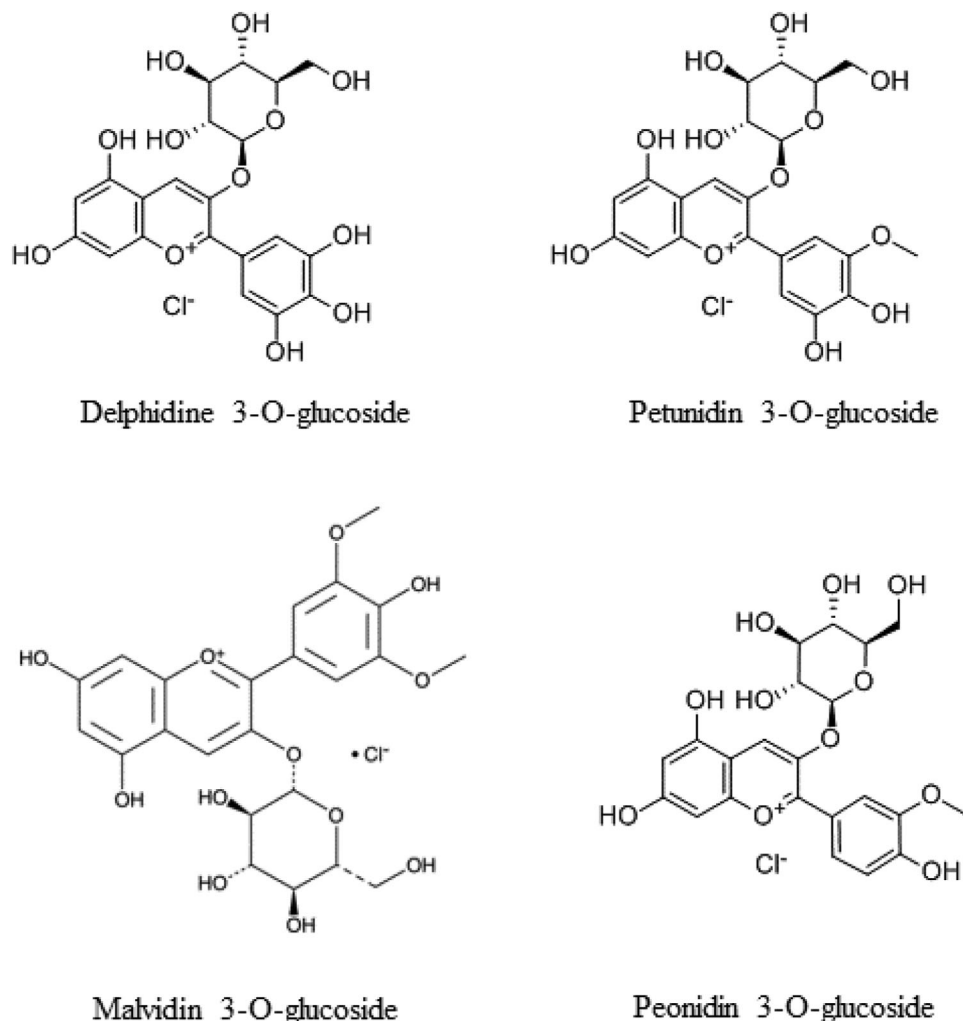
respectively, according to the myrtle variety and the methods used for extraction and analysis (Aidi Wannes & Marzouk, 2016; Jabri et al., 2017; Jabri et al., 2016). Interestingly, berry seeds are very rich in total tannins (about 18.01 mg GAE/g dry weight), which can be even twofold higher than those present in the whole fruit (9.11 mg GAE/g dry weight) (Aidi Wannes & Marzouk, 2013, 2016) and that contribute to the astringent taste of the myrtle berry.

The most common tannins found in myrtle seeds are hydrolysable tannins, especially ellagitannins, including eugeniflorin D2, oenothain B, pedunculagin, strictinin, tellimagrandin I, casuarictin, and hexahydroxydiphenoyl hexoside (Figure 5) (D'Urso, Sarais, Lai, Pizza, & Montoro, 2017; Franco et al., 2019).

Other phenolic compounds have been also found in seeds in lower concentrations, such as, for example, flavonols, including myricetin-galloyl-hexoside, quercetin-galloyl-hexoside, myricetin-galloyldeoxyhexose, and myricetin-deoxyhexose-hexose (D'Urso et al., 2017); anthocyanins, such as peonidin diglucoside, petunidin 3-O-glucoside, delphinidin 3-O-galactoside, and delphinidin 3-(6 coumaroyl)-glucoside; and some hydroxybenzoic acid derivatives (Jabri et al., 2016).

### 3 | TOTAL ANTIOXIDANT CAPACITY

Antioxidants are molecules able to react and neutralize free radicals, thus preventing and reducing the oxidative stress and its damaging effects in human body cells (Alvarez-Suarez et al., 2016). In the last years, in order to avoid the use of synthetic antioxidants, there has been growing interest in searching and studying new natural compounds to use in food and cosmetic industry; in addition, also consumers all around the world have become more and more aware of the importance of antioxidants in maintaining a good health and in preventing the onset of the most common diseases, as demonstrated by the global annual increase of nutraceutical and dietary supplement market (Augustin & Sanguansri, 2015).



**FIGURE 3** Most common anthocyanins present in myrtle berry

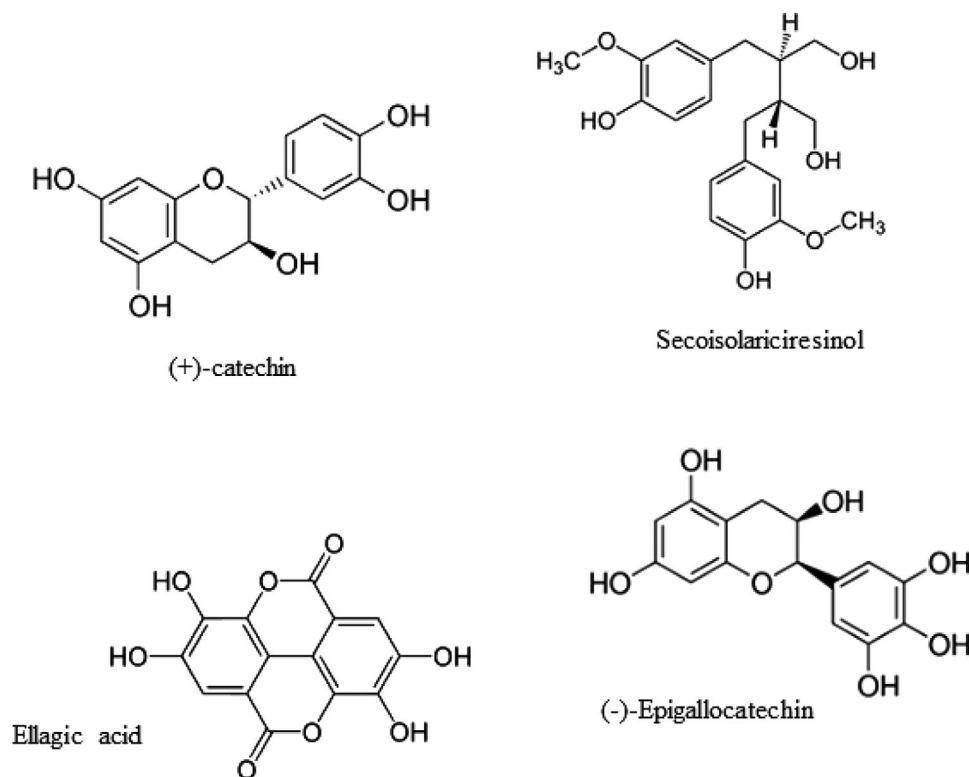
Together with several medicinal and aromatic plants, myrtle is a rich source of antioxidants: indeed, the high amounts of bioactive compounds present in its berries and leaves significantly contribute to a high total antioxidant capacity (TAC) and free-radical scavenging property. In particular, polyphenols display a high antioxidant capacity, because they are excellent hydrogen donors, reducing agents, metal chelators, and singlet oxygen quenchers (Rice-Evans, Miller, & Paganga, 1997); higher is the number of phenolic hydroxyls in the aromatic ring, higher is the TAC exerted by these compounds (Duthie & Crosier, 2000).

Many studies have evaluated the TAC of myrtle extracts, as shown in Table 2.

However, it is very difficult to compare the published results, because different myrtle genotypes (i.e., with white and black fruits), different parts of the plants (berry, leaves, seeds, and oils), different period of maturation of the fruits (unripe and ripe), different extraction solvents (water, methanol, ethanol, ethyl acetate, dichloromethane, and acetone), different protocols (trolox equivalent antioxidant activity assay, ferric reducing antioxidant power assay, 2,2-diphenyl-1-picrylhydrazyl assay, and  $\beta$ -carotene assay), and even different ways of

presenting the results (i.e., diverse units of measure) have been used in these reports. For these reasons, in the future it should be necessary to adopt and uniform all the protocols used by the researchers to evaluate the antioxidant capacity of myrtle extracts in order to make possible a comparison between the data obtained worldwide.

Finally, some more sophisticated methods have been applied to assess the TAC of different myrtle parts (Romani et al., 2004; Rosa et al., 2015; Sanna, Mulas, Molinu, & Fadda, 2019; Tuberoso et al., 2010). For example, berry extracts at 150 and 300 g/L showed a high hydroxyl radical scavenging activity measured by the electron paramagnetic resonance spin trapping method, even after 10 months of storage (Sanna et al., 2019), whereas extracts of myrtle leaves and berry, as well as oligomeric acylphloroglucinols extracted from leaves, were able to inhibit, in a dose-dependent way, the oxidation of Low density lipoprotein (LDL) isolated from health volunteers and exposed to copper ions, as well as to decrease the formation of conjugated dienes (Romani et al., 2004; Rosa et al., 2008; Tuberoso et al., 2010). Similarly, myrtle berry jam extract has been showed to reduce the peroxidation of liposome exposed to copper, by chelating  $\text{Cu}^{2+}$  ions and scavenging free radicals, preventing the degradation of unsaturated fatty



**FIGURE 4** Most common phytochemicals present in myrtle leaves

acids, and decreasing the levels of malondialdehyde, but it was not able to decrease the levels of intracellular reactive oxygen species (ROS) in Caco-2 cells stressed with the oxidant tert-butyl hydroperoxide (Rosa et al., 2015).

## 4 | EFFECTS ON HUMAN HEALTH

The biological activities of myrtle, including the antimicrobial, gastrointestinal, antidiabetic, anti-inflammatory, antitumor, hypolipidemic, antithrombotic, anti-ischemic, and antifibrotic effects, have been described in several studies, as reported in Tables 3–8.

### 4.1 | Antimicrobial activities

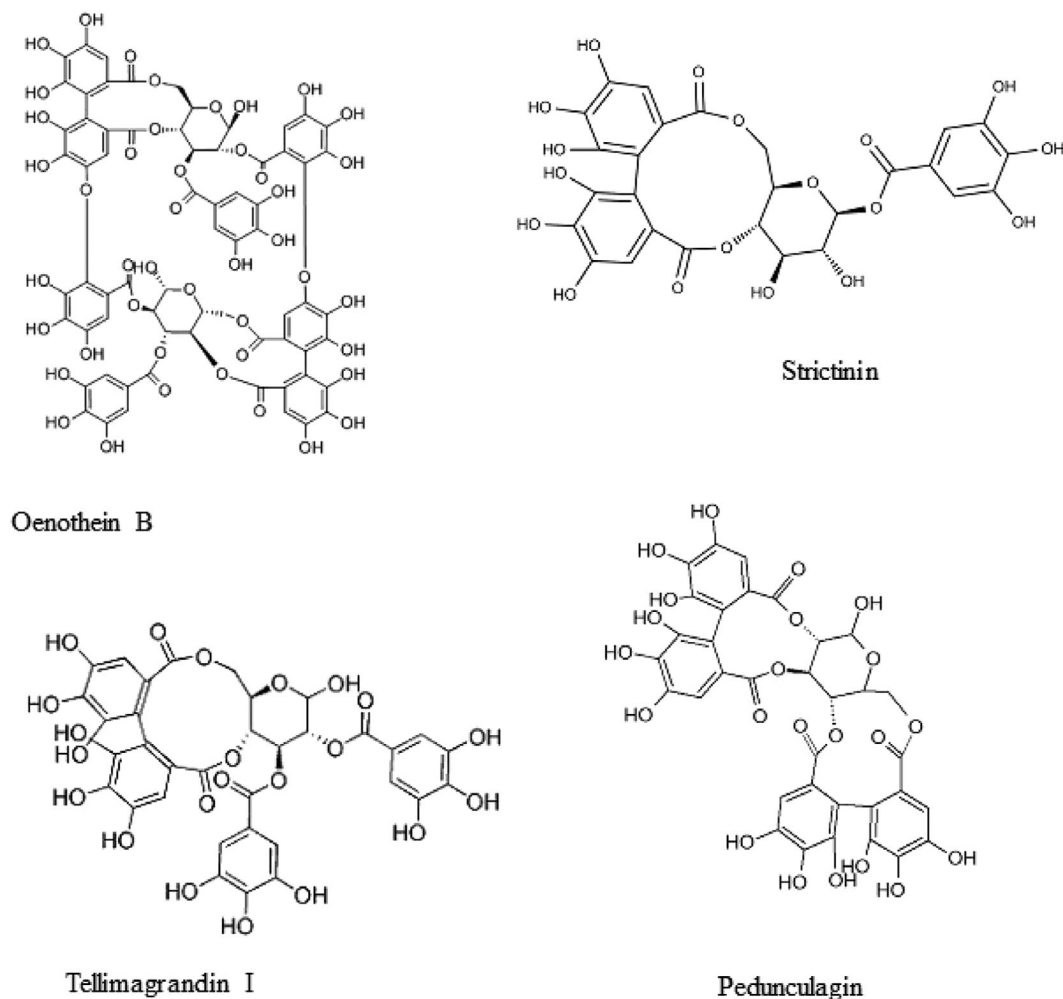
Different extracts of myrtle berry, leaves, and essential oils have been extensively studied for their antibacterial and antifungal properties (Table 3).

Myrtle extracts and essential oils exert antibacterial activities by affecting the permeability of bacterial cell wall and membrane, promoting the release of cellular contents outside the cell and leading to the disruption of essential membrane function, including nutrient absorption, enzyme activity, and electron transfer (Amensour et al., 2010). For example, myrtle leaf extracts strongly inhibited the growth of Gram-positive bacteria, such as *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Mycobacterium smegmatis*, with a minimum inhibitory concentration (MIC) and a minimum bacteri-

cidal concentration (MBC) around 4.87–78 and 0.3–20  $\mu\text{g/ml}$ , respectively. However, no effects were observed against Gram-negative bacteria (Mir, Bashir, Alfaify, & Oteef, 2020). In another study, leaf extracts showed potent inhibition against *S. aureus* (MIC: 0.2 mg/ml; Minimum Lethal Concentration [MLC]: 2 mg/ml) and *Vibrio cholera* (MIC: 2 mg/ml and MLC: 20 mg/ml), but little or no effects against *Escherichia coli* (MIC: 8 mg/ml and MLC: 40 mg/ml) and *Pseudomonas aeruginosa* were highlighted (Taheri, Seyfan, Jalalinezhad, & Nasery, 2013). Additionally, Mansouri, Foroumadi, Ghaneie, and Najari (2001) found that methanolic myrtle leaf extract inhibited the growth of six Gram-positive (*S. aureus*, *Micrococcus luteus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Listeria monocytogenes*) and three Gram-negative bacteria (*Escherichia coli*, *Proteus vulgaris*, and *P. aeruginosa*), with MIC ranging between 0.1 (*M. luteus* and *S. aureus*) and 2 mg/ml (*E. coli*), but had no effects against *Campylobacter jejuni*. Similar results were found by Al-Saimary et al. (2002), who highlighted an inhibitory effect of myrtle leaf extract against *P. aeruginosa* with MIC values of 140–150  $\mu\text{g/ml}$ .

Myrtle leaf and berry extracts showed relevant antibacterial potential against different Gram-positive and Gram-negative bacteria (*Bacillus subtilis*, *Listeria innocua*, *L. innocua*, *L. monocytogenes*, *S. aureus*, *P. vulgaris*, *P. aeruginosa*, and *P. fluorescens*) with MIC ranging between  $<0.075$  (*S. aureus*) and  $>5$  (*P. vulgaris*) mg/ml for both extracts; no effects have been observed against *E. coli* K12 (Amensour et al., 2010).

Finally, essential oil derived from myrtle plants has been shown to inhibit (a) the growth of different strains of *Mycobacterium tuberculosis* and *Mycobacterium paratuberculosis*, with MIC values ranging from



**FIGURE 5** Some common hydrolysable tannins found in myrtle seeds

0.17 to 2% (Zanetti et al., 2010), (b) the growth of *S. aureus*, *L. monocytogenes*, *E. coli*, *Enterococcus durans*, *Salmonella Thypi*, *P. aeruginosa*, and *B. subtilis*, reporting MIC values between 0.5 and 1% (*P. aeruginosa*) (Akin, Aktumsek, & Nostro, 2010), (c) the growth of *S. typhimurium* deposited on shredded iceberg lettuce and on the skin of whole tomatoes (Gündüz, Gönül, & Karapinar, 2009), (d) the growth of *S. aureus*, *P. mirabilis*, and *Klebsiella pneumonia*, with MIC values ranging between 0.12 and 4  $\mu\text{g/ml}$  (Hennia, Brada, Nemmiche, Fauconnier, & Lognay, 2015), (e) the growth of *P. aeruginosa* with MIC and MBC values of 64  $\mu\text{g/ml}$  (Owlia, Saderi, Rasooli, & Sefidkon, 2009), (f) the growth of *E. coli*, *S. aureus*, and *C. albicans*, reporting MIC and MBC values of 2–4 and 4–8  $\mu\text{g/ml}$ , respectively (Yadegarinia et al., 2006), and (g) the growth of a panel of 12 pathological microorganisms, including Gram-positive and Gram-negative bacteria, fungi, and yeast, as shown in Table 3 (Berka-Zougali, Ferhat, Hassani, Chemat, & Allaf, 2012).

The antifungal activities of myrtle essential oils are strictly related to the presence of oxygenated monoterpenes and other polyphenols that are able to affect irreversibly cell membranes, promoting the release of cellular materials and the death of the microorganism, as occurred with bacteria (Cox, Mann, & Markham, 2001). Essential oils

derived from myrtle berry were reported to inhibit the growth of 19 phytopathogenic fungi, including *Rhizoctonia solani*, *Fusarium tabacinum*, *Fusarium culmorum*, *Botrytis cinerea*, *Sclerotinia minor*, *Cladosporium herbarum*, and *Nigrospora oryzae*, with different percentage of inhibition, according to the different strain (Kordali et al., 2016), whereas essential oils derived from myrtle leaves exerted antifungal effects against different strains of *Candida*, with MIC values ranging between 2 and 4  $\mu\text{g/ml}$  (Cannas et al., 2013).

Finally, two studies have evaluated the effects of myrtle against Protozoa: the former showed that essential oils derived from aerial parts inhibited the growth rate of promastigote and amastigote forms of *Leishmania tropica* in a dose-dependent manner with  $\text{IC}_{50}$  of 8.4 and 11.6  $\mu\text{g/ml}$ , respectively (Mahmoudvand et al., 2015); the latter highlighted the capacity of essential oils derived from leaves in promoting the death of *Trichomonas vaginalis* at pH 4.65, but not at pH 6 (Mahdi, Gany, & Sharief, 2006).

On the basis of these promising results, the antimicrobial activities of myrtle plant should be deeply assessed in the future, also considering the serious problems associated with the use of synthetic antibiotics and antifungal drugs, such as the antimicrobial resistance, the

**TABLE 2** Antioxidant capacity of myrtle berry, leaves, seed, and oil extracts

Samples	TEAC	FRAP	DPPH	$\beta$ -Carotene assay	References
Berry					
Methanolic extract	0.46 mM TE/100 g FW	-	0.68 mM TE/100 g FW	-	Fadda et al., 2016
Ethanol extract	-	84.7 mmol Fe <sup>2+</sup> /L	41.4 mmol TEAC/L	-	Tuberoso et al., 2010
Water extract		7.6 mmol Fe <sup>2+</sup> /L	3.7 mmol TEAC/L		
Ethyl acetate extract		40.7 mmol Fe <sup>2+</sup> /L	17.7 mmol TEAC/L		
Ethanol extract	-	-	65.0-87.5%	-	Snoussi et al., 2012
Methanolic extract	-	-	IC <sub>50</sub> : 2.34-8.24 $\mu$ g/ml	74.53-91.65%	Serçe et al., 2010
Methanolic extract	-	2.1-2.7 mmol Fe <sup>2+</sup> /g	IC <sub>50</sub> : 2.1-2.8 mg/ml	-	Messaoud et al., 2011
Methanolic extract	1,889.43 mM TE/g	-	-	-	Amensour et al., 2010
Ethanol extract	625.18 mM TE/g				
Water extract	307.61 mM TE/g				
Ethyl acetate extract	906.66 mM TE/g				
Dichloromethane extract	-	0.732 at 2,000 $\mu$ g/ml	-	-	Tumen et al., 2012
Acetone extract		3.369 at 2,000 $\mu$ g/ml			
Ethyl acetate extract		3.372 at 2,000 $\mu$ g/ml			
Methanolic extract		3.346 at 2,000 $\mu$ g/ml			
Methanolic extract	-	130 $\mu$ g/ml	IC <sub>50</sub> : 136 $\mu$ g/ml	78 $\mu$ g/ml	Aidi Wannas et al., 2012
Methanolic extract	-	-	77.64-83.56%	-	Özcan et al., 2020
Methanolic extract	-	-	IC <sub>50</sub> : 19.02-26.51 $\mu$ g/ml	-	Babou et al., 2016
Water extract			IC <sub>50</sub> : 8.42-23.70 $\mu$ g/ml		
Methanolic extract	179 $\mu$ mol TE/g				Pereira, Cebola, Oliveira, & Gil, 2017
Water extract			21.2% (white berry) 35.1% (black berry)		Ferchichi et al., 2011
Leaves					
Methanolic extract	2,594.34 mM TE/g	-	-	-	Amensour et al., 2010
Ethanol extract	2,039.80 mM TE/g				
Ethyl acetate extract	311.23 mM TE/g				
Water extract	2,406.68 mM TE/g				
Methanolic extract	-	-	93.76-98.37%	-	Özcan et al., 2020
Dichloromethane extract	-	0.732 at 2,000 $\mu$ g/ml	-	-	Tumen et al., 2012
Acetone extract		3.369 at 2,000 $\mu$ g/ml			
Ethyl acetate extract		3.372 at 2,000 $\mu$ g/ml			
Methanolic extract		3.346 at 2,000 $\mu$ g/ml			

(Continues)

TABLE 2 (Continued)

Samples	TEAC	FRAP	DPPH	$\beta$ -Carotene assay	References
Methanolic extract	-	-	IC <sub>50</sub> : 8.45–9.51 $\mu$ g/ml	-	Babou et al., 2016
Water extract			IC <sub>50</sub> : 8.29–9.44 $\mu$ g/ml		
Methanolic extract	358 $\mu$ mol TE/g	-	-	-	Pereira et al., 2017
Methanolic extract	IC <sub>50</sub> : 0.0098 mg/ml	EC <sub>50</sub> : 0.047 mg/ml	IC <sub>50</sub> : 0.009 mg/ml	73.24%	Benchikh, Amira, & Benabdallah, 2018
Chloroform extract	IC <sub>50</sub> : 0.0096 mg/ml	EC <sub>50</sub> : 0.226 mg/ml	IC <sub>50</sub> : 0.035 mg/ml	93.95%	
Ethyl acetate extract	IC <sub>50</sub> : 0.0015 mg/ml	EC <sub>50</sub> : 0.065 mg/ml	IC <sub>50</sub> : 0.003 mg/ml	90.29%	
Water extract	IC <sub>50</sub> : 0.004 mg/ml	EC <sub>50</sub> : 0.033 mg/ml	IC <sub>50</sub> : 0.011 mg/ml	79.58%	
Water extract			90.7% (from white berry) 86.5% (from black berry)		Ferchichi et al., 2011
Seed					
Methanolic extract	-	EC <sub>50</sub> : 0.01 mg/ml	IC <sub>50</sub> : 0.01 mg/ml	IC <sub>50</sub> : 0.07 mg/ml	Aidi Wannes et al., 2016
Water extract	EC <sub>50</sub> : 184.34 $\mu$ g/ml	-	-	-	Jabri et al., 2016
Water extract	-	-	IC <sub>50</sub> : 172.1 $\mu$ g/ml	-	Jabri et al., 2017
Methanolic extract	-	8 $\mu$ g/ml	IC <sub>50</sub> : 8 $\mu$ g/ml	70 $\mu$ g/ml	Aidi Wannes et al., 2012
Methanolic extract	-	-	IC <sub>50</sub> : 3.89 $\mu$ g/ml	-	Babou et al., 2016
Water extract			IC <sub>50</sub> : 6.50 $\mu$ g/ml		
Essential oil					
Seed oil		EC <sub>50</sub> : 20 mg/ml	IC <sub>50</sub> : 10 mg/ml	IC <sub>50</sub> : 40 mg/ml	Aidi Wannes et al., 2016
Plant oil			3.53%	42.98%	Yadegarinia et al., 2006
Leaves oil			IC <sub>50</sub> : 693–768 $\mu$ g/ml		Berka-Zougali et al., 2012

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl assay; EC, effective concentration; FRAP, ferric reducing antioxidant power assay; FW, fresh fruit; IC, inhibitory concentration; TE, trolox equivalent; TEAC, trolox equivalent antioxidant capacity assay.

scarcity of antifungal treatments, the environmental problems, the side effects, the relapse of infections, the toxicity, and the high costs (Aleksic & Knezevic, 2014).??

## 4.2 | Gastrointestinal diseases

In the last years, the effects of myrtle on digestive tract have been extensively evaluated (Table 4).

Gastroesophageal reflux is the normal passage of the stomach contents into the esophagus during the postprandial period and it can become pathological if it causes ulceration and destroys the normal esophagus squamous epithelium (Jabri et al., 2016). Even if the biological mechanisms underlying this process are still unknown, there is increasing evidence that ROS, oxidative stress, and lipid peroxidation are strongly involved (Singh, Singh, Sengupta, & Palit, 2012). For these reasons, the use of plant extracts, particularly rich in antioxidants, has been studied to produce new drugs against this pathological

condition (Kawahara et al., 2007; Mahattanadul et al., 2011). Regarding myrtle, in laparotomized Wistar rats, seed extract (25, 50, and 100 mg/kg) was able to improve the macroscopic and histopathological damages of the esophagus; decrease the levels of malondialdehyde (MDA); and increase the activity of the main antioxidant enzymes (catalase [CAT], superoxide dismutase [SOD], and glutathione peroxidase [GPx]), the level of glutathione (GSH), and plasma scavenging activities, as well as protect against calcium deregulation, restoring ion homeostasis (Jabri et al., 2016). Myrtle seeds have been shown to protect also the gastric mucosa, exerting antiulcer effects (Jabri et al., 2017; Sumbul, Ahmad, Asif, Saud, & Akhtar, 2010). In adult Wistar rats intoxicated with ethanol, aqueous seed extracts (25, 50, and 100 mg/kg) protected against gastric and duodenal lesions, reducing the morphological and histopathological damage, decreased oxidative stress (MDA levels), improved the antioxidant defense system (GSH, CAT, SOD, GPx, and plasma scavenging activities), and restored calcium and iron homeostasis (Jabri et al., 2017). Similar results have been found also for myrtle berry extracts, which in adult Wistar rats stressed with ethanol or

**TABLE 3** Antimicrobial activities of myrtle berries, leaves, seeds, and essential oils

Sample	Experimental models	Dose and duration	Effects	References
Ethanol leaf extract	<i>E. faecalis</i> <i>S. aureus</i> and <i>S. epidermidis</i> <i>M. smegmatis</i> <i>P. aeruginosa</i> <i>S. typhi</i> <i>E. coli</i> <i>Shigella</i> <i>K. pneumonia</i> <i>C. albicans</i>	0.4 g/ml for 24 hr	<ul style="list-style-type: none"> <li>High MIC (4.87–78 µg/ml) and MBC (0.3–20 µg/ml) against Gram-positive and acid-fast bacteria</li> <li>No effects against Gram-negative bacteria</li> </ul>	Mir et al., 2020
Ethyl alcohol leaf extract	<i>S. aureus</i> <i>P. aeruginosa</i> <i>V. cholerae</i> (Ogawa) <i>E. coli</i>	10, 20, 40, and 80 mg/ml	<ul style="list-style-type: none"> <li>High MIC and MLC against <i>S. aureus</i> (0.2 and 2 mg/ml) and <i>V. Cholerae</i> (2 and 20 mg/ml)</li> <li>Moderate effects on <i>E. coli</i> (8 and 40 mg/ml)</li> <li>No effects against <i>P. aeruginosa</i></li> </ul>	Taheri et al., 2013
Methanolic leaf extract Essential oils	<i>S. aureus</i> <i>M. luteus</i> <i>S. agalactiae</i> , <i>S. pyogenes</i> , and <i>S. pneumoniae</i> <i>L. monocytogenes</i> <i>E. coli</i> <i>P. vulgaris</i> <i>P. aeruginosa</i> <i>C. jejuni</i>	0.5 mg in 10% methanol	<ul style="list-style-type: none"> <li>Inhibitory effects on all the tested bacteria except <i>C. Jejuni</i></li> </ul>	Mansouri et al., 2001
Water leaf extract	<i>P. aeruginosa</i>	50, 100, 250, 500, 750, and 1,000 µg/ml	<ul style="list-style-type: none"> <li>Inhibitory effects with MIC values around 140–150 µg/ml</li> </ul>	Al-Saimary et al., 2002
Methanolic leaf/berry extract Ethanol leaf/berry extract Ethyl acetate leaf/berry extract	<i>B. subtilis</i> <i>E. faecium</i> <i>L. innocua</i> <i>L. monocytogenes</i> <i>P. aeruginosa</i> <i>S. aureus</i> <i>P. vulgaris</i> <i>P. aeruginosa</i> <i>P. fluorescens</i> <i>E. coli</i> K12	0.019–5 mg/ml for 18 hr	<ul style="list-style-type: none"> <li>High antibacterial activity against most of the tested microorganisms, except <i>E. coli</i> K12</li> </ul>	Amensour et al., 2010
Essential oil from leaves	<i>M. tuberculosis</i> <i>M. paratuberculosis</i>	0.17%, 1%, 2%, 4%, 8%, 10%, 12%, 14%, and 16% (v/v)	<ul style="list-style-type: none"> <li>Inhibitory effects against all the studied strains, especially for <i>M. tuberculosis</i> (MIC: 0.17%)</li> </ul>	Zanetti et al., 2010
Essential oil from leaves	<i>S. aureus</i> <i>L. monocytogenes</i> <i>E. durans</i> <i>S. typhi</i> <i>E. coli</i> <i>B. subtilis</i> <i>P. aeruginosa</i>	0.0625–1% (v/v) for 18–24 hr	<ul style="list-style-type: none"> <li>Inhibitory effects against all the studied strains (MIC: 0.5% to &gt;1%)</li> </ul>	Akin et al., (2010)
Essential oil from leaves	<i>S. Typhimurium</i>	500, 750, and 1,000 ppm for 5, 10, 15, and 20 min of washing	<ul style="list-style-type: none"> <li>Significant reduction in the number of <i>S. Typhimurium</i></li> </ul>	Gündüz et al., 2009
Essential oil from leaves	<i>S. aureus</i> <i>P. mirabilis</i> <i>K. pneumonia</i>	3.2% for 24 hr	<ul style="list-style-type: none"> <li>Inhibitory effects (MIC comprised between 0.12 and 4 µg/ml)</li> </ul>	Hennia et al., 2015

(Continues)

TABLE 3 (Continued)

Sample	Experimental models	Dose and duration	Effects	References
Essentials oils	<i>P. aeruginosa</i>	50:50 for 18 hr	• Inhibitory effects, with MIB and MBC values of 64 µg/ml	Owlia et al., 2009
Essentials oils	<i>E. coli</i> <i>S. aureus</i> <i>C. albicans</i>	0.036–72.0 mg/ml for 24 hr	• Inhibitory effects, with MIB and MBC values of 2–4 and 4–8 µg/ml, respectively	Yadegarinia et al., 2006
Essential oil from leaves	<i>B. subtilis</i> <i>S. Enterica</i> <i>E. cloacae</i> <i>P. aeruginosa</i> <i>K. pneumonia</i> <i>S. aureus</i> <i>L. monocytogenes</i> <i>C. albicans</i> <i>A. flavus</i> <i>E. coli</i> <i>A. ochraceus</i> <i>F. culmorum</i>	24–48 hr	• Inhibitory effects against all the bacteria, yeast, and fungi	Berka-Zougali et al., 2012
Essential oil from leaves	19 phytopathogenic fungi	1%	• Inhibitory effects against all fungi, with different % of inhibition	Kordali et al., 2016
Essential oil from berry	<i>C. albicans</i> and <i>C. glabrata</i> <i>C. krusei</i> , <i>C. tropicalis</i> , and <i>C. parapsilosis</i>	0.06–32 µg/ml for 48 hr	• Antifungal effects with MIC values comprised between 2 and 4 µg/ml	Cannas et al., 2013
Essential oil from aerial parts	<i>L. tropica</i>		• Inhibition of promastigote (IC <sub>50</sub> : 8.4 µg/ml) and amastigote growth rate (IC <sub>50</sub> : 11.6 µg/ml)	Mahmoudvand et al., 2015
Essential oil from leaves	<i>T. vaginalis</i>	10, 20, 50, and 100 mg for 0.5, 1, and 24 hr	• Dead effects at pH 4.65 but no at pH 6	Mahdi et al., 2006

Abbreviations: MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; MLC, minimum lethal concentration.

with Indomethacin were able to decrease the ulcer index, the gastric acidity, and mucus, as well as the gastric juice volume, improving the histopathological damage (Sumbul et al., 2010).

Another common chronic gastric disease is the ulcerative colitis, caused by several factors, including immune system dysregulations, intestinal dysbiosis, inflammation, genetic predisposition, and oxidative stress (Jabri et al., 2018a). Thanks to the high contents of antioxidant and anti-inflammatory compounds, myrtle plant is a promising candidate to prevent and treat this disease. In Wistar rats treated with acetic acid, seed extracts (25, 50, and 100 mg/kg) significantly decreased the lesions in colonic mucosa, improving the histopathological damage; reduced the lipid peroxidation; prevented the depletion of the antioxidant enzymes (GSH, CAT, SOD, and GPx); and restored ion homeostasis (Jabri et al., 2015).

Finally, myrtle seed extract has shown interesting antidiarrheic properties. Diarrhea can be due to malabsorption, accelerated transit, excessive intestinal secretion, or osmotic effect causing fluid inflow (Jabri et al., 2018a). In Wistar rats treated with castor oil, myrtle seed extracts (25, 50, and 100 mg/kg) protected against intestinal fluid accumulation and diarrhea in a dose-dependent manner, decreased oxida-

tive stress, improved antioxidant enzyme activities, and restored the disturbances of intracellular mediators (Jabri et al., 2016). In the same experimental model, myrtle berries juice (5 and 10 ml/kg) inhibited the gastric emptying and the intestinal mobility, protected against intestinal fluid accumulation, decreased the oxidative stress, and improved antioxidant enzyme activities in the intestine (Jabri, Rtibi, Sakly, Marzouki, & Sebai, 2016).

### 4.3 | Antidiabetic effects

Diabetes mellitus is a metabolic disorder, caused by serious defects in carbohydrate and lipid metabolism and characterized by chronic insulin resistance and hyperglycemia. In the last years, its incidence has grown vertiginously: 415 million adults had diabetes in 2015 and it is expected to reach 642 million within 2040 (Herman, 2017). The main two factors that contribute to the development and progression of diabetes are dietary habits and health lifestyle. Indeed, several studies have shown that the consumption of plant foods, rich in antioxidants and bioactive compounds, exerts a preventive role, lowering the

**TABLE 4** Gastrointestinal effects of myrtle berries and seeds

Sample	Experimental models	Dose and duration	Effects	References
Seed water extract	Laparotomized adult male Wistar rats with esophagitis	25, 50, and 100 mg/kg for 6 hr	<ul style="list-style-type: none"> <li>• Improvement of macroscopic and histopathological damages</li> <li>• Decrease of oxidative stress biomarkers</li> <li>• Increase of the activity of the main antioxidant enzyme</li> <li>• Restoration of ion homeostasis</li> </ul>	Jabri et al., 2016
Seed water extract	Adult male Wistar rats intoxicated with ethanol to induce peptic ulcer	25, 50, and 100 mg/kg for 15 days	<ul style="list-style-type: none"> <li>• Improvement of macroscopic and histopathological damages</li> <li>• Decrease of oxidative stress biomarkers and inflammatory cell infiltration</li> <li>• Increase of the activity of the main antioxidant enzymes</li> <li>• Restoration of ion homeostasis</li> </ul>	Jabri et al., 2017
Berry water extract Berry methanolic extract	Adult male Wistar rats intoxicated with ethanol to induce gastric ulcer	105 and 175 mg/kg 93 and 154 mg/kg for 1–5 hr	<ul style="list-style-type: none"> <li>• Decrease the ulcer index, the gastric acidity and mucus, as well as the gastric juice volume</li> <li>• Improvement of the histopathological damage</li> </ul>	Sumbul et al., 2010
Seed water extract	Adult male Wistar rats stressed with acetic acid to induce colitis	25, 50, and 100 mg/kg for 7 days	<ul style="list-style-type: none"> <li>• Improvement of colonic mucosa lesion and histopathological damages</li> <li>• Decrease of oxidative stress biomarkers</li> <li>• Increase of the activity of the main antioxidant enzyme</li> <li>• Restoration of ion homeostasis</li> </ul>	Jabri et al., 2015
Seed water extract	Adult male Wistar rats stressed with castor oil to induce diarrhea	25, 50, and 100 mg/kg for 1 hr	<ul style="list-style-type: none"> <li>• Protection against intestinal fluid accumulation and diarrhea</li> <li>• Decrease of oxidative stress</li> <li>• Increase of the activity of the main antioxidant enzyme</li> <li>• Restoration of ion homeostasis</li> </ul>	Jabri et al., 2016
Berries juice	Adult male Wistar rats stressed with castor oil to induce diarrhea	5 and 10 ml/kg for 1 hr	<ul style="list-style-type: none"> <li>• Inhibition of gastric emptying and intestinal mobility</li> <li>• Protection against intestinal fluid accumulation and diarrhea</li> <li>• Decrease of oxidative stress</li> <li>• Increase of the activity of the main antioxidant enzyme</li> </ul>	Jabri et al., 2016

risk to develop this diseases (Olfert & Wattick, 2018). In the case of myrtle, some few reports have evaluated the antidiabetic effects of its berries, leaves, and essential oils in different experimental animal models (Table 5). In streptozotocin-induced diabetic mice, leaves and branchlets extracts (2 g/kg) prevented and decreased hyperglycemia (Elfellah, Akhter, & Khan, 1984), whereas in rats it ameliorated the levels of blood glucose, the serum lipid profile (total cholesterol, HDL, LDL, and triglycerides), the levels of hepatic enzymes (alanine and aspartate aminotransferase), and the amount of blood urea and serum creatinine, especially at the higher concentrations (400 and 800 mg/kg) (Fahim, El-Ghaithi, Amesh, & Dhayabaran, 2009). Similarly,

in rats treated with streptozotocin (for the induction of type I diabetes) or dexamethasone (for the induction of type II diabetes), myrtle berry extract decreased the levels of hyperglycemia and ameliorated the lipid profile and MDA concentration, as well as the volume and protein contents of urine (Talebianpoor, Talebianpoor, Mansourian, & Vafaiee-Nejad, 2019). Finally, in alloxan diabetic rabbits, myrtle essential oils, after an acute (50 and 100 mg/kg once a day for 1 week) or chronic (2.5–5 drops 50–100 mg/kg for 4 hr until 21 days) consumption, significantly reduced the levels of blood glucose, serum triglycerides, hepatic nitrite, and MDA as well as augmented the hepatic activity of glucokinase and the concentration of glycogen, but it did not affect the

**TABLE 5** Antidiabetic effects of myrtle berries, leaves, and essential oils

Sample	Experimental models	Dose and duration	Effects	References
Leaf and branchlets ethanolic extract	Mice treated with streptozotocin	2 g/kg for 30 min before the injection of streptozotocin	<ul style="list-style-type: none"> <li>Prevention and reduction of hyperglycemia</li> </ul>	Elfellah et al., 1984
Leaf ethanolic extract	Male albino Wistar rats treated with streptozotocin	400 and 800 mg/kg for 30 min before the injection of streptozotocin	<ul style="list-style-type: none"> <li>Improvement of blood glucose, lipid profile, hepatic enzymes, urea, and creatinine</li> </ul>	Fahim et al., 2009
Berry methanolic extract	Adult male Wistar rats treated with streptozotocin or dexamethasone	250 and 500 mg/kg for 45 and 10 days	<ul style="list-style-type: none"> <li>Decrease of hyperglycemia</li> <li>Improvement of serum lipid profile and plasma MDA</li> <li>Improvement of urine volume and protein contents</li> </ul>	Talebianpoor et al., 2019
Essential oils	Adult New Zealand albino rabbits treated with alloxan	50 and 100 mg/kg doses once a day for 1 week	<ul style="list-style-type: none"> <li>Reduction of blood glucose and serum triglycerides</li> <li>Increase of glucokinase activity and glycogen in diabetic liver</li> <li>No effects on serum insulin</li> </ul>	Sepici et al., 2004
Essential oils	Adult New Zealand albino rabbits treated with alloxan	2.5–5 drops 50–100 mg/kg for 4 hr until 21 days	<ul style="list-style-type: none"> <li>Reduction of blood glucose and serum triglycerides</li> <li>Increase of antioxidant enzyme activities</li> <li>Reduction of hepatic nitrite and MDA</li> </ul>	Sepici-Dincel et al., 2007

Abbreviation: MDA, malondialdehyde.

levels of serum insulin (Dineel, Acikgoz, Cevik, Sengelen, & Yesilada, 2007; Sepici, Gurbuz, Cevik, & Yesilada, 2004).

As evident, there is a very limited information about the effects of myrtle plant on diabetes, so more deep studies are urgently needed.

#### 4.4 | Anti-inflammatory effects

Together with oxidative stress, inflammation is the main cause that contributes to the onset and the development of the most common human diseases, such as metabolic disorders, cardiovascular diseases, and cancer (Joseph, Edirisinghe, & Burton-Freeman, 2014). In physiological condition, inflammation represents the normal and temporary response of the immune system to the presence of pathogenic antigens; however, its hyperactivation induces tissue damage and oxidative stress, due to an excessive production of free radicals (Schieber & Chandel, 2014). Therefore, the use of natural antioxidants able to counteract the levels of free radicals, thus reducing both inflammation and oxidative stress, could represent a strategic tool to prevent several human pathologies. To the best of our knowledge, only three studies focused on the anti-inflammatory effects of myrtle extracts (Al-Hindawi, Al-Deen, Nabi, & Ismail, 1989; Hosseinzadeh, Khoshdel, & Ghorbani, 2011; Jabri et al., 2018b) (Table 6). On one side, myrtle plant extracts (10 ml/kg corresponding to 1/10 of the lethal dose) played a modest anti-inflammatory activities compared to other plant extracts in rats with carrageenan-induced edema (Al-Hindawi et al.,

1989); on the other side, myrtle leaves extracts (different concentrations 2.5 hr or 7 days) have been shown to protect albino mice stressed with xylene against acute and chronic inflammation (Hossein-zadeh et al., 2011). Finally, in the latter study, seeds extract (25, 50, and 100 mg/kg for 2 months) decreased the plasma levels of inflammatory cytokines, such as tumor necrosis factor  $\alpha$ , interleukin (IL)-8, IL-6, and IL-1 $\beta$ , and the erythrocyte concentrations of ROS and lipid peroxidation, and increased the activity of the main antioxidant enzymes in rats intoxicated with ethanol (Jabri et al., 2018b).

#### 4.5 | Other health effects

Only few researches have evaluated the biological effects of myrtle plant in other common human diseases, including cancer, cardiovascular, pulmonary, and neurodegenerative pathologies (Table 7).

Cancer is one of the main causes of death in the world, with 16.9 million diagnosed people in 2019 and 22.1 million expected in 2030 (Miller et al., 2019). In the last years, many studies have shown a strong correlation between a diet rich in vegetable foods, including berries, and a lower risk to develop different kinds of tumor (Battino et al., 2019; Chen, Yang, Fan, & Deng, 2020; Grosso et al., 2013; Pan et al., 2020; Papandreou et al., 2019). In this context, essential oils derived from myrtle leaves (0.05, 0.75, 0.1, and 0.15  $\mu$ L/plate) were reported to exert antimutagenic effects in *E. coli*, reducing the percentage of spontaneous and tert-butyl hydroperoxide-induced

**TABLE 6** Anti-inflammatory effects of myrtle leaves and seeds

Sample	Experimental models	Dose and duration	Effects	References
Plant ethanolic extract	Wistar rats with carrageenan-induced edema	10 ml/kg (1/10 lethal dose)	<ul style="list-style-type: none"> <li>• Modest anti-inflammatory activities</li> </ul>	Al-Hindawi et al., 1989
Leaf aqueous extract Leaf ethanolic extract	Male albino mice stressed with xylene applied to ears	0.005, 0.015, 0.03, 0.1, and 0.2 g/kg 0.05, 0.15, and 0.35 g/kg for 2.5 hr or 7 days	<ul style="list-style-type: none"> <li>• Decrease of acute and chronic inflammation</li> </ul>	Hosseinzadeh et al., 2011
Seed water extract	Adult male Wistar rats treated with ethanol	25, 50, and 100 mg/kg for 2 months	<ul style="list-style-type: none"> <li>• Decrease of plasma inflammatory cytokines,</li> <li>• Decrease of erythrocyte ROS and lipid peroxidation</li> <li>• Increase of antioxidant enzymes activity</li> </ul>	Jabri et al., 2018b

mutagenesis in a dose-dependent manner (Mimica-Dukić et al., 2010), whereas, in human chronic myelogenous leukemia, myricetin 3-O-galactoside and myricetin 3-O-rhamnoside (different concentrations), extracted from myrtle leaves, played similar effects, decreasing the mutagenicity induced by nifuroxazide, aflatoxin-B1, and hydrogen peroxide, by modulating the expression of several genes involved in apoptosis, DNA repair, and oxidative stress (Hayder et al., 2008). Similarly, myrtucommulone extracted from myrtle leaves promoted apoptotic cell death, by activating caspases, inducing the cleavage of poly (ADP-ribose) polymerase, the release of nucleosomes, the fragmentation of DNA, and the mitochondrial membrane potential loss in different type of cancer cells (Tretiakova et al., 2008).

Together with cancer, cardiovascular diseases are the main cause of death in the world, with diabetes, obesity, and metabolic syndrome being the main risk factors (McCullough et al., 2012). The contribution of dietary bioactive compounds in ameliorating cardiovascular health is a matter of great interest: the reduction of LDL oxidation, the modulation of nitric oxide synthase expression/activity, the inhibition of endothelial oxidase, and the improvement of plasma lipid profile are the main mechanisms through which bioactive compounds exert their effects on cardiovascular system (Forbes-Hernandez et al., 2016). Regarding myrtle, in cholesterol-fed rabbits, berry extracts (50 mg/kg for 30 and 45 days) played hypolipidemic and antithrombotic effects, by decreasing the levels of serum triglycerides, LDL, and cholesterol and increasing those of HDL and fibrinogen time (Khan, Feroz, Jami, & Ahmed, 2014).

Liver ischemia/reperfusion injury represents the main complication of hepatic trauma, resection, or transplantation. The anti-ischemic activities of myrtle have been demonstrated in a rat hepatic model of ischemia-reperfusion, where berry and leaves extracts (25 mg/kg for 15 min before reperfusion) protected against ischemia, reducing the hepatic levels of MDA and transaminase activities (alanine and aspartate transaminase), as well as improving liver metabolic function (Ferchichi et al., 2011; Salouage et al., 2010).

Finally, two researches have assessed the effects on myrtle on pulmonary fibrosis (Fekri et al., 2018) and neurodegenerative diseases (Tumen, Senol, & Orhan, 2012). On one side, in

bleomycin-induced pulmonary fibrosis rats myrtle leaves extracts (50 mg/kg) decreased the fibrotic changes, the parenchymal inflammation, the lipid peroxidation, and the content of hydroxyproline and increased the activity of catalase in lung tissue, especially in the early phase of fibrosis (Fekri et al., 2018); on the other side, berry extracts were more effective than leaves extracts in inhibiting the *in vitro* activities of acetylcholinesterase, butyrylcholinesterase, and tyrosinase, which are enzymes correlated to neurodegenerative diseases, such as Alzheimer's and Parkinson's pathologies (Tumen et al., 2012).

#### 4.6 | Clinical trials

Five clinical trials have assessed the effects of myrtle consumption on human health (Table 8). For example, the effects of myrtle berries freeze-dried capsules (1,000 mg/d for 4 weeks) has been assessed in patients affected by gastroesophageal reflux, highlighting that myrtle consumption reduced reflux and dyspeptic scores compared with baseline values and had the same effectiveness of omeprazole, the common drug used to lower the stomach acidity (Zohalinezhad et al., 2016); at the same time, a new paste containing myrtle leaves, applied for 6 days in two consecutive episodes, reduced the size of ulcer, pain severity, and the levels of exudation and erythema, improving the life quality of patients affected by recurrent aphthous stomatitis (Babae, Mansourian, Momen-Heravi, Moghadamnia, & Momen-Beitollahi, 2010). In addition, in women with grade I and II hemorrhoids, myrtle herbal ointment, applied twice a day for 4 and 8 weeks, reduced all symptoms, especially the mean of anal itching, and increased the satisfaction of the patients (Malekutei, Mirghafourvand, Samadi, Abbasalizadeh, & Khodaei, 2019), whereas in women suffering from abnormal uterine bleeding-menometrorrhagia the daily consumption of myrtle syrup (5 ml three times a day) for 7 days for three consecutive menstrual periods significantly reduced the number of bleeding days and pads and improved the quality of life (Qaraaty et al., 2014).

Finally, in patients with dandruff myrtle solution, applied every 3–4 days for 1 month, improved all indices, such as the excoriation

**TABLE 7** Other health effects of myrtle berries, leaves, and essential oils

Sample	Experimental models	Dose and duration	Effects	References
<b>Anticancer effects</b>				
Essential oils	<i>E. coli</i> treated with tert-butyl hydroperoxide to induce mutagenesis	0.05, 0.75, 0.1, and 0.15 $\mu\text{L}/\text{plate}$	<ul style="list-style-type: none"> <li>Decrease of spontaneous and induced mutagenesis (%)</li> </ul>	Mimica-Dukić et al., 2010
Myricetin 3-O-galactoside and myricetin 3-O-rhamnoside isolated from leaves	Human chronic myelogenous leukemia treated with nifuroxazide, aflatoxin B <sub>1</sub> , and H <sub>2</sub> O <sub>2</sub>	Different concentrations and incubation time according to the test performed	<ul style="list-style-type: none"> <li>Decrease of mutagenesis (%)</li> <li>Modulation of genes involved in apoptosis, DNA repair, and oxidative stress</li> </ul>	Hayder et al., 2008
Myrtucommulone extracted from myrtle leaves	Several types of cancer cells	Different concentrations and incubation time according to the test performed	<ul style="list-style-type: none"> <li>Promotion of apoptotic cell death</li> <li>Induction of caspases, poly (ADP-ribose) polymerase cleavage, DNA fragmentation, and mitochondrial membrane potential loss</li> <li>Release of nucleosomes and cytochrome c</li> </ul>	Tretiakova et al., 2008
<b>Hypolipidemic and antithrombotic effects</b>				
Berry water extract	Cholesterol-fed rabbits	50 mg/kg for 30 and 45 days	<ul style="list-style-type: none"> <li>Decrease of serum triglycerides, LDL, and cholesterol</li> <li>Increase of serum HDL levels and fibrinogen time</li> </ul>	Khan et al., 2014
<b>Anti-ischemic effects</b>				
Berry extracts Leaves extracts	Adult male Wistar rats	25 mg/kg for 15 min before reperfusion	<ul style="list-style-type: none"> <li>Reduction of hepatic MDA, AST, and ALT</li> <li>Improvement of liver metabolic function</li> </ul>	Ferchichi et al., 2011; Salouage et al., 2010
<b>Anti-fibrotic effects</b>				
Leaves methanolic extract	Male albino rats treated with bleomycin	50 mg/kg from 0 to 13 days and from 14 to 27 days	<ul style="list-style-type: none"> <li>Decreased of fibrotic changes, parenchymal inflammation, lipid peroxidation, and hydroxyproline content</li> <li>Increases of catalase activity</li> </ul>	Fekri et al., 2018
<b>Neurodegenerative diseases</b>				
Leaves methanolic/ dichloromethane/ acetone/ethyl acetate extracts Berry methanolic/ dichloromethane/ acetone/ethyl acetate extracts	In vitro assay		<ul style="list-style-type: none"> <li>Inhibition of acetylcholinesterase, butyrylcholinesterase, and tyrosinase</li> </ul>	Tumen et al., 2012

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HDL, high density lipoprotein; LDL, low density lipoprotein; MDA, malondialdehyde.

**TABLE 8** Clinical trials performed with myrtle

Sample	Patients	Dose and duration	Effects	References
Berries freeze-dried in capsules	45 patients affected by gastroesophageal reflux (double-blind, randomized controlled clinical trial)	1,000 mg/day for 4 weeks	<ul style="list-style-type: none"> <li>• Decrease of reflux and dyspeptic scores compared with baseline</li> <li>• Same effectiveness of omeprazole</li> </ul>	Zohalinezhad et al., 2016
Paste containing myrtle leaves	45 patients affected by recurrent aphthous stomatitis (randomized, double-blind, controlled before–after clinical trial)	6 days in two consecutive episodes	<ul style="list-style-type: none"> <li>• Reduction of the size of ulcer, pain severity and the levels of exudation and erythema</li> <li>• Improvement of life quality</li> </ul>	Babae et al., 2010
Myrtle herbal ointment	134 women with grade I and II hemorrhoids (triple-blind, randomized controlled trial)	Twice a day for 4 and 8 week	<ul style="list-style-type: none"> <li>• Reduction of all symptoms of hemorrhoids</li> <li>• Increase of patient's satisfaction</li> </ul>	Malekoti et al., 2019
Myrtle syrup	30 women suffering from abnormal uterine bleeding–menometrorrhagia (randomized, double-blind, placebo-controlled study)	5 ml three times a day for 7 days for three consecutive menstrual periods	<ul style="list-style-type: none"> <li>• Reduction of the number of bleeding days and pads</li> <li>• Improvement of life quality</li> </ul>	Qaraaty et al., 2014
Myrtle solution	90 patients with dandruff (two-arm, double-blinded, blocked randomized comparative clinical trial)	Every 3–4 days for 1 month	<ul style="list-style-type: none"> <li>• Improvement of all dandruff indices</li> <li>• Reduction of itching</li> </ul>	Chaijan et al., 2018.

pruritus grading, the adherent scalp flaking score, the redness of scalp skin, and grading of scalp skin involvement, with a more marked effects compared to ketoconazole shampoo, and reduced the itching (Chaijan, Handjani, Zarshenas, Rahimabadi, & Tavakkoli, 2018).

## 5 | CONCLUSION

Myrtle is an aromatic plant used in traditional medicine as a remedy for many common diseases. Its fruits, leaves, seeds, and essential oils are important sources of nutrients, phytochemicals, and antioxidants, with promising health benefits. In this work, the nutritional and phytochemical composition of myrtle as well as its biological effects, such as antioxidant, anti-inflammatory, antimicrobial, antireflux, antiulcer, antidiarrheal, antidiabetic, antimutagenic, hypolipidemic, antithrombotic, and antifibrotic activities, has been highlighted. However, several aspects need to be still elucidated in the future. First, it is very important to validate the extraction materials and methods because extracting with different solvents may enrich or remove different important compounds, consequently leading to different pharmacological and biological effects. Then, studies on myrtle bioavailability do not exist and the metabolites that are formed after in vivo digestion and that exert the pharmacological effects are still unknown; the same is for the concentrations that these metabolites reach in the blood and eventually in the urine. Finally, the researches on animals and humans are too scarce, some important diseases are not considered, the molecular mecha-

nisms involved in these health benefits are unidentified, and new clinical trials with a bigger sample size, a more precise design, and for a longer period should be performed soon.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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