Received: 10 September 2019 | Revised: 18 December 2019 | Accepted: 14 January 2020

DOI: 10.1002/ptr.6622

REVIEW

WILEY

Rosmarinus plants: Key farm concepts towards food applications

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Funding information
NORTE 2020—Programa Operacional Regional do Norte, Grant/Award Number: NORTE-

Rosmarinus species are aromatic plants that mainly grow in the Mediterranean region. They are widely used in folk medicine, food, and flavor industries and represent a valuable source of biologically active compounds (e.g., terpenoids, flavonoids, and phenolic acids). The extraction of rosemary essential oil is being done using three main methods: carbon dioxide supercritical extraction, steam distillation, and hydrodistillation. Furthermore, interesting antioxidant, antibacterial, antifungal, antileishmanial, anthelmintic, anticancer, anti-inflammatory, antidepressant, and antiamnesic effects have also been broadly recognized for rosemary plant extracts. Thus the present review summarized data on economically important *Rosmarinus officinalis* species, including isolation, extraction techniques, chemical composition, pharmaceutical, and food applications.

KEYWORDS
extraction techniques, food applications, phytoconstituents, *Rosmarinus*

01-0145-FEDER-000012; Foundation for Science and Technology, Grant/Award Number: UID/BIM/04293/2013

1 | INTRODUCTION

Rosemary plant, belonging to *Lamiaceae* family, is known to be a rich source of essential oil (EO; Antolak, Czyzowska, & Kregiel, 2016). This is a plant popularly used by the residents of Mediterranean countries because of its beautiful flavor (Raadt, Wirtz, Vos, & Verhagen, 2015). The important member of rosemary plant, *Rosmarinus officinalis* L., is an aromatic plant that has been extensively investigated for its biologically active compounds and valuable use in food, medicine, and perfumery. Indeed, a wide variety of useful secondary metabolites has been isolated from *Rosmarinus* plants, including EO, terpenoids, flavonoids, and phenolic acids. However, the accumulation of bioactive compounds depends on many factors, such as climatic conditions, variety, plant part, extraction technique, and many others (Ribeiro-Santos et al., 2015).

Rosmarinus plants, particularly *R. officinalis*, have been conceived as economically important species for food and pharmaceutics, besides being well-known for its biological activities (Barreto et al., 2014; da Silva Bomfim et al., 2015; Kiran & Prakash, 2015; Mezza et al., 2018). Their possible use in packaging (Esmaeili, Goli, Shirvani, & Shakerardakani, 2018), as an adjuvant of the antibiotic therapy (Barreto et al., 2014) and even as insecticide (Alipour & Saharkhiz, 2016; Badreddine, Olfa, Samir, Hnia, & Lahbib, 2015) have also been proposed. For instance, (2012) reported that *R. officinalis* supplementation in dairy ewes affects their milk positively and alleviates the lactation-associated stress and improved the organic production quality in animals. Dietary supplementation of *R. officinalis* in sheep affects the rumen degradability of alfalfa hay, the ruminal bacterial population, and rumen metabolism in sheep (Cobellis et al., 2015). Moreover, the milk obtained from goats fed with rosemary by-product showed to be healthier and with greater technological suitability for cheese making (Boutoial, Ferrandini, Rovira, García, & López, 2013).

On the other hand, the potent fumigant toxicity of *R. officinalis* EO has been proposed as being associated with acetylcholinesterase activity inhibition coupled to oxidative imbalance (Kiran & Prakash, 2015), and it has been suggested to enhance the shelf life of agri-food commodities during storage (Kiran & Prakash, 2015). In fact, Sirocchi et al. (2017) demonstrated that the *R. officinalis* EO prolongs the shelf life of beef until Day 15 instead of 5–6 days. Likewise, Pesavento et al. (2015) suggested the possible use of rosemary EO as a food preservative at a concentration of 0.5% (v/w) or lower against *Staphylococcus aureus* and *Listeria monocytogenes* in beef meatballs. Rasooli et al. (2008) studied the antimycotoxigenic characteristics of *R. officinalis* EO with special reference to the inhibition of *Aspergillus parasiticus* growth and aflatoxin production. Researchers reported that if aflatoxin production was inhibited at 450 ppm of *R. officinalis* oil, it could be safely used as preservative materials on some kinds of foods to protect them from toxigenic fungal infections. Indeed, *R. officinalis* plant is a source of antifungal molecules, such as 1,8-cineole, for human and veterinary medicine. For example, 1,8-cineole has promoted morphological alterations in *Aspergillus* spp. through degeneration of fungal cell wall (Waller et al., 2017). Moreover, over the last few years, hydrosols, or hydrolates that consist of the distillation water with very small amounts of EOs, remain considered as potential candidates for new antimicrobials to control microorganisms in foods. The latest research related to the use of rosemary EO for medical purposes has mainly been focused on its antibacterial (Al-Mariri & Safi, 2013), antifungal (Carvalhinho, Costa, Coelho, Martins, & Sampaio, 2012), insecticidal (Zoubiri & Baaliouamer, 2011), anticancer (Mothana, Hasson, Schultze, Mowitz, & Lindequist, 2011), antispasmolytic, anti-inflammatory, and antinociceptive effects, as well as antioxidant properties (Menghini et al., 2010). All these biological activities make rosemary EO very interesting for the pharmaceutical industry, both as a source of active components and, increasingly, for its potential future use in drug formulations. *R. officinalis* applications in aromatherapy have also been described in several publications. Promising results have been reported regarding the improvement of cognitive function in both healthy adults and Alzheimer's disease patients (Pengelly et al., 2012; Sayorwan et al., 2013).

In this sense, the present review summarizes the research efforts in the isolation, extraction techniques, chemical composition, pharmaceutical, and food applications of *Rosmarinus* plants.

2 | HABITAT AND CULTIVATION OF ROSMARINUS SPECIES

2.1 | Habitat

Rosemary is one of the most common shrubs in the Mediterranean region. Its original habitat includes the Mediterranean regions of Europe, Asia, and Africa, especially in the major islands, such as Sardinia, Sicily, Balearic Islands, Elba, and other minor islands (Camarda & Valsecchi, 1983). It grows from the sea level up to 1,200 m above sea level. It has naturalized throughout much of Europe and is widely common in gardens. It is a perennial species and usually grows to about 1 m in height, though some plants can reach up to 2 m in height, with some varieties having a trailing or cascading habit. The plants have linear leaves 5 to 40 mm long and 1 to 5 mm wide, resembling somehow small, curved pine needles. They are dark green and shiny above, with a white underside and curled leaf margins (Camarda & Valsecchi, 1983). Tutin et al. (1972) in the *Flora Europaea* described two *Rosmarinus* species:

1. *Rosmarinus eriocalix* Jordan and Fourr including species *Rosmarinus tournefortii* De Noë ex Turiil and *Rosmarinus tomentosus* Huber-Morath and Maire. These species are similar to *R. officinalis* but usually procumbent, with gray branches. Leaves are smaller (5–15 × 1–2-mm), glabrous, and green or greyish-tomentose; indumentum on peduncle, pedicels, and calyx with both stellate and long, simple, glandular hairs. These species are typical of habitat like rock and very common in South of Spain. Both species tend to be variable in leaf indumentum depending on habitat. Coastal plants tend to be densely stellate-tomentose whereas mountain plants are glabrous (Tutin et al., 1972).
2. *R. officinalis* L., a shrub growing up to 2 m in height, with erect, ascending, or rarely procumbent brown branches. Leaves are 15–40 mm long and 1 to 5 mm wide, linear, coriaceous, with revolute margins, bright green and rugulose above, white-tomentose beneath, sessile. Peduncle and pedicels stellate-tomentose. Calyx 3–4 mm in size, green or purplish and sparsely tomentose when young, growing up to 5–7 mm, subglabrous, and distinctly veined. The corolla is 10–12 mm large, pale blue, rarely pink or white, producing brown nutlets. This species is specifically growing in dry areas in the Mediterranean region, extending to Portugal and north-west of Spain, although cultivated elsewhere (Tutin et al., 1972). *R. officinalis* is the most common species found and cultivated in many regions. The species is highly tolerant to different climatic conditions and soils. The species grows vigorously in fertile soils but with less aroma than when it grows in sandy and gravelly soils, where it is highly aromatic. The plant is xenophile, thus it easily grows in arid areas, and is not tolerant to cold climatic conditions, especially to winter freezing. The species can grow in soil with a wide range of pH (4.5–8.7), although the best conditions for plant growth are in basic soils. According to Manunta (1987), the variation of soil pH affects the quality of the EO. The author reported that rosemary growing in basic soils produces an EO rich in camphor, whereas when growing in acid soils, it produces an EO rich in 1,8-cineole, terpineol, and geraniol.

2.2 | Cultivation

Rosemary is a perennial species that can also last from 5 to 6 years (Nicola, Casale, Pignata, & Scarpa, 2018) and up to 10 years (Marzi & De Mastro, 2008), after when the productivity drops. The species can return in the same field after at least 3 years of turnover (Nicola et al., 2018). Flowering is from spring to August, depending on the regions. Seeds are difficult to germinate, very slow to grow, and give rise to plants with a minor development (Ferretti & Ferretti, 2001). In addition, seed dormancy often reduces germination rate (Macchia, Angelini, & Ceccarini, 1997). The best way to propagate rosemary is either by cuttings or by plant division (Nicola et al., 2018; Nicola, Fontana, & Hoeberechts, 2003). The most used propagation system in commercial production is by cutting, which allows not only for cloned plants, thus assuring crop uniformity, but also with a greater root system development than having seed-propagated plants (D'Andrea, 1998). Cuttings are obtained in spring, from February to April, or at the end of the summer, from August to September, when they are cut from the mother plants at a length of 150 mm and planted in rooting substrates submerged for half of their length (Nicola et al., 2003; Putievsky, 1993). Well-developed rooting of the cuttings occurs in the following 2 months, and differences in percentage of rooting success have been reported depending on rosemary biotypes (Marzi & De Mastro, 2008). Plantation in the field occurs in prepared soils either in autumn or in spring, depending on the local climatic conditions (Marzi & De Mastro, 2008). Total plants per hectare is 10,000–15,000. Before plantation, the field must be adequately prepared by soil tillage and fertilization. Irrigation is necessary at planting to allow stand establishment and during spring and summer in typical Mediterranean climates, which have hot and dry summers. Weed control is one of the major concerns when growing minor species. In fact, in many countries, herbicides are rarely registered for rosemary, and they are not allowed under organic farming (Fontana, Hoeberechts, & Nicola, 2006). In addition, weed control is very important because none of the aromatic plants can successfully compete with weeds (Weller, 1986) and could adulterate EOs by mixing themselves with flowered stems at harvesting (Hoeberechts, Nicola, & Fontana, 2004). Mulching is often used as an alternative cultural technique to control weeds (Fontana et al., 2006). Experiments on several herbs demonstrated that, in regard to rosemary, plants grown on bare ground with no herbicide were less vigorous than when grown on plastic with herbicide (Ricotta & Masiunas, 1991); moreover, in many crops, plant vigor, growth, and yield were enhanced by paper mulching (Runham, Town, & Fitzpatrick, 1998). Mulching treatments significantly improved rosemary height growth compared with no mulching (Fontana et al., 2006). Weeding can also be controlled by hoeing between rows, either manually or mechanically or with hoeing machines. Plant training is by top pruning at the second year of the crop to favor basal branching emission. In the following years, plants are cleaned of the dead and old branches. The first harvest of the crop can occur at the first year of plantation. If dry biomass is the requested product, harvest has to take place at the beginning of plant flowering, whereas if EO is the requested product, harvest has to take place at full blooming (D'Andrea, 1998). Harvest takes place at the beginning of the summer, cutting the canopy at 0.3 m from the soil (Marzi & De Mastro, 2008). The bottom 0.3 m of the bush are left to produce new branches (D'Andrea, 1998). In hot climates, a second harvest can also take place in late summer. In Mediterranean climates, rosemary plants are in flower most of the year, but the EO quantity and quality are best at the end of spring and beginning of summer (Mulè, Moretti, Pirisino, & Satta, 1996).

Fresh biomass is in average 8–10 (Maghami, 1979) up to 10–15 t ha^{-1} (Marzi & De Mastro, 2008; Nicola et al., 2018), with 40–50% leaves compared with stems. Dry biomass is obtained by drying at 30–40°C (Institut Technique Interprofessionnel des plantes à Parfum, Médicinales et Aromatiques, Henry, & Simonnet, 1995) and is in average 1.5–2 t ha^{-1}, according to Putievsky (1993); or

1–1.3 t ha^{-1}, according to Marzi and De Mastro (2008). EO is 0.5–0.6% of fresh biomass (Maghami, 1979) up to 2% (Putievsky, 1993) and is 10–15% of dry biomass (Putievsky, 1993). The world production of rosemary EO is around 400 tons per year, with major producers including Spain, Morocco, Egypt, Italy, and France (Nuvoli, 1996). The major consumers are France, Tunisia, Great Britain, Germany, and Italy.

3 | PHYTOCHEMICAL COMPOSITION OF ROSMARINUS PLANTS

Rosemary (*R. officinalis*) has been widely used since ancient times for herbal purposes and culinary uses and recognized as one of the plants rich in active compounds with many phytotherapeutic activities (Kaloustian, Portugal, Pauli, & Pastor, 2002; Mezza et al., 2018; Selmi, Rtibi, Grami, Sebai, & Marzouki, 2017; Sirocchi et al., 2017). Potential bioactivities of rosemary plant are due to the many bioactive compounds that the species possess. These are phenolic diterpenes (carnosic acid, carnosol, or rosmanol), flavonoids (genkwanin, cirsimaritin, or homoplantaginin), and triterpenes (ursolic acid; Borras-Linares et al., 2014) but mostly EO.

3.1 | Rosemary extracts: Insights on phenolic composition

Maldini et al. (2016) reported 12 main components belonging to flavonoids and phenolic acids families, such as rosmarinic, caffeic, *p*-coumaric, quinic, syringic, chlorogenic, caffeoylquinic isomers 1 and 2, and dicaffeoylquinic acids, kaempferol, quercetin, and rutin. Five terpenoid glycosides (officinoterpenosides A_1, A_2, B, C, and D) were also identified by other authors in *R. officinalis* aerial parts (Zhang et al., 2014). Abietane-type diterpenoids, 7β-methoxyabieta-8,13-diene-11,12-dione-(20,6β)-olide (rosmaquinone A) and 7α-methoxyabieta-8,13-diene-11,12-dione- (20,6β)-olide (rosmaquinone B), were also discovered in *R. officinalis* aerial parts (Mahmoud, Al-Shihry, & Son, 2005), whereas 7β-hydroxy-20-deoxo-rosmaquinone and 7β-methoxy-20-deoxo-rosmanol, carnosol, 7α-methoxyrosmanol, 7β-methoxyrosmanol, 12-methoxy-canosic acid, rosmanol, and rosmadial were found in *R. officinalis* MeOH-soluble extract (Cui et al., 2012). Brückner et al. (2014) have identified and characterized a copalyl diphosphate synthase (RoCPS1) and two kaurene synthase-like (RoKSL1 and RoKSL2) encoding genes for the biosynthesis of abietane-type diterpenes carnosic acid and carnosol in rosemary glandular trichomes. As well, authors successfully produced an abietane diterpene by genes expression in yeast (*Saccharomyces cerevisiae*) and *Nicotiana benthamiana*. Marin et al. (2006) have described two types of glandular trichomes—peltate and capitate on *R. officinalis* leaves. They reported that the phenolic substances were found only in peltate trichomes, and proteins and polysaccharides were presented in both types of trichomes. Also, Bendif et al. (2017) analyzed the phenolic composition of polar extracts obtained from stems, leaves, and flowers of *Rosmarinus eriocalyx* and recommended as an alternative to *R. officinalis*.

3.2 | Rosemary extracts: Insights on EOs composition

The main bioactive constituents of the EO (Figure 1) are considered to be 1,8-cineole, camphor along with antioxidant compounds such as carnosol, carnosic acid, and rosmarinic acid (Elbanna et al., 2018), and it also contains α-pinene (Nouri, Tavakkoli Yaraki, Ghorbanpour, & Wang, 2018), β-pinene, myrcene, borneol, and verbenone (Gutiérrez-del-Río, Fernández, & Lombó, 2018). Several studies from different countries were conducted on the rosemary EO composition, mainly focusing on the Mediterranean region where the plant originated from (Katerinopoulos, Pagona, Afratis, Stratigakis, & Roditakis, 2005). The EO is mainly obtained by distillation of their top flowering aerial parts (Bendif et al., 2017). The EO yield varies approximately between 0.5% and 2.6% (Conde-Hernandez, Espinosa-Victoria, Trejo, & Guerrero-Beltran, 2017). Regarding the main chemotypes of the EO chemical composition, it consisted mainly of monoterpene hydrocarbons (camphene, verbenene, α-pinene, β-pinene, and limonene) and oxygenated monoterpenes (linalool, camphor, borneol, verbenone, and 1,8-cineole; Figure 1; Sirocchi et al., 2017; Conde-Hernandez et al., 2017; Jordán, Lax, Rota, Lorán, & Sotomayor, 2013a; Lahlou & Berrada, 2003). However, it may vary according to different factors such as plant variety, plant phenological stage, climatic conditions, country of origin, location, time of harvest, the extraction methods, and part of the plant studied (Alipour & Saharkhiz, 2016; Bendif et al., 2017; Conde-Hernandez et al., 2017; Jordán, Lax, Rota, Lorán, & Sotomayor, 2013b).

For instance, the rosemary EO composition from plants collected during the fruit maturation cycle showed better biological activities than flowering period as it contains the higher concentration of γ-terpinene, α-terpinene, terpinolene, and carypophyllene (Jordán et al., 2013a). Alipour and Saharkhiz (2016) reported a variation in the phytotoxic activity and in the composition of rosemary EO during different phenological growth stages with the main components varied between 25.8% and 27.7% for α-pinene, 8.6% and 9.0% for camphor, 6.5% and 7.7% for camphene, and 9.4% and 9.6% for 1,8-cineole during full flowering, fruit setting, and fruit ripening.

The extraction of aromatic plants, such as rosemary, has gained great interest in the last years. Rosemary EO was mainly obtained by three different methods: carbon dioxide supercritical extraction, steam distillation, and hydrodistillation (HD) (Conde-Hernandez et al., 2017) and lead to major compounds of rosemary EO—camphor, 1,8-cineole, β-caryophyllene, and borneol acetate in different proportion (Conde-Hernandez et al., 2017). However, the supercritical fluid extraction (SFE) resulted in higher yields of EO when compared with steam and HD (Conde-Hernandez et al., 2017). Khalili, Mazloomifar, Larijani, Tehrani, and Pazar (2017) also found that SFE is advantageous over HD by shorter extraction times, less energy consumption, and no need of polar cosolvent. The main components of *R. officinalis* EO were α-pinene (HD: 30.4% and SFE: 0.5%), 1,8-cineole (HD:

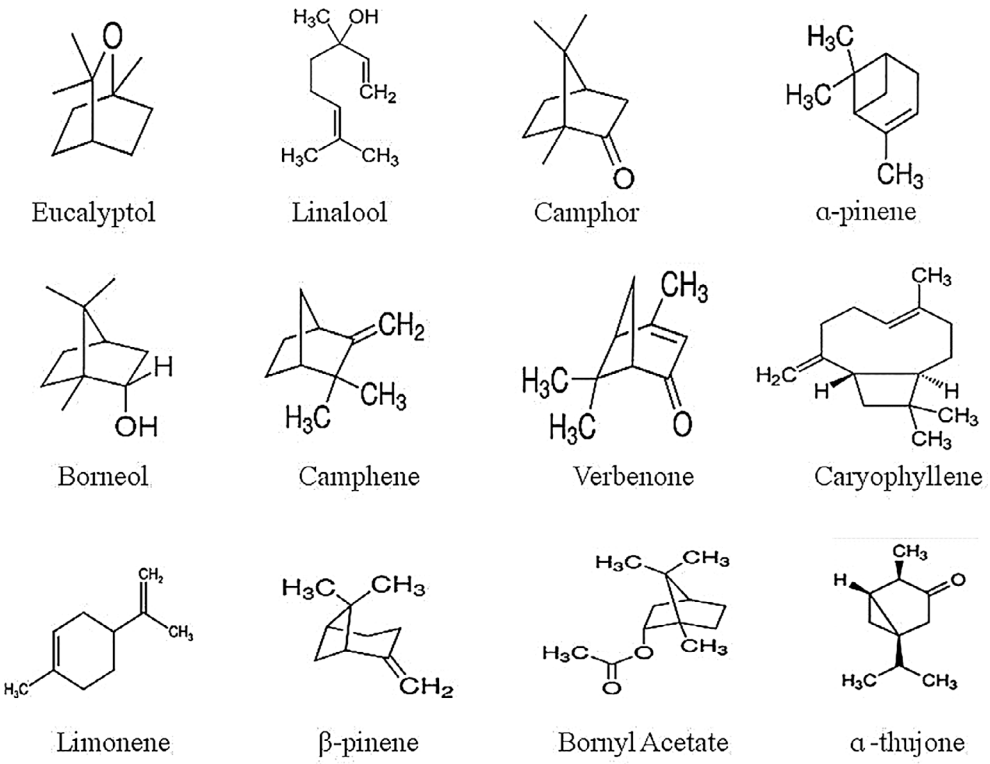

FIGURE 1 Chemical composition of major compounds of *Rosmarinus officinalis* essential oil

15.5% and SFE: 25.1%), verbenone (HD: 13.1% and SFE: 5.2%), camphor (HD: 9.0% and SFE:15.7%), borneol (HD: 7.2% and SFE: 9.2%), and β-caryophyllene (SFE: 6.8%). Moreover, rosemary EO has a concentration of valuable components, such as 1,8-cineole, camphor, and β-caryophyllene that became remarkably higher in EO obtained with SFE. Besides, *R. eriocalyx* extracts obtained with SFE contain a significantly higher content in tocopherols than *R. officinalis* (Bendif et al., 2018).

On the other hand, the investigation on 87 flowering branches of *R. officinalis* identified α-pinene, 1,8-cineole, camphor, and verbenone with more than 0.1% as the most characteristic components of EOs (Varela et al., 2009). Raskovic et al. (2014) rather reported 1,8-cineole (43.8%), camphor (12.5%), and α-pinene (11.5%) as main constituents of the *R. officinalis* EO. As well, camphor (14–17.5%), 1,8-cineole (11–22%), and α-pinene (10–12.5%) were the major components of *R. officinalis* EO obtained by steam distillation with extraction yield ranging from 0.35% to 2.08% (Gurbuz, Bagdat, Uyanik, & Rezaeieh, 2016).

The EO obtained by molecular distillation showed that the rosemary EO is mainly composed of oxygenated monoterpenes (56.53%), and the main components were 1,8-cineole (2.24%), α-pinene (15%), and camphor (20.33%; Mezza et al., 2018) and that obtained by steam distillation was richest in α-pinene (23%), camphene (7.6%), borneol (16%), camphor (4.5%), verbenone (9.4%), and bornyl acetate (10.4%; Angioni et al., 2004). Boutekedjiret, Bentahar, Belabbes, and Bessiere (2003) showed that the major compounds obtained by HD were 1,8-cineole (52.4%), camphor (12.6%), and β-pinene (5.7%) and by steam distillation were 1,8-cineole (31.9%), camphor (19.7%), and α-terpineol (12.8%). A solvent-free microwave extraction method was used in comparison with HD of rosemary EO; the technique is quicker and gives an increased proportion in oxygenated compounds that are more odoriferous than monoterpene hydrocarbon compounds (Filly et al., 2014).

Growing and geographic conditions are also important parameters that affect EO composition; in the study reported by Tawfeeq, Culham, Davis, and Reeves (2016), the fertilizer type and method of application have caused significant differences in rosemary EO yield and composition obtained by HD. The major rosemary EO components from Morocco, extracted by steam distillation or HD, were α-pinene (14.07%), 1,8-cineole (23.67%), and camphor (18.74%; Bouyahya et al., 2017; Khia et al., 2014). Similarly to *R. officinalis*, *R. tournefortii* EO from Morocco, obtained by HD, showed camphor (39.27%), camphene (11.62%), β-pinene (14.72%), 1,8-cineole (2.24%), and camphor (39.27%) as major constituents (Tahri, Imelouane, Aouinti, Amhamdi, & Elbachiri, 2014). Whereas, the leaf EO from seven populations of rosemary (*R. officinalis*) growing in different collection sites in western Iran contained mainly 1,8-cineole (5.63–26.89%), camphor (1.66–24.82%), and α-pinene (14.69–20.81%; Bajalan, Rouzbahani, Pirbalouti, & Maggi, 2017). Furthermore, *R. officinalis* oil from Algeria and its main constituents were identified as camphor (17.09%), Z-β-ocimene (10.88%), isoborneol (9.68%), α-bisabolol (7.89%), and borneol (5.11%; Mehalaine, Belfadel, Menasria, & Messaili, 2017) whereas Touafek, Nacer, Kabouche, Kabouche, and Bruneau (2004) reported 1,8-cineole (29.5%), 2-ethyl-4,5-dimethylphenol (12.0%), and camphor (11.5%) as its major components. Bendif et al. (2017) showed that the EO composition varies according to the plant part studied. Indeed, *R. eriocalyx* oil, which is endemic to Algeria, showed as major constituents the following: camphor (29.7% in flowers, 36.9% in leaves, and 41.2% in stems), α-pinene (7.8% in stems, 15.1% in flowers, and 17.8% in leaves), camphene

(10.0% in stems, 13.1% in flowers, and 15.6% in leaves), and 1,8-cineole (3.5% in flowers, 5.8% in stems, and 10.2% in leaves). In Tunisia, rosemary EO consists mostly in 1,8-cineole (35.32%), trans-caryophyllene (14.47%), borneol (9.37%), camphor (8.97%), α-pinene (7.90%), and α-thujone (6.42%; Selmi et al., 2017). Another study reported the toxic activities of *R. officinalis* oil from Tunisia that consisted mostly major compounds were 1,8-cineole (34.82%), camphor (12.91%), and α-pinene (11.87%; Badreddine et al., 2015; Jardak, Elloumi-Mseddi, Aifa, & Mnif, 2017). Irmak, Solakyildirim, Hesenov, and Erbatur (2010) showed that storage conditions and durations have an influence on the composition of supercritical fluid extracted in rosemary EO from Turkey. Studies from Brazil showed the presence of α-pinene (9.79%), camphene (5.14%), 1,8-cineole (30.87%), β-pinene (9.24%), camphor (10.13%), and caryophyllene (6.76%; Barreto et al., 2014; Borges et al., 2018; Pereira et al., 2017; Takayama et al., 2016). However, methoxy-3-(2-propenyl)-phenol (28.19%) was found as the main component in the EO extracted by HD of *R. officinalis* from India followed by 1,8-cineole (25.10%) and camphor (14.65%; Kiran & Prakash, 2015). Another study also reported camphor (22.00%), α-pinene (16.33%), 1,8-cineole (14.32%), camphene (9.28%), β-pinene (5.97%), β-phellandrene (5.9%), bornyl acetate (4.59%), myrcene (4.31%), and borneol (3.35) as major components of *R. officinalis* oil growing as an exotic species in the Himalayas, India (Tantry, Shabir, Khan, Habib, & Akbar, 2012). *R. officinalis* oil from France showed the presence of high camphor (30–45%) levels (Kaloustian et al., 2002). *R. officinalis* oil from Belgrade consisted of 1,8-cineole (43.77%), camphor (12.53%), and α-pinene (11.51%) as the major compounds (Rašković et al., 2014).

In summary, apart from few exception cases, main compounds of rosemary EO show similarities in different studies, but they can be greatly affected by abovementioned factors such as location, growing conditions, and extraction methods.

4 | FOOD PRESERVATIVE APPLICATIONS OF ROSMARINUS PLANTS

Fresh foodstuff like fish is extremely perishable due to their high water activities and presence of autolytic enzymes (Abdeldaiem, Mohammad, & Ramadan, 2018) that results in some chemical reactions, including oxidation, that alter biomolecules found within food (Albarracín, Alfonso, & Sánchez, 2012; Salehi et al., 2018; Sharifi-Rad et al., 2018), leading to inedible or lower quality food (Seham & Mona, 2017). Food spoilage may also occur during storage and transport, especially in food following harvest (Arik & Arık, 2017). Meat spoilage occur mainly during processing or storage through conversion of muscle to meat due to some biochemical changes that lead to discoloration, texture changes, loss of nutritional quality, development of odor, decreasing of shelf life, and most importantly formation of secondary compounds that might be harmful for humans (Cunha et al., 2018). Color seems to be the most important sensory property that affects the decision of consumers to buy certain meat products, so the preservative should maintain the color in addition to having antimicrobial properties as well (Lahmar, Morcuende, Andrade, Chekir-Ghedira, & Estévez, 2018). Chicken is also susceptible for oxidation (both raw and cooked; Al-Hijazeen & Al-Rawashdeh, n.d.) and spoilage of chicken meat, especially in hot climates, leading to gastrointestinal problems and intoxications (Dong, Xu, Ahmed, Li, & Lin, 2018). Food products, such as shrimps and pastry, are also susceptible to microbial contamination and spoilage due to their high protein, unsaturated fatty acids, and water content and produce an unpleasant smell during storage as well (Caleja et al., 2018; Dong et al., 2018). As well, cheese also spoils easily, like Minas Frescal cheese, for example, has high moisture content, does not undergo maturation, has short durability, and generally has no preservatives (Fernandes et al., 2017). Moreover, food spoilage represents a threat for 30% people living in industrialized countries suffering from food-transmitted diseases every year associated with various complications and many deaths (Albarracín et al., 2012; Elbanna et al., 2018; Pesavento et al., 2015). Besides being an important health issue, it may also result in great economic losses (Fernandes et al., 2017) and food poisoning (Dong et al., 2018).

Therefore, food preservation has become an important problem, and additives are being used to extend their shelf lives with technologies that aim to slow the reproduction of pathogenic microorganisms (Fernandes et al., 2017; Pesavento et al., 2015). Ideally, the preservative should be harmless for consumers without negatively affecting human digestive enzymes and should not decompose into toxic materials (Tzima, Makris, Nikiforidis, & Mourtzinos, 2015). Currently, synthetic antimicrobials, such as organic acids and salts (e.g., sodium benzoates and propionates, potassium sorbates, sorbic acid, sulfites, chlorides, nitrites, triclosan, nisin, natamycin, etc.) have been in use as food preservatives. However, they represent a nutritional or health threat (Gutiérrez-del-Río et al., 2018). For example, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) that have been used as preservatives in food products are found to be potential carcinogenic agents, so their utilization have been limited (Raadt et al., 2015). Though modern technologies like freezing, pasteurization, and so forth provide some protection, they failed to eliminate the risk for food spoilage (Gutierrez, Barry-Ryan, & Bourke, 2009). For this purpose, EOs that inherently possess antimicrobial and antioxidant activities have been examined for their food preserving activities as alternatives to chemical/synthetic additives (Pesavento et al., 2015; Sharifi-Rad et al., 2018).

4.1 | Antimicrobial properties of *Rosmarinus*

EOs are naturally occurring antimicrobials (Lahmar et al., 2018). In fact, they sensitize the cell membrane of pathogenic microorganismsa and increase its permeability and leads to the leakage of important cellular constituents, and as a result, both bacterial enzyme system and cell respiration are impaired (Witwit, 2018). For example, microencapsulated rosemary EO controlled the proliferation of mesophilic bacteria in Minas Frescal cheese (this cheese has high moisture content and generally contains no preservatives) by delaying microbial growth and thus extending the shelf life of the cheese (Fernandes et al., 2017). Mozzarella is also an expensive cheese

that spoils easily, and EOs are known to inhibit bacterial reproduction that lead to the spoilage of these cheese types (Kumar Tyagi et al., 2014). Rosemary oil used as an antimicrobial agent in mozzarella cheese against *L. monocytogenes* was potent in protecting the cheese and neutralizing free radicals and preventing oxidation of unsaturated fatty acids (Witwit, 2018).

In addition to their antimicrobial properties, EOs were also found to extend the shelf life of foodstuff (Baj, Baryluk, & Sieniawska, 2018). *R. officinalis* extract, besides to exert antimicrobial and free radical scavenging effects, also interrupts lipid oxidative chain reactions in foodstuff and is used to delay lipid oxidation in fish or meat products during refrigerated storage; thus, the quality of the products are improved, and their shelf lives are prolonged (Wang et al., 2018). Specifically, the antioxidant activity of carnosic acid from *R. officinalis* was more potent than some of common food additives, such as BHT and BHA (Seham & Mona, 2017).

Nonetheless, globally, rosemary is differently applied to preserve food. Their EO or extracts are commonly added to foodstuff but can also be fed to animals. EO is also use in active packaging or in edible film coatings that aim to inhibit microbial growth. Rosemary extract applied to chicken patties (Al-Hijazeen & Al-Rawashdeh, n. d.). Rosemary extract and EO tested against different chicken products (such as burgers, sausages, fresh, or minced chicken breasts) extend the shelf life of the products by inhibiting the growth of some pathogenic microorganisms and potently delayed the formation of aldehydes and positively affected the sensory attributes of the meat, supporting its uses in meat preservation (Al-Hijazeen & Al-Rawashdeh, n.d.; Seham & Mona, 2017). Beef meatballs and cooked meatballs containing 0.5% rosemary EO were acceptable in respect to taste, and the oil suppressed the pathogens. It was also found to be beneficial in the preservation of other ready-to-cook or ready-to-eat products (Pesavento et al., 2015). A study was performed on salami (a kind of meat product) with whey protein concentrate film containing rosemary EO, and it was observed that lipid oxidation induced by ultraviolet (UV) was delayed and the shelf life of the product was extended (Ribeiro-Santos et al., 2015). A study performed on lamb cutlets demonstrated that sprayable EO was able to protect whole-meat muscle foods against oxidation and microbial deterioration along with the application of high-oxygen active packaging (Lahmar et al., 2018). Rosemary EO used in the preparation of a low-density polyethylene-based active packaging film was found to effectively maintained the freshness of packaged shrimps and extended the shelf life of the product up to 4 days (Dong et al., 2018). Rosemary EO-based coating solution (4.7% protein powder in a water-ethyl alcohol mixture [3:1, v/v] and rosemary EO [0.5%, v/v]) used to coat fresh silver carp fillets along with gamma irradiation eliminated bacteria and extended the shelf life of the fish fillets without altering the chemical and sensory properties of the fish (Abdeldaiem et al., 2018). A study performed on crayfish also yielded similar results where the EOs demonstrated a positive effect on the shelf life of the fish, and it also had a positive impact on the chemical and microbiological quality of the fish product (Duman, Emir Çoban, & Özpolat, 2012).

4.2 | Antioxidant properties of *Rosmarinus*

R. officinalis has been used since ancient times where it grows; it is known to be a potent antioxidant and a powerful EO in respect to food preservation (Mhiri, Kchaou, Belhadj, El Feki, & Allouche, 2018), besides to be used for culinary purposes and ornamental plant (Andrade et al., 2018). In addition to its EO, extracts prepared from this plant are also widely used in the food industry as a potential antioxidant (Al-Hijazeen & Al-Rawashdeh, n.d.). Indeed, rosemary EO delays oxidation in foodstuff (Lahmar et al., 2018); and therefore, they attract a quiet deal of attention because they can be added to raw or processed foods for preservation purposes (Rassem, Nour, & Yunus, 2018). Rosemary extract sprayed over steak surface prevented lipid oxidation in fresh lamb steaks that were stored for 13 days and thereby improving the shelf life of some meat products such as sheep and goat cuts, ground meat, and muscle products (Cunha et al., 2018).

Similarly, different fish species (Nile tilapia) fillets immersed in rosemary EO added to a solution of water, propyleneglycol and an emulsifying agent, diminished the oxidative processes (Albarracín et al., 2012). Rosemary extract, prepared from the plant with a mixture of ethanol and water (80:20) delayed the oxidation of sunflower oil, therefore increasing its oxidative stability. It especially delayed the formation of primary and secondary oxidation products. Sunflower oil is a source for essential linoleic acid and is commonly used for culinary purposes, but it is prone to oxidation due to its polyunsaturated fatty acid content. Oxidation of the sunflower oil will also contribute to alterations in the texture, taste, and odor of foods and also will eliminate the lipid soluble vitamin content of foodstuff; therefore, rosemary can be an important additive in the preservation of sunflower oil along with other vegetable oils that are rich in omega-3 polyunsaturated fatty acids and will contribute to human health (Tabar, Baştürk, Tabar, & Baştürk, 2018; Wang et al., 2018). Moreover, some studies examined the direct administration of this EO to animals. For example, rosemary EO administered to Barbarine male lambs in doses of 0.3 and 0.6 ml per day did not yield a change in the chemical composition and physical properties of the meat and rather improved the sensorial characteristics and increased the meat nutritional value by increasing the polyunsaturated fatty acid content (especially omega-3; Smeti, Hajji, Mekki, Mahouachi, & Atti, 2018).

5 | BIOLOGICAL ACTIVITIES OF ROSMARINUS PLANTS in vitro AND IN VIVO

5.1 | Antimicrobial activity

Nowadays, with the rapid spread of multidrug-resistant bacteria worldwide, nosocomial infections, low efficiency of new generations of antibiotics, and increasing rates of foodborne pathogens, the exploitation of natural resources has been increasingly emphasized as a way to find new antibacterial agents once they provide unlimited opportunities for novel drug discovery especially against multidrug-resistant bacteria (Abdullah, Hatem, & Jumaa, 2015; Balouiri et al.,

TABLE 1 Antimicrobial effects of rosemary against gram-positive bacteria

Bacteria	Extract/compounds	Used method	Effects	References
Bacillus cereus	Essential oil	Disc diffusion assay	IZ = 10.2 mm	(Ben Chobba et al., 2012)
		Microdilution method	IC50 = 113 μg/ml, MIC = 50 μg/ml	(Ben Chobba et al., 2012)
	Commercial rosemary extract formulations	Disc diffusion, agar dilution, microdilution, macrodilution methods	MICdiff = 0.313–20 mg/ml, MICdil = 0.078–5 mg/ml, MICmdil = 0.078–2.5 mg/ml and MICmac = 0.078–2.5 mg/ml	(Klancnik, Guzej, Kolar, Abramovic, & Mozina, 2009)
	Different leaves extract prepared by supercritical fluid extraction	Broth microdilution method	MIC = 0.02–0.125 mg/ml	(Abramovic et al., 2012; Genena, Hense, Smânia Junior, & Souza, 2008)
Bacillus circulans	Essential oil	Disc diffusion assay	IZ =8–10 mm, MIC = 25–75 μl/ml	(Abu-Zaid, Alopidi, & EL-Sehrawy, 2013)
Bacillus sphaericus	Essential oil	Disc diffusion assay	IZ = 22 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 0.5 μg/ml	(Kazemi et al., 2012)
Bacillus subtilis	Aqueous, 80% ethanol and chloroformic extracts	Disc diffusion assay	IZ =15.5, 14.5, 15 mm,	(El Kichaoui et al., 2017)
		Microdilution method	MIC = 6.25, 3.125, 100 mg/ml	(El Kichaoui et al., 2017)
	Different methanolic extracts	Disc diffusion assay	IZ = 10–12 mm	(Balouiri et al., 2014)
	Essential oil	Disc diffusion assay	IZ = 5–20.4 mm, MIC = 25 μl/ml	(Abu-Zaid et al., 2013; Amaral et al., 2013; Ben Chobba et al., 2012)
		Broth microdilution method	IC50 = 130 μg/ml, MIC = 90 μg/ml, MIC = 0.0625%, v/v, MBC = 0.0625%, v/v	(Ben Chobba et al., 2012; Wang, Li, Luo, Zu, & Efferth, 2012)
	Essential oil–rich fractions	Disc diffusion assay	IZ = 17–33 mm	(Santonyo et al., 2005)
		Broth dilution assay	MBC = 2.25–0.25 mg/ml	(Santonyo et al., 2005)
	Extract	Disc diffusion assay	IZ = 18.49 mm	(Kumuda et al., 2017)
Enterobacter cloacae	Essential oil	Disc diffusion assay and	IZ = 16.6 mm	(Ben Chobba et al., 2012)
		Microdilution method	IC50 = 161 μg/ml, MIC = 70 μg/ml	(Ben Chobba et al., 2012)
Enterococcus faecalis	Essential oil	Disc diffusion assay	IZ = 11.8–22 mm	(Ben Chobba et al., 2012)
		Microdilution method	IC50 = 140 μg/ml, MIC = 80 μg/ml, MIC = 1 μg/ml, MBC = 1 μg/ml	(Ben Chobba et al., 2012; Kazemi et al., 2012)
	Essential oil	Disc diffusion assay	IZ = 21–32 mm	(Abdullah et al., 2015)
	Leaves extract	Broth dilution assay	MIC = 50 mg/ml, MMC > 50 mg/ml	(de Oliveira et al., 2017)
Lactobacillus delbruekii	Essential oil	Broth dilution assay	MBC = 1.5 mg/ml	(Tavassoli, Mousavi, Emam-Djomeh, & Razavi, 2011)

(Continues)

TABLE 1 (Continued)

Bacteria	Extract/compounds	Used method	Effects	References
Leuconostocmesenteroides	Essential oil	Broth dilution assay	MBC = 1 mg/ml	(Tavassoli et al., 2011)
Listeria species	Ethanolic extracts containing different levels of carnosic acid	Disc diffusion assay and broth dilution assay	MIC = 312.5–5,000 μg extract per millil EtOH, MBC = 15.63- to 98.5-μg/ml TSB	(Rožman & Jeršek, 2009)
Listeria monocytogenes	Different leaves extracts	Broth microdilution method	MIC = 0.02 mg/ml	(Abramovic et al., 2012)
Micrococcus luteus	Essential oil	Disc diffusion assay	IZ = 12–30 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 1–90 μg/ml, MBC = 1 μg/ml, IC50 = 120 ± 5 μg/ml	(Ben Chobba et al., 2012)
Sarcina lutea	Essential oil	Disc diffusion assay	IZ = 24 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 1 μg/ml	(Kazemi et al., 2012)
Staphylococcus arlettae	Essential oil	Disc diffusion assay	IZ = 9.02–9.9 mm	(Issabeagloo, Kermanizadeh, Taghizadieh, & Forughi, 2012)
Staphylococcus aureus	Aqueous extract of the leaves	Agar well diffusion method	IZ = 11–20 mm	(Adam et al., 2014)
	Aqueous, 80% ethanol and chloroformic extracts	Disc diffusion assay	IZ = 18.5, 15, and 18 mm, respectively	(El Kichaoui et al., 2017)
		Microdilution method	MIC = 0.39 mg/ml each	(El Kichaoui et al., 2017)
	Different extracts	Disc diffusion assay, agar dilution, and microdilution method	MICdiff = 0.625–20 mg/ml, MICdil = 0.156–5 mg/ml, MICmdil = 0.156–5 mg/ml	(Klancnik et al., 2009)
		Broth macrodilution method	MIC = 0.156–5 mg/ml, MBC = 0.156–5 mg/ml	(Klancnik et al., 2009)
	Different leaves extracts	Broth microdilution method	MIC = 0.02 ± 0.005–0.02 ± 0.01 mg/ml	(Abramovic et al., 2012)
	Different leaves extract prepared by supercritical fluid extraction	Microdilution method	MIC = 0.25–0.5 mg/ml	(Genena et al., 2008)
	Different methanolic extracts	Disc diffusion assay	IZ = 11–13.5 mm	(Balouiri et al., 2014)
	Essential oil	Agar well diffusion method	IZ = 20 mm	(Tural & Turhan, 2017)
		Broth microdilution method	MIC = 0.0313%, v/v, MBC = 0.0625%, v/v	(Wang et al., 2012)
		Disc diffusion assay	IZ = 7–38 mm, MIC = 25–75 μl/ml	(Abdullah et al., 2015; Abu-Zaid et al., 2013; Chahboun et al., 2014; Djelloul,

(Continues)

TABLE 1 (Continued)

Bacteria	Extract/compounds	Used method	Effects	References
				Mokrani, & Hacini, 2017; Issabeagloo et al., 2012; Kazemi et al., 2012; Kesatebrhan & Tesema, 2014; Martins et al., 2012)
		Microdilution method	IC_{50} = 190 ± 5 μg/ml. MIC = 0.5–100 μg/ml, MBC = 1.5–5 μg/ml	(Ben Chobba et al., 2012; Jardak et al., 2017; Kazemi et al., 2012)
		RAPD analysis-microdilution method	MIC = 5 μl/ml, MBC = 1.25 μl/ml	(Hamedo, 2009)
	Essential oil-rich fractions	Disc diffusion assay and broth dilution assay	IZ = 17–33 mm MBC = 0.25–2.25 mg/ml	(Santonyo et al., 2005)
	Extract	Disc diffusion assay	IZ = 19.56 mm	(Kumuda et al., 2017)
	Leaves extract	Broth dilution assay	MIC = 25 mg/ml, MMC > 50 mg/ml	(de Oliveira et al., 2017)
	Leaves extract	Antibiofilm activity	% inhibition = 41.30, 22.67, and 23.91 at 10, 20, and 40 mg/ml, respectively	(Nasr-Eldin, Abdelhamid, & Baraka, 2017)
	Methanolic extract	Agar well diffusion method	IZ = 19 mm	(Tirumalasetty & Basavaraju, 2014)
	Methanolic extract of the leaves	Agar well diffusion method	IZ = 13–16 mm	(Adam et al., 2014)
	Petroleum ether extract of the leaves	Agar well diffusion method	No activity	(Adam et al., 2014)
Staphylococcus aureus ssp. Anaerobious	Essential oil	Disc diffusion assay	IZ = 9.30–10.03 mm	(Issabeagloo et al., 2012)
Staphylococcus capare	Essential oil	Disc diffusion assay	IZ = 7.92–9.35 mm	(Issabeagloo et al., 2012)
Staphylococcus chromogenes	Essential oil	Disc diffusion assay	IZ = 8.86–9.63 mm	(Issabeagloo et al., 2012)
Staphylococcus delphini	Essential oil	Disc diffusion assay	IZ = 7.98–9.98 mm	(Issabeagloo et al., 2012)
Staphylococcus epidermidis	Essential oil	Disc diffusion assay	IZ = 29.4 ± 0.7 mm	(Ben Chobba et al., 2012)
		Broth microdilution method	IC_{50} = 110 ± 6 μg/ml, MIC = 90 μg/ml, MIC = 0.0313%, v/v, MBC = 0.0625%, v/v	(Ben Chobba et al., 2012; Wang et al., 2012)
		Microdilution method	MIC = 0.312–0.625 μg/ml, MBC = 2.5 μg/ml	(Jardak et al., 2017)
		Biofilm inhibition	57% and 67% reduction at 25 and 50 μg/ml, respectively	(Jardak et al., 2017)
		Disc diffusion assay	IZ = 8.9–9.52 mm	(Issabeagloo et al., 2012)
Staphylococcus equorum	Essential oil	Disc diffusion assay	IZ = 9.63–10.26 mm	(Issabeagloo et al., 2012)
Staphylococcus gallinarum	Essential oil	Disc diffusion assay	IZ = 8.40–9.61 mm	(Issabeagloo et al., 2012)
Staphylococcus hyicus	Essential oil	Disc diffusion assay	IZ = 9–10.4 mm	(Issabeagloo et al., 2012)
Staphylococcus intermedius	Essential oil	Disc diffusion assay	IZ = 8.68–30 mm	

(Continues)

TABLE 1 (Continued)

Bacteria	Extract/compounds	Used method	Effects	References
				(Issabeagloo et al., 2012; Kazemi et al., 2012)
	Essential oil	Microdilution method	MIC = 0.5 μg/ml, MBC = 1 μg/ml	(Kazemi et al., 2012)
Staphylococcus lentus	Essential oil	Disc diffusion assay	IZ = 8.93–10.01 mm	(Issabeagloo et al., 2012)
Staphylococcus saprophyticus	Essential oil	Disc diffusion assay	IZ = 9.12–9.86 mm	(Issabeagloo et al., 2012)
Staphylococcus simulans	Essential oil	Disc diffusion assay	IZ = 8.23–9.91 mm	(Issabeagloo et al., 2012)
Streptococcus iniae	Essential oil	Disc diffusion assay	IZ = 45 mm	(Roomiani et al., 2013)
		Microdilution method	MIC = 3.9 μg/ml, MBC = 7.8 μg/ml	(Roomiani et al., 2013)
	Methanolic extract	Disc diffusion assay	IZ = 30 mm	(Roomiani et al., 2013)
		Microdilution method	MIC = 7.8 μg/ml, MBC = 15.6 μg/ml	(Roomiani et al., 2013)
Streptococcus mutans	Leaves extract	Broth dilution assay	MIC = 25 mg/ml, MMC > 50 mg/ml	(de Oliveira et al., 2017)

Note: IC50, concentration that provided 50% inhibition.
Abbreviations: IZ, inhibition zone; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; RAPD, randomly amplified polymorphic DNA; TSB, trypticase soy broth.

2014; Sharifi-Rad, Nazaruk, et al., 2018). Disc diffusion assays, agar well diffusion, and broth macrodiluation and microdilution methods, in addition to the assessment of antibiofilm activity, are the major methods employed for the evaluation of the antimicrobial activities of rosemary EO and extracts. As shown in Tables 1–3, microbial growth inhibitions zones and percentages along with the minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) reveal the potential of rosemary as a promising antimicrobial agent and foresee their effectiveness as a functional food. It is generally admitted that a substance with antimicrobial activity determined by the agar or disc diffusion method that displayed inhibition halo greater than 13 mm is active (Clinical and Laboratory Standards Institute, 2003). For MIC value obtained using microdilution/macrodilution methods, a plant extract is classified as highly active if MICs < 100 μg/ml; active if 100 < MICs ≤ 500 μg/ml; moderately active if 500 < MICs ≤ 1,000 μg/ml; low activity if 1,000 < MICs ≤ 2,000 μg/ml; and inactive if MICs > 2,000 μg/ml (Saraiva et al., 2011).

5.1.1 | Antibacterial activity against gram-positive bacteria

Numerous researches evaluated the antibacterial activity of rosemary oil and extracts against different gram-positive bacteria such as *Bacillus sphaericus*, *Bacillus subtilis*, *Bacillus circulans*, *Bacillus cereus*, *S. aureus*, *Staphylococcus intermedius*, *Staphylococcus hyicus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus capare*, *Staphylococcus gallinarum*, *Staphylococcus arlettae*, *Staphylococcus lentus*, *Staphylococcus equorum*, *Staphylococcus simulans*, *Staphylococcus delphini*, *Staphylococcus chromogenes*, *Micrococcus luteus*, *Sarcinalutea*, *Enterococcus faecalis*, *Leuconostoc mesenteroides*, *Lactobacillus delbruekii*, *Streptococcus mutans*, *Streptococcus iniae*, *Enterobacter cloacae*, and *L. monocytogenes* (Table 1). Rosemary oil showed a high to modearate antimicrobial potency on the majority of bacteria. Among the studied bacteria, *S. iniae* was the most sensitive to rosemary oil, showing a zone of inhibition of 45 mm as evaluated by disc diffusion assay (Roomiani et al., 2013), whereas through the microdilution method, the most sensitive one could be *S. epidermidis*, with an MIC value as low as 0.312–0.625 μg/ml (Jardak et al., 2017). On the other hand, *S. mutans and E. faecalis* were less sensitve to rosemary extract, with an MBC > 50 mg/ml (de Oliveira et al., 2017), and the petroleum ether extract of leaves did not cause any inhibition on *S. aureus* growth (Adam et al., 2014). Rosemary plant was also effective against *S. aureus*, *B. cereus*, *B. subtilis*, *Bacillus pumilis*, (Burt, 2004; Hussain et al., 2010), *Bacillus thermosphacta*, and *Shewanella putrefaciens* (Teixeira et al., 2013). Rožman & Jeršek (2009) evaluated the effects of rosemary ethanolic extracts containing different levels of carnosic acid on the growth of different *Listeria* species, where their MIC and MBC values were found to be in the ranges of 312.5–5,000 μg extract per milliliter EtOH and 15.63–98.5 μg/ml, respectively. Rosemary plant was still effective against *Listeria innocua*, and *L. monocytogenes* (Teixeira et al., 2013). A recent study was focused on the antimicrobial effectiveness of carnosic acid in combination with gentamicin against methicillin-resistant *S. aureus* (MRSA). The anti-MRSA activity was

TABLE 2 Antimicrobial effects of rosemary against gram-negative bacteria

Bacteria	Extract/compounds	Used method	Effects	References
Acinetobacter baumannii	Essential oil	Disc diffusion assay	IZ = 14–20 mm	(Abdullah et al., 2015; Chahboun et al., 2014)
Campylobacter jejuni	Different extracts	Disc diffusion assay, agar dilution, and microdilution method	MICdiff = 20 to >40 mg/ml, MICdil = 5–10 mg/ml, MICmdil = 0.156–2.5 mg/ml	(Klancnik et al., 2009)
		Broth macrodilution method	MIC = 0.156–2.5 mg/ml, MBC = 0.313–5 mg/ml	(Klancnik et al., 2009)
	Different leaves extracts	Broth microdilution method	MIC = 0.04 ± 0.01–0.15 ± 0.03 mg/ml	(Abramovic et al., 2012)
Escherichia coli	Aqueous extract of the leaves	Agar well diffusion method	IZ = 10–20 mm	(Adam et al., 2014)
	Aqueous, 80% ethanol, and chloroformic extracts	Microdilution method	MIC = 1.56, 1.56, and 3.125 mg/ml, respectively	(El Kichaoui et al., 2017)
	Different leaves extracts	Broth microdilution method	MIC = 0.51–0.70 mg/ml	(Abramovic et al., 2012)
	Different leaves extract prepared by supercritical fluid extraction	Microdilution method	MIC = 1 mg/ml	(Genena et al., 2008)
		Disc diffusion assay and microdilution method	IZ = 8.2 ± 0.4 mm, IC_{50} = 452 ± 8 μg/ml, MIC = 320 μg/ml	(Ben Chobba et al., 2012)
		Broth microdilution method	MIC = 0.0625%, v/v, MBC = 0.125%, v/v	(Wang et al., 2012)
		Disc diffusion assay	MIC = 25 μl/ml	(Abu-Zaid et al., 2013)
			IZ = 8–20 mm	(Chahboun et al., 2014; Djelloul et al., 2017; Kazemi et al., 2012; Kesatebrhan & Tesema, 2014; Martins et al., 2012)
		RAPD analysis-microdilution method	MIC = 25 μl/ml, MBC = 2.5 μl/ml	(Hamedo, 2009)
	Essential oil-rich fractions	Disc diffusion assay and broth dilution assay	IZ = 17–33 mm, MBC = 2.25 to 0.25 mg/ml	(Santonyo et al., 2005)
	Extract	Disc diffusion assay	IZ = 10.37 mm	(Kumuda et al., 2017)
	Methanolic extract	Agar well diffusion method	IZ = 19 mm	(Tirumalasetty & Basavaraju, 2014)
	Leaves methanol extract	Agar well diffusion method	IZ = 10–18 mm	(Adam et al., 2014)

(Continues)

TABLE 2 (Continued)

Bacteria	Extract/compounds	Used method	Effects	References
	Leaves petroleum ether extract	Agar well diffusion method	IZ = 12–15 mm	(Adam et al., 2014)
Klebsiellaoxytoca	Essential oil	Disc diffusion assay	IZ = 22 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 3 μg/ml, MBC = 3 μg/ml	(Kazemi et al., 2012)
Klebsielle pneumonia	Aqueous, 80% ethanol, and chloroformic extracts	Microdilution method	MIC = 12.5, 12.5, and 25 mg/ml, respectively	(El Kichaoui et al., 2017)
	Essential oil	Disc diffusion assay	IZ = 12.8–15 mm	(Ben Chobba et al., 2012; Kazemi et al., 2012; Martins et al., 2012)
		Microdilution method	IC50 = 330 μg/ml, MIC = 3–282 μg/ml, MBC = 2 μg/ml	(Ben Chobba et al., 2012; Kazemi et al., 2012)
Proteus vulgaris	Aqueous extract of the leaves	Agar well diffusion method	IZ = 11–21 mm	(Adam et al., 2014)
	Essential oil	Disc diffusion assay	IZ = 16 mm	(Chahboun et al., 2014)
	Methanolic extract of the leaves	Agar well diffusion method	IZ = 9–12 mm	(Adam et al., 2014)
	Petroleum ether extract of the leaves	Agar well diffusion method	IZ = 10–12 mm	(Adam et al., 2014)
Pseudomonas aeruginosa	Aqueous extract of the leaves	Agar well diffusion method	IZ = 12–17 mm	(Adam et al., 2014)
	Aqueous, 80% ethanol, and chloroformic extracts	Microdilution method	MIC = 6.25, 12.5 and 50 mg/ml, respectively	(El Kichaoui et al., 2017)
	Different leaves extract prepared by supercritical fluid extraction	Microdilution method	MIC = 1 mg/ml	(Genena et al., 2008)
	Essential oil	Disc diffusion assay	IZ = 16 mm	(Djelloul et al., 2017)
	Essential oil	Disc diffusion assay	IZ = 6.2 ± 0.5 mm	(Ben Chobba et al., 2012)
		Microdilution method	IC50 = 470 ± 15 μg/ml, MIC = 300 μg/ml	(Ben Chobba et al., 2012)
	Essential oil	Broth microdilution method	MIC = 0.0313%, v/v; MBC = 0.25%, v/v	(Wang et al., 2012)
	Essential oil	Disc diffusion assay and microdilution method	IZ = 20 mm and MIC = 4 μg/ml	(Kazemi et al., 2012)
	Essential oil	Disc diffusion assay	IZ = 18–34 mm	(Abdullah et al., 2015)
	Essential oil-rich fractions	Disc diffusion assay and broth dilution assay	IZ = 17 to 33 mm, MBC = 2.25 to 0.25 mg/ml	(Santonyo et al., 2005)

(Continues)

TABLE 2 (Continued)

Bacteria	Extract/compounds	Used method	Effects	References
	Leaves extract	Broth dilution assay	MIC = 6.25 mg/ml, MMC = 6.25 mg/ml	(de Oliveira et al., 2017)
	Methanolic extract	Agar well diffusion method	IZ = 17 mm	(Tirumalasetty & Basavaraju, 2014)
	Leaves methanol extract	Agar well diffusion method	IZ = 10 mm at concentration 25%	(Adam et al., 2014)
Pseudomonas fluorescens	Extract	Disc diffusion assay	IZ = 11.03 mm	(Kumuda et al., 2017)
Salmonella infantis	Different extracts	Disc diffusion, agar dilution, and microdilution methods	MICdiff ≥ 100 mg/ml, MICdil = 8–9 mg/ml, MICmdil = 2.5–5 mg/ml, respectively	(Klancnik et al., 2009)
	Different extracts	Broth macrodilution method	MIC = 2.5–5 mg/ml, MBC = 20 mg/ml	(Klancnik et al., 2009)
	Different leaves extracts	Broth microdilution method	MIC = 0.59–1.03 mg/ml	(Abramovic et al., 2012)
Salmonella typhi	Essential oil	Disc diffusion and microdilution methods	IZ = 18 mm and MIC = 3 μg/ml, MBC = 3 μg/ml	(Kazemi et al., 2012)
Serratia marcescens	Essential oil	Disc diffusion and microdilution methods	IZ = 21 mm and MIC = 2 μg/ml, MBC = 5 μg/ml	(Kazemi et al., 2012)
Shigella boydii	Essential oil	Disc diffusion and microdilution methods	IZ = 22 mm and MIC = 2 μg/ml, MBC = 2 μg/ml	(Kazemi et al., 2012)
Shigella sonnei	Essential oil	Disc diffusion and microdilution methods	IZ = 15 mm and MIC = 4 μg/ml, MBC = 3 μg/ml	(Kazemi et al., 2012)

Note: IC50, concentration that provided 50% inhibition.
Abbreviations: IZ, inhibition zone; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; RAPD, randomly amplified polymorphic DNA.

examined using subinhibitory concentrations combination of carnosic acid and gentamicin in pediatric patients diagnosed with bacteremia. Carnosic acid exhibited good antibacterial activity against all the tested MRSA clinical isolates, but the combination of carnosic acid with gentamicin not only decreased the MIC of both compounds by fourfold to fivefold but also improved the bactericidal potency of the gentamicin by 32- to 40-fold against both gentamicin-susceptible and gentamicin-resistant MRSA. These findings show the potential use of carnosic acid in combination with gentamicin as a promising alternative to control healthcare-associated infections caused by MRSA (Vazquez, Fiorilli, Caceres Guido, & Moreno, 2016). In general, it was found that the rosemary oil was more potent than different rosemary extracts against gram-positive bacteria.

5.1.2 | Antibacterial activity against gram-negative Bacteria

Salmonella typhi, *Salmonella infantis*, *Klebsiella enteritidis*, *Klebsiella oxytoca*, *Acinetobacter baumannii*, *Shigella sonnei*, *Shigella boydii*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Pseudomonas mirabilis*, *Pseudomonas fluorescens*, *Campylobacter jejuni*, *Escherichia coli*, and *Proteus vulgaris* were the most frequently used gram-negative bacteria for evaluation of rosemary oil and extracts antibacterial effects. The most sensitive one was *A. baumannii*, with an inhibition zone of 35 mm when treated by rosemary oil as evaluated by the disc diffusion assay (Abdullah et al., 2015), along with *S. boydii* with MIC and MBC of 2 μg/ml, as reported by Kazemi, Rostami, and Ameri (2012). Rosemary plant was also effective against *P. aeruginosa*, *Salmonella poona*, and *E. coli* (Burt, 2004; Hussain et al., 2010). On the contrary, neither rosemary oil nor extract showed activity against *P. aeruginosa* as proven by previous studies (Adam et al., 2014; Balouiri et al., 2014; Chahboun et al., 2014; Martins, Tinoco, Almeida, & Cruz-Morais, 2012). Both rosemary oil and extract exhibited more potent antibacterial activities against gram-positive than gram-negative bacteria, although the effect was higher against the gram-positive ones. However, rosemary oil showed higher antibacterial activity against gram-positive than gram-negative bacteria (Hussain et al., 2010; Pesavento et al., 2015). However, the same study with EO has shown high MIC against microorganisms (de Azeredo et al., 2011; de Sousa et al., 2013; Teixeira et al., 2013). The different MICs obtained are probably due to different microbial susceptibilities, microorganisms' classes, and characteristics of EOs used, closely related to the large variability of the chemical composition of each EO chemotypes (Flamini, Cioni, Morelli, Macchia, & Ceccarini, 2002; Pesavento et al., 2015). The main reason behind the bacterial susceptibility could be due to the outer membrane surrounding the cell wall in gram-negative bacteria and the enzymes present in the periplasmatic space that hydrolyze foreign molecules (Vaara, 1992). Generally, when rosemary extract is addressed, it is meant to be the alcoholic extracts of the leaves in particular as the extracts from the stems are less potent as demonstrated by the bioassay-guided study (Bernardes et al., 2010). Also, the extracts with other solvents as petroleum ether and chloroform showed lower potencies than the alcoholic ones (Adam et al., 2014; El Kichaoui, Abdelmoneim, Elbaba, & El Hindi, 2017).

As persistent multidrug-resistant infections are an actual problem, the therapeutic use of rosemary (*R. officinalis*) EOs was assessed against multidrug-resistant *E. coli* strains obtained from patients with respiratory tract, abdominal cavity, urinary tract, and skin infections and isolated from hospital equipment. The results showed that both tested EOs are active against all *E. coli* clinical strains, including extended-spectrum β-lactamase positive bacteria. These studies may hasten the application of EOs in both treatment and prevention of emergent resistant strains in nosocomial infections (Sienkiewicz, Lysakowska, Pastuszka, Bienias, & Kowalczyk, 2013). Similarly, the methanolic extracts of six plants, among which *R. officinalis* were subject of a study related to the antimicrobial and anti-inflammatory properties in opportunistic infections of oral cavity caused by *S. aureus*, *P. aeruginosa*, and *Candida albicans*. Their ability to suppress the release of the proinflammatory cytokine interleukin (IL)-6 and stimulate the anti-inflammatory cytokine IL-10 release in peripheral blood mononuclear cells were also investigated. Notably, the mixture of *Origanumsyriacum* and *R. officinalis* showed anti-inflammatory (inhibited IL-6 expression and diminished IL-10 secretion) and synergistic antimicrobial effects. These findings sustain that intake of herbs-based diet could have a preventive action against various infections, including those related to the oral cavity (Assaf, Amro, Mashallah, & Haddadin, 2016).

Thus the rosemary plant is effective against some pathogens and can reduce the risk and incidence of foodborne diseases. However, little is known about their mode of action.

5.1.3 | Antifungal and antiyeast activity

Fumigation bioassay and contact bioassay methods were also employed for the assessment of antifungal activities of rosemary oils and extract along with the traditional methods as disc diffusion assay, well-plate diffusion method, and broth dilution method. The antifungal activity was evaluated against *Penicillium digitatum*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, *Vasin factum*, *Mucor sp*., *C. albicans*, *Candida krusei*, *Fusarium oxysporum*, *Fusarium solani*, *Colletotrichum falcatum*, *S. cerevisiae*, and *Botrytis cinereal* (Table 1). *A. niger* was very sensitive to rosemary oil (MIC and MBC of 1.5 and 3 μg/ml, respectively) as represented in a previous study (Kazemi et al., 2012). These results were in contrast to the results of previous works (Kesatebrhan & Tesema, 2014; Martins et al., 2012) that reported no activity. Rosemary plant was also effective against *A. flavus* and *A. niger* (de Sousa et al., 2013).

Aiming at exploring the mechanism of antiyeast activity of rosemary oil, Cavalcanti, Almeida, and Padilha (2011) evaluated its anti-adherent activity against *C. albicans* using scanning electron microscopy analysis and found that at 0.56 mg/ml, the effect of rosemary oil was similar to nystatin (t = 0 hr and t = 24 hr), and at 2.25 mg/ml, it caused significant cell disruption and adhesion

TABLE 3 Antifungal effects of rosemary

Fungi	Extract/compounds	Used method	Effects	References
Aspergillus flavus	Essential oil	Disc diffusion assay	IZ = 15 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 2.5 μg/ml, MBC = 2 μg/ml	(Kazemi et al., 2012)
Aspergillus fumigatus	Essential oil	Disc diffusion assay	IZ = 16 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 3 μg/ml, MBC = 1.5 μg/ml	(Kazemi et al., 2012)
Aspergillus Niger	Essential oil	Disc diffusion assay and microdilution method	IZ = 4.3 ± 0.3 mm, IC50 = 140 ± 18 μg/ml, MIC = 180 μg/ml	(Ben Chobba et al., 2012)
		Disc diffusion assay	IZ = 15 mm; IZ = 0 and 8 mm at 10 and 20 μl, respectively	(Kazemi et al., 2012; Kesatebrhan & Tesema, 2014)
		Microdilution method	MIC = 1.5 μg/ml, MBC = 3 μg/ml	(Kazemi et al., 2012)
	Essential oil-rich fractions	Disc diffusion assay and broth dilution assay	IZ = 17 to 33 mm MBC = 2.25 to 0.25 mg/ml	(Santonyo et al., 2005)
Botrytis cinereal	Essential oil	Disc diffusion and microdilution methods	IZ = 06.2 ± 0.5 mm, IC_{50} = 190 ± 12 μg/ml, MIC = 100 μg/ml	(Ben Chobba et al., 2012)
Candida albicans	Different leaves extract prepared by supercritical fluid extraction	Microdilution method	MIC = 0.5 to >2 mg/ml	(Genena et al., 2008)
	Essential oil	Disc diffusion assay	IZ = 8–16 mm	(Kazemi et al., 2012; Martins et al., 2012)
	Essential oil-rich fractions	Disc diffusion and broth dilution assays	IZ = 17 to 33 mm; MBC = 2.25 to 0.25 mg/ml	(Santonyo et al., 2005)
	Leaves extract	Broth dilution assay	MIC = 0.78 mg/ml, MMC = 3.13 mg/ml	(de Oliveira et al., 2017)
Candida krusei	Essential oil	Broth dilution assay	MBC = 2 mg/ml	(Tavassoli et al., 2011)
Colletotrichumfalcatum	Essential oil	Disc diffusion assay	IZ = 15 mm	(Kazemi et al., 2012)
Fusarium oxysporum	Essential oil	Disc diffusion assay	IZ = 16 mm IZ = 11.7 and 13.4 mm at 10 and 20 μl, respectively	(Kazemi et al., 2012; Kesatebrhan & Tesema, 2014)
Fusarium solani	Essential oil	Disc diffusion and microdilution methods	IZ = 16.4 ± 0.5 mm, IC50 = 220 ± 20 μg/ml, MIC = 90 μg/ml	(Ben Chobba et al., 2012)
Mucor sp.	Essential oil	Disc diffusion assay	IZ = 15 mm	(Kazemi et al., 2012)
Penicillium digitatum	Essential oil	Disc diffusion and microdilution methods	IZ = 10.3 ± 0.4 mm, IC_{50} = 250 ± 16 μg/ml, MIC = 120 μg/ml	(Ben Chobba et al., 2012)
	Essential oil and methanol extract	Fumigation bioassay	More than 50% growth inhibition at 30, 40, And 50 μl	(Hendel et al., 2016)
		Contact bioassay method	Inhibition at sixth day was estimated to be 13–50%	(Hendel et al., 2016)

(Continues)

TABLE 3 (Continued)

Fungi	Extract/compounds	Used method	Effects	References
		Disc diffusion assay	IZ = 14, 20 and 32.5 mm at 15, 20 and 25 μl, respectively	(Hendel et al., 2016)
	Methanol extract	Well-plate diffusion method	More than 50% inhibition at 0.8 g/ml	(Hendel et al., 2016)
Saccharomyces cerevisiae	Essential oil	Broth dilution assay	MBC = 1.75 mg/ml	(Tavassoli et al., 2011)
Vasin factum	Essential oil	Disc diffusion assay	IZ = 18 mm	(Kazemi et al., 2012)
		Microdilution method	MIC = 2.5 μg/ml, MBC = 1.5 μg/ml	(Kazemi et al., 2012)

Note: IC50, concentration that provided 50% inhibition.
Abbreviations: IZ, inhibition zone; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration.

inhibition. Basically, the mechanism underlying the antimicrobial activities of EOs is not well-established; nevertheless, it may be dependent on their hydrophobicity and partition in microbial membranes, or they may cause structural and functional microbial damages by disrupting the membrane permeability and the osmotic balance of cells (Hendel, Larous, & Belbey, 2016). Another study analyzed the effects of *R. officinalis* EO on germ tube formation by *C. albicans* isolated from denture wearers. A product with 10% fetal bovine serum with/without 4% *R. officinalis* EO was tested on 10 *C. albicans* isolates. *R. officinalis* EO modulated *C. albicans* pathogenicity through its primary virulence factor (i.e., germ tube formation suppression; Gauch et al., 2014).

The results of these antimicrobial studies are more or less similar, although the differences could be attributed to the divergent geographical origins, parts used, plant population density, physical and chemical characteristics of the soil, time of harvest methods of oil/extract preparations, or methods of antimicrobial evaluation (Kesatebrhan & Tesema, 2014).

The antimicrobial activities of rosemary extract could be explained by the presence of carnosic acid, carnosol, and rosmarinic acid and that of rosemary oil is mainly due to oxygenated mono and sesquiterpene hydrocarbons, although most of the studies did not correlate the antimicrobial activities of rosemary extract and oil to their active metabolites, suggesting these activities are achieved through interactions or synergism among the various phenolic constituents (Abramovic et al., 2012). Rosemary oil exhibited better antibacterial activity than 1,8-cineol, the main component of this EO (Hussain et al., 2010). This might be due to the synergistic effect of some minor components present in the oil. The minor components are critical to the activity and may have a potential influence (Burt, 2004). On another point of view, the volatile compounds, 1,8-cineole, camphor, eugenol, and α-pinene (Abdollahzadeh, Rezaei, & Hosseini, 2014; de Azeredo et al., 2011; Ojeda-Sana, van Baren, Elechosa, Juárez, & Moreno, 2013; Ribeiro-Santos et al., 2015; Teixeira et al., 2013); and the phenolic compound, carnosic acid, have been associated with the rosemary oil antimicrobial activity (Rožman & Jeršek, 2009). Despite the antimicrobial potential of rosemary in vitro, its effectiveness in animal models still needs to be documented.

5.2 | Antioxidant activity

The etiology and pathophysiology of human diseases, such as inflammation, viral infections, autoimmune and cardiovascular diseases, ulcers, diabetes, and even cancer, are basically implicated with reactive oxygen species (ROS; Rubió, Motilva, & Romero, 2013; Howlett, 2008). These free radicals generated in vivo damage many targets, including lipids, proteins, DNA, and small molecules. The body's innate defenses need to be supported by a wide variety of low molecular-weight antioxidants found in the daily diet, and many of them are of plant origin. Fortunately, it has been postulated that natural antioxidant compounds can terminate free radical-mediated oxidative reaction (Havsteen, 2002) by countering ROS directly or boost regenerative systems to restore antioxidant capacity (Naghavi et al., 2003).

TABLE 4 In vitro antioxidant activity of rosemary

Plant part	Extract/ compound	Method	Effects	Reference
Aerial parts	Essential oil	DPPH radical scavenging assay, β-carotene bleaching, and reducing power	IC50 = 110.20 and 20.00 μg/ml and EC_{50} = 38.68 μg/ml, respectively	(Kadri et al., 2011)
Leaves	Essential oil	DPPH radical scavenging assay	%inhibition = 48.8, 61.6, and 67%, respectively, at concentrations 0.33, 0.5, and 1 mg/ml	(Okoh, Sadimenko, & Afolayan, 2011)
		DPPH radical scavenging assay	%inhibition = 52.2, 55, and 65.3%, respectively, at 0.33, 0.5, and 1 mg/ml	(Okoh et al., 2011)
		DPPH radical scavenging assay and lipid peroxidation capacity	IC50 = 10.08 and 1.76, respectively	(Gezici, Sekeroglu, & Kijjoa, 2017)
		DPPH radical scavenging assay	IC50 = 77.6 μl/ml	(Raskovic et al., 2014)
		DPPH radical scavenging assay	%inhibition = 73.08%, 84.49%, and 85.53%, respectively, at concentrations of 10, 25, and 30 μl/ml	(Abu-Zaid et al., 2013)
		DPPH radical scavenging and inhibition of linoleic acid oxidation assays	%DPPH inhibition = 25.5, 28.0 and 29.6% and %LAO inhibition = 4.5, 8.3 and 13.0% at concentrations 1, 2, and 4 mg/ml	(Martins et al., 2012)
	Supercritical carbon dioxide extract	DPPH radical scavenging assay	0.5 mg/ml reduced 81% of the DPPH radicals	(Jasna et al., 2009)
	Methanolic extract	Total antioxidant capacity, DPPH radical scavenging assay, scavenging activity of OH iron chelating DPPH radical scavenging assay, ferrous ion chelating activity, and superoxide anion scavenging activity	184.9 (mg AAE/g) 1.4 (A0 at 700 nm) IC_{50} = 41.0, 72.6 and 241.0 μg/ml 80.2% at 150 μg/ml, 38.31% at 200 μg/ml and 69.12% at 300 μg/ml, respectively	(Bilto & Alabdallat, 2015; El-Beltagi & Badawi, 2013)
	Ethanolic extract	DPPH radical scavenging assay	72–85% at 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 96%	(Kasparavičienė et al., 2013)
		Cell-free ABTS radical scavenging assay	8.1 and 12.6 μM of the Trolox equivalents, respectively, with 1/10 and 1/5 dilutions	(Cheung & Tai, 2007)
		DPPH radical scavenging assay and ferric reducing power	EC_{50} = 4.63 and 63.85 μg/ml, respectively	(Gird et al., 2017)
	Different extract formulations	Superoxide anion radical scavenging activity, hydroxyl radical assay, and DPPH radical scavenging assay	EC_{50} = 7.94, 109.54, and 27.4 μg/ml, respectively	(Đilas et al., 2012)
	Different extracts prepared by	DPPH radical scavenging assay	IC50 = 9.23–27.34 μl/ml	(Genena et al., 2008)

(Continues)

TABLE 4 (Continued)

Plant part	Extract/ compound	Method	Effects	Reference
	supercritical fluid extraction			
	Methanol extract and essential oil	DPPH radical scavenging assay	IC_{50} = 11.74 and 3.53 μg/ml, respectively	(Hendel et al., 2016)
	Caffeic acid	DPPH radical, alkyl radical, and ABTS radical scavenging assays	SC_{50} = 12.1, 27.2, and 81.8 μM, respectively	(Hyun, Shrestha, Boo, & Cho, 2015)
	Rosmarinic acid		SC_{50} = 4.0, 63.2, and 56.7 μM, respectively	(Hyun et al., 2015)
	Rosmarinic acid methyl ester		SC_{50} = 3.0, 46.8, and 37.7 μM, respectively	(Hyun et al., 2015)
	Luteolin		SC_{50} = 5.7, 32.2, and >100 μM, respectively	(Hyun et al., 2015)
	Apigenin		SC_{50} ≥ 20, 94.3, and >100 μM, respectively	(Hyun et al., 2015)
	Hispidulin		SC_{50} ≥ 20, 45.0, and 93.3 μM, respectively	(Hyun et al., 2015)
Not specified	Essential oil	FRAP and DPPH scavenging activity methods	3.67 mg/ml and 21.31%, respectively	(Tural & Turhan, 2017)
	Commercial rosemary extract formulations	Reducing power assay DPPH radical scavenging assay β-carotene bleaching test	Reducing power = 27.2–124 mg/ml, DPPH EC_{50} = 0.0074–0.0227, antioxidant activity coefficient: 0.12–0.79	(Klancnik et al., 2009)
	Methanolic extracts at 100, 200, 300, 400 and 500 ppm	FRAP assay, DPPH radical scavenging assay, metal chelating activity	FRAP = 0.528, 0.861, 1.287, 1.849, and 2.162 abs, respectively; DPPH = 77.37, 76.54%, 75.17%, 73.18%, and 69.92%, respectively; MCA = 23.17%, 31.28%, 39.63%, 44.40%, and 50.28%, respectively	(Kumuda et al., 2017)
	Acetone extracts of (McConnell's blue) and (Tuscan blue) rosemary	DPPH radical scavenging assay	IC_{50} = 3.48 and 10.84 μg/ml, respectively	(Berrington & Lall, 2012)
Seeds	Methanolic extract	DPPH radical scavenging assay	%inhibition = 55.08%	(Nagy et al., 2014)

Abbreviations: FRAP, ferric-reducing antioxidant power; LAO, L-amino acid oxidase.

The well-known antioxidant effect of phenolic compounds is mainly due to their redox properties and their capacity to block the production of ROS formed in several in vitro and in vivo systems. Lipid oxidation inhibition, free radical scavenging (e.g., lipoxygenase inhibition, singlet oxygen quenching, metal chelation, transition-metal-chelating activity, and singlet-oxygen-quenching capacity) are the most common mechanisms (El-Beltagi & Badawi, 2013).

Most of the pharmacological actions of rosemary are attributed to the high antioxidant activity of its main phenolic metabolites; hence, in Europe and the United States, it is the only commercially available spice for use as an antioxidant (Bilto & Alabdallat, 2015). The antioxidant potential of rosemary oil and its extract was mainly assessed by DPPH radical scavenging, β-carotene bleaching, lipid peroxidation capacity, inhibition of linoleic acid oxidation, ferric-reducing antioxidant power radical scavenging, total antioxidant capacity, cell-free ABTS OH radical scavenging, superoxide anion radical scavenging, and alkyl radical scavenging assays. Most of the studies were performed on EO or extracts from its leaves under different extraction procedures. Table 4 shows the inhibition percentages (IC_{50} and EC_{50} values), as a direct measure of rosemary oil and extract antioxidant effect. Although most researches focused on rosemary extract antioxidant capacity, the antioxidant activities of individual metabolites of the extract, such as caffeic and rosmarinic acids, rosmarinic acid methyl ester, luteolin, apigenin, and hispidulin, as well as its total extract have also been made. Rosemary extract shows to be more effective than single isolated compounds. Additionally, both rosemary oil and extract exert potent antioxidant effects in a concentration-dependent fashion, but yet again, rosemary oil was the most potent, as demonstrated by Hendel et al. (2016). However, the active metabolites that confer rosemary oil antioxidant potential are still unclear, but most probably, these effects are due to a mixture of different components acting synergically(Kadri et al., 2011). The antioxidant activity of rosemary has also been attributed to phenolic constituents, such as carnosic acid, carnosol (Babovic et al., 2010; Hussain et al., 2010; Peng et al., 2007; Peter & Nirmal Babu, 2012), rosmarinic acid (Kontogianni et al., 2013; Peter & Nirmal Babu, 2012), rosmanol (Kontogianni et al., 2013; Peng et al., 2007), methyl carnosate(Peng et al., 2007), luteolin (Valdes et al., 2013), betulinic acid (Kontogianni et al., 2013), myrcene (Ojeda-Sana et al., 2013), cirsimartin and genkwain (Peng et al., 2007), and volatile compounds (Hussain et al., 2010). Moreover, rosemary extract possesses better antioxidant activity than the synthetic antioxidants BHA (Babovic et al., 2010), trolox, and ascorbic acid (Peng et al., 2007). Still, carnosic and rosmarinic acids had a considerably higher activity than BHT and α-tocopherol (Pesavento et al., 2015). Thus, synergistic effects can maximize the antioxidant activity of rosemary oil and minimize the concentrations required to achieve a particular effect (Babovic et al., 2010).

5.3 | Anticancer activity

Numerous evidence suggests that the several risk factors that can induce cancer initiation and propagation has a basis of chronic inflammation. Inflammatory gene products are regulated by transcription factors, such as nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3); and NF-κB and STAT3 activation lead to tumor cells proliferation, survival, invasion, angiogenesis, and metastasis, besides to induce resistance to chemotherapy and radiation. Therefore targeting these pathways may provide opportunities for both prevention and treatment of cancer and other chronic diseases. In fact, epidemiological studies indicate that cancer incidence in countries, such as India where spices are daily consumed, is much lower (94/100,000) than in countries where spices are not consumed, such as the Uniyed States (318/100,000), suggesting the potential role of spices in cancer prevention (Lu, Zou, Liu, & Niu, 2017). Despite the newly therapeutic antitumor procedures, cancer is considered the main health threat nowadays, and, therefore, new therapeutic options should be explored. Compounds of plant origin, including food components, have attracted scientific attention on cancer prevention and treatment. Natural products exploitation offers a great opportunity to evaluate new anticancer agents and to understand novel and potentially relevant mechanisms of action (Moore, Yousef, & Tsiani, 2016). The antitumor effects of rosemary were initially attributed to its antioxidant activity, but recently, a lack of correlation between antioxidant and antitumor effects exerted by rosemary was reported, and different molecular mechanisms were related to its tumor inhibitory properties. Moreover, supported by the U.S. Food and Drug Administration and the European Food and Safety Authority, specific compositions of rosemary extract were demonstrated to be safe for human health and used as an antioxidant additive in foods, suggesting the potential easy application of this agent as a complementary approach in cancer therapy (Gonzalez-Vallinas, Reglero, & Ramirez de Molina, 2015). Indeed, a meta-analysis designed to gather literature findings from 2010 to 2016 revealed that carnosol has beneficial effects on human health and may act as an antitumor agent in different types of cancer by inducing apoptosis and inhibiting cell cycle (Samarghandian, Azimi-Nezhad, & Farkhondeh, 2018). There are many in vitro and in vivo studies focusing on rosemary extract and its polyphenols, carnosic, and rosmarinic acids antiproliferative effects (Moore et al., 2016). Although preclinical studies comprising phytochemicals combined with standard antitumor drugs are less tested in human clinical trials, notable progress has been achieved regarding in vitro/in vivo studies involving natural compounds. As shown in Table 5, the antiproliferative activities of rosemary oil and extract have been evaluated by cell viability percentages and IC_{50} values through the application of several in vitro assays. The most often used malignant cell lines are colon (HCT), hepatocellular (HEPG-2, Bel-7402, and Hep-3B), ovarian (SK-OV-3 and HO-8910), cervical (HeLa), colon (HT-29), prostate (DU-145 and PC-3), lung (A549 and NCI-H82) and nonsmall cell lung (H1299) carcinoma cells, breast adenocarcinoma (MCF-7 and MDA-MB-231), melanoma (A375) and rhabdomyosarcoma (RD), chronic myeloid leukemia (K-562), glioblastoma cells (GBM U87 MG), murine macrophages (RAW 264.7), human gingival fibroblasts (FMM-1), and even normal cell lines as nontumor human umbilical vein endothelial cells, mouse embryo fibroblast, and African green monkey kidney (Vero) cell lines. The total EO has shown to be the most potent

against human ovarian cancer (SK-OV-3 and HO-8910) and human hepatocellular carcinoma (Bel-7402), whereas carnosic acid, carnosol, and betulinic acid were identified as the main antiproliferative rosemary agents. Volatile compounds, that is, 1,8-cineol, camphor, and α-pinene, have also shown prominent antiproliferative activity against breast and prostate cancers (Hussain et al., 2010). Phenolic compounds in association with monoterpenes provided synergistic effects (Sánchez-Camargo et al., 2014; Sanchez-Camargo & Herrero, 2017). Thus, rosemary cytotoxic activity could be attributed to carnosic acid, monoterpenes, and triterpenoids (betulinic and ursolic acids), and the synergism observed among them suggests that the combination of two features (cytotoxic and antioxidant effects) could provide direct cancer cells destruction and healthy cells protection during cancer treatment (Burt, 2004; Sánchez-Camargo et al., 2014).

Rosemary constituents have also demonstrated different cytotoxic effects depending on tumor cell type, oil concentration, and exposure time (Valdes et al., 2013). Therefore, these findings strongly support that the anticancer activity is a property of the whole oil/extract (Gonzalez-Vallinas et al., 2014). It is also well-established that rosemary oil has more potent anticancer activities than the extract, although the mechanism of rosemary oil anticancer activity needs to be further addressed, but it could be hypothesized that the malignant cells membranes could be crossed (or interacted with) by hydrophobic compounds leading to structural integrity loss, and this increased protons and ions permeability leading to apoptosis (Sikkema, de Bont, & Poolman, 1995). Specifically, carnosic acid has shown to be able to destabilize the mitochondrial membrane, causing the release of proapoptotic proteins into the cytoplasm to activate other proteins that can promote apoptosis (Fernández-Ochoa et al., 2017). Another possible mechanism seems to be through the reduction of Akt phosphorylation involved in cancer cells proliferation, growth, and survival (Sanchez-Camargo & Herrero, 2017). More recently, rosemary extract has also shown to be a complementary agent to be used with the monoclonal antibody trastuzumab in breast and other HER2 modified tumors (Gonzalez-Vallinas et al., 2014; Salehi et al., 2018).

The in vivo studies reporting the distinct anticancer potencies of rosemary extract and its major constituents (carnosic acid and carnosol) are briefly summarized in Table 6.

5.4 | Neuroprotective effect

So far, little is known on rosmarinic acid neuroprotective abilities. As shown in Table 7, only rosemary tea (2%, w/w) and carnosic acid were assessed in neuroprotection.

Rosemary tea, given at an equivalent dose of 130-mg dry extract per kg body weight, the usually recommended of rosemary tea (Daher & Kashour, 2008), resulted in significant inhibition of cholinesterase activity in the whole brain, besides to exert anxiolytic and antidepressant effects (Ferlemi et al., 2015). These effects may be attributed to its phytochemicals that have some structural similarities with anti-acetylcholinesterase drugs. For example, both rosmarinic acid and luteolin-7-*O*-glucuronide have a structural alignment to donepezil, which contains five pharmacophore sites: two aromatic rings (brown features) at 6.437 Å and three hydrogen bond acceptors (red spheres). Similarly, four common features are found in the alignment of rivastigmine and carnosic acid: two hydrogen bond acceptors, one aromatic ring, and one hydrophobic site (green sphere). The superposition of galantamine with rosmarinic acid and luteolin-7-*O*-glucuronide with four common pharmacophore sites: one aromatic ring and three hydrogen bond acceptors (Ferlemi et al., 2015). With regards to carnosic acid neuroprotective effects, it was shown that it improves the locomotor activity and reduces the apomorphine-caused rotation in 6-OHDA-stimulated rats. It also reduced glutathione (GSH), protected against lipid peroxidation, and increased protein expression of c-glutamate-cysteine ligase catalytic subunit, c-glutamate-cysteine ligase modifier subunit, superoxide dismutase (SOD), and glutathione reductase. Also, 6-OHDA-mediated activation of c-Jun NH_2-terminal kinase, and p38 was reversed, tyrosine hydroxylase protein and Bcl-2/Bax ratio downregulated, and cleaved caspase 3/caspase 3 and cleaved poly-(adenosine diphosphate)-ribose polymerase/poly-(adenosine diphosphate)-ribose polymerase ratio upregulated. The observed neuroprotective effects may be, thus, attributed to rosemary antiapoptotic and antioxidant actions.

5.5 | Skin protective effects of rosemary

R. officinalis extracts gained importance therapeutically in skin conditions, such as alopecia (Table 8).

Hair regrowth improvement, through inhibition of testosterone 5α-reductase (Murata et al., 2013; Panahi, Taghizadeh, Marzony, & Sahebkar, 2015), skin permeation, and antiwrinkle activity with a moderate decrease in epidermis thickness with no pigmentation, by metalloproteinase (matrix metallopeptidase [MMP]-2 and MMP-9) gene expression inhibition (Ezzat, Salama, ElMeshad, Teaima, & Rashad, 2016), has been recorded through topical application of rosemary extracts. More recently, rosemary oil and its components have also been assessed in various cutaneous illnesses. For instance, carnosol has shown positive effects in atopic dermatitis by inhibiting lipopolysaccharide-induced nitric oxide release and inflammatory marker proteins (inducible nitric oxide synthase [iNOS] and cyclooxygenase-2 [COX-2]) expression through suppressing STAT3 activity. It is also able to significantly reduce skin inflammation through inhibition of iNOS and COX-2 expression in the skin tissue and to decrease the serum levels of some proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and IL-1β. Thus these findings put carnosol as a potential antiatopic dermatitis agent on the basis of its STAT3 suppressing activity (Lee et al., 2017).

5.6 | Memory enhancement

Rosemary preparations have also shown memory enhancement abilities (Table 9).

TABLE 5 In vitro antiproliferative effects of rosemary

Extract/compound	Cell line	Methods	Results	Mechanism of action	References
Acetone extracts of (McConnell's blue) and (Tuscan blue) rosemary aerial parts	Noncancerous African green monkey kidney (Vero) cell line	XTT colorimetric assay	IC_{50} = 12.03 and 23.64, respectively	ND	(Berrington & Lall, 2012)
	Adenocarcinoma cervical cancer (HeLa) cell line	XTT colorimetric assay	IC_{50} ≥ 100 and 23.31, respectively	ND	(Berrington & Lall, 2012)
Aqueous and methanolic leaves extracts	Rhabdomyosarcoma (RD) cell line	Freshney cell culture method	%inhibition = 23.0–84.0% at 50–1,000 μg/ml	ND	(Salih, Alobaidi, & Alobaidi, 2015)
	Normal cell line; MEF	Freshney cell culture method	%inhibition = 10.6–15.0% at 50–1,000 μg/ml	ND	(Salih et al., 2015)
Aqueous herb extract	Glioblastoma GBM U87 MG cells, MEF cell	MTT and NR assays	A dilution of 1/75 (v/v) reduced the viability of GBM cells 54% and 65%, respectively, after 3 and 5 days in MTT assay whereas in NR assay, it reduced the viability of GBM cells by 38% and 57%, after 1 and 3 days, respectively	ND	(Ozdemir & Gokturk, 2017)
Commercial extract (glycolic, methanol, and ethyl acetate extract) at different concentrations	Murine macrophages (RAW 264.7), human gingival fibroblasts (FMM-1), human breast carcinoma cells (MCF-7), and cervical carcinoma cells (HeLa)	MTT, NR, and CV assays	50-100 mg/ml provided low cell viability compared with the control group, verified on RAW 264.7, MCF-7, and HeLa cells by MTT assay, on all lines, by NR assay and on FMM-1, MCF-7, and HeLa by CV assay	ND	(de Oliveira et al., 2017)
Different extract formulations (VivOX 20, VivOX 40, Inolens 50)	Cervix epithelioid carcinoma (HeLa)	SRB assay	IC_{50} = 10.020–11.320 μg/ml	ND	(Đilas et al., 2012)
	Breast adenocarcinoma (MCF7)	SRB assay	IC_{50} = 13.260–13.890 μg/ml	ND	(Đilas et al., 2012)
	Colon adenocarcinoma (HT-29) cell lines	SRB assay	IC_{50} ≥ 62.500 > 62.500 μg/ml	ND	(Đilas et al., 2012)
Different methanolic and supercritical carbon dioxide leaves extracts	NCI-H82 (human, small cell lung, and carcinoma), DU-145 (human, prostate, and carcinoma), Hep-3B (human, black, liver, carcinoma, and hepatocellular), K-562 (human chronic myeloid leukemia), MCF-7 (human, breast, and adenocarcinoma), PC-3 (human, prostate, and adenocarcinoma) and MDA-MB-231 (human, breast, and adenocarcinoma)	MTT assay	NCI-H82: IC_{50} = 24.08–94.92 μg/ml DU-145: IC_{50} = 8.82 to >100 μg/ml Hep-3B: IC_{50} = 22.88–96.86 μg/ml K-562: IC_{50} = 12.50–47.55 μg/ml MCF-7: IC_{50} = 20.42–60.41 μg/ml	ND	(Yesil-Celiktas, Sevimli, Bedir, & Vardar-Sukan, 2010)
Essential oil	Colon carcinoma cells (HCT)	Cell viability assay	IC_{50} = 60.9 μl/ml	ND	(Abu-Zaid et al., 2013)
	A549 cells (human lung adenocarcinoma)	MTT assay	IC_{50} = 3.06 μg/ml	ND	(Gezici et al., 2017)
		MTT assay	IC_{50} = 4.34 μg/ml	ND	(Gezici et al., 2017)

(Continues)

TABLE 5 (Continued)

Extract/compound	Cell line	Methods	Results	Mechanism of action	References
	H1299 (human non-small cell lung cancer)				
	Nontumor HUVECs	MTT assay	IC_{50} = 30.68 μg/ml	ND	(Gezici et al., 2017)
	MCF-7 cells (human breast adenocarcinoma)	MTT assay	IC_{50} = 0.253 μl/ml to 7.38 μg/ml	ND	(Gezici et al., 2017; Jardak et al., 2017)
	Human ovarian cancer cell lines (SK-OV-3 and HO-8910)	MTT assay	IC_{50} = 0.025%, v/v	ND	(Wang et al., 2012)
	Human hepatocellular liver carcinoma cell line (Bel-7402)	MTT assay	IC_{50} = 0.13%, v/v	ND	(Wang et al., 2012)
	Liver cancer cell line (HepG2)	MTT and NR assays	IC_{50} = 94.6 μl/ml to 909.6 μg/ml	Expression of bcl-2 gene reduced and expression of bax gene increased in a dose and time-dependent manner	(Abu-Zaid et al., 2013; Santos et al., 2016; Wei, Liu, Wang, Li, & Luo, 2008)
	HeLa cells (cervical cancer line and adherent)	MTT and NR assays	% viable HeLa cell line: 76.93–0.11% at concentrations 3.9–1,500 μg/ml; IC_{50} = 0.011 μl/ml to 633 μg/ml	ND	(Ben Chobba et al., 2012; Jardak et al., 2017; Santos et al., 2016)
Hydroalcoholic extract 65% (w/w)	Human melanoma A375 cell line	MTT and trypan blue assays	Drastic loss of cell proliferation 72 hr IC_{50} = 1:480	ND	(Cattaneo et al., 2015)
Leaves ethanol dry extract	*Daphnia magna* invertebrate	*Daphnia magna* bioassay	Lethality = 90% to 100% at 500 and 1,500 μg/ml after 24 hr. Lethality = 50% at 250 μg/ml at 24 hr. Lethality = 90% after 48 hr	ND	(Gird et al., 2017)
Leaves extract	Cancerous and noncancerous human gastric and colon tissues	ADA activity	Gastric tissue: 5.61 and 9.10 mIU/mg, respectively; colon tissues: 4.18 and 6.18 mIU/mg, respectively	Inhibition of ADA activity	(Durak, Cubukcu, Buber, Kocaoglu, & Durak, 2016)
α-Pinene	Human ovarian cancer cell lines (SK-OV-3 and HO-8910) Human hepatocellular liver carcinoma cell line (Bel-7402)	MTT assay	IC_{50} = 0.052%, v/v IC_{50} = 0.32%, v/v	ND	(Wang et al., 2012)
1,8-cineole	Human ovarian cancer cell lines (SK-OV-3 and HO-8910) Human hepatocellular liver carcinoma cell line (Bel-7402)	MTT assay	IC_{50} = 1.1%, v/v IC_{50} = 3.47%, v/v	ND	(Wang et al., 2012)
β-Pinene	Human ovarian cancer cell lines (SK-OV-3 and HO-8910) Human hepatocellular liver carcinoma cell line (Bel-7402)	MTT assay	IC_{50} = 0.12%, v/v IC_{50} = 0.43%, v/v	ND	(Wang et al., 2012)

Abbreviations: ADA, adenosine deaminase; CV, crystal violet; HUVEC, human umbilical vein endothelial cell; MEF, mouse embryo fibroblast; ND, not determined; NR, neutral red; SRB, sulforhodamine B.

TABLE 6 In vivo anticancer activity of rosemary extracts and its major constituents

Extract/ compound	Doses	Route of administration	Model	Effect	Mode of action	Reference
Rosemary extract	0.5% by weight 200 mg/kg body weight	Diet supplement for 2 weeks (IP) for 5 days	DMBA-induced mammary tumorigenesis in female rats	Inhibited mammary adduct formation by 44%	ND	(Singletary, MacDonald, & Wallig, 1996)
Rosemary extracts	1-mg rosemary extract per milliliter for 32–35 days	Drinking water	SW620 colon cancer xenografts	24–27% tumor inhibition	Upregulation of the metabolic-related gene GCNT3 and downregulation of its potential epigenetic modulator miR-15b	(Gonzalez-Vallinas, Molina, Vicente, Zarza, et al., 2014)
Rosemary extract	200-mg/kg body weight three times per week	Oral gavage	Human colon cancer cells (HT-29) were induced in Athymic nude mice	34% reduction in tumor size	Altered RNA post-transcriptional modification, the protein synthesis and the amino acid metabolism functions	(Valdes et al., 2017)
Rosemary extracts (with 43% of carnosic acid)	100-mg/kg rosemary extract (100 mg/kg) for 22 days	Oral administration	22Rv1 xenograft mouse xenograft with prostate cancer cells	46% reduction of tumor growth	Induce ER stress proteins and regulates CHOP/ GADD153/BIP pathway of androgen receptor degradation	(Petiwala et al., 2014; Petiwala & Johnson, 2015)
Carnosic acid	0 and 0.02%	Supplemented in diet	HFD mice	Reduction of colon tumors number	Downregulation of Bcl-2 and IAP proteins (XIAP, cIAP1, and cIAP2). Increased expression of cleaved caspase −8, −9, −3, −7, PARP, and PTEN proteins. Increase in Bax protein expression and cytohrome c release	(Kim et al., 2014)
	10-mg/kg body three times a week for 14 weeks	Oral administration	DMBA-induced tumor in Syrian hamsters	Eliminated oral carcinoma	Inhibit lipid peroxidative potential and modulating effect on carcinogen detoxification enzymes	(Manoharan et al., 2010)
	10-mg/kg body weight per day, on alternate days for 14 weeks	Oral administration-	Oral carcinogenesis induced in Syrian hamsters	Chemoprotective effect with only One (8%) malignant tumor (1.05 mm^3)	ND	(Gomez-Garcia et al., 2013)
Carnosic acid + tamoxifen	30 + 10 mg/kg	Oral administration	Athymic nude mice bearing the established MCF-7		Downregulated antiapoptotic molecules Bcl-2 and Bcl-xl	(Han, Zhou, Huang, & Liu, 2017)

(Continues)

TABLE 6 (Continued)

Extract/ compound	Doses	Route of administration	Model	Effect	Mode of action	Reference
				Strong antitumor action in controlling tumor volume and weight	Upregulated proapoptotic signals Bax and Bad.	
Carnosic acid-rich rosemary extract	2 μg	IP injections	Leukemia model mouse	55% reduction in tumor incidence and tumor formation	Cell cycle arrest in G0 + G1 phase	(Sharabani et al., 2006)
Carnosol	0.1% carnosol	Oral administration	C57BL/6 J/min/+, a colonic tumorogenesis mouse model	Reduced the incidence of intestinal tumors by 46%	Suppress beta-catenin tyrosine phosphorylation Enhance E-cadherin-mediated adhesion	(Moran, Carothers, Weyant, Redston, & Bertagnolli, 2005)
	30 mg/kg	Oral administration	Athymic nude mice having prostate cancer	Inhibited prostate cancer growth by 36%, and 26% decreased serum prostate-specific antigen levels	Decreased protein expression of AR and estrogen receptor-alpha	(Johnson et al., 2010)
	200 mg/kg body wt	IP for 5 days	DMBA-induced mammary tumorigenesis in female rats	Inhibited the in vivo formation of DMBA-DNA adducts by 40%	ND	(Singletary et al., 1996)
	1, 3, or 10 mumol carnosol together with 5 nmol TPA twice weekly for 20 weeks	Applied to the back of mice	12-O-tetradecanoylphorbol-13-acetate (TPA)-induced promotion of DMBA-induced tumors	Inhibited the number of skin tumors per mouse by 38, 63, or 78%	ND	(Huang et al., 1994)
	5 or 10 mg/kg daily, for 7 days	Intraperitoneally	Balb/c mice bearing fibrosarcoma tumors	Suppressed tumor growth	Increases in IFN-γ decreases in IL-10 and IL-4 production and reductions in splenic/tumor-associated Treg cell levels	(Rahnama et al., 2015)
Ursolic acid	0.1, 0.3, 1, or 2 mumol together with 5 nmol TPA for 20 weeks	Topical application twice weekly	12-O-tetradecanoylphorbol-13-acetate (TPA)-induced promotion of DMBA-induced tumors	Inhibited the number of tumors per mouse by 45–61%	ND	(Rahnama et al., 2015)

Abbreviations: AR, androgen receptor; ER, endoplasmic reticulum; HFD, high-fat diet; IFN-γ, interferon gamma; IL, interleukin; IP, intraperitoneal.

TABLE 7 In vivo neuroprotective effects of rosemary extracts and its major constituents

Extract/compound	Doses	Route of administration	Model	Effect	Reference
Rosemary tea (2%, w/w)	Equivalent to 130-mg dry extract/kg	Oral administration every day for 4 weeks	Mice	Anxiolytic-like effect	(Ferlemi et al., 2015)
Carnosic acid	20 mg/kg body weight	Oral intubation three times each week for 3 weeks	6-Hydroxydopamine (6-OHDA) induced-Parkinson's disease rat model	Neuroprotection through antiapoptotic and antioxidant action	(Wu et al., 2015)

TABLE 8 In vivo skin protection effects of rosemary extracts and its major constituents

Extract/ compound	Doses	Route of administration	Model	Effect	Reference
Rosemary and citrus extracts combination	250 mg per day	Oral administration	Human volunteers	Stronger protection was achieved after 12 weeks (56%)	(Perez-Sanchez et al., 2014)
Standardized defatted rosemary extract	50, 100 mg, and a transferosome formulation containing 20-mg extract	Topical application	UVB-irradiated mice	50 and 100 mg significantly inhibited metalloproteinase (MMP-2 and MMP-9) gene expression and recorded low wrinkle scores together with a moderate decrease in epidermis thickness with no pigmentation	

Abbreviation: UVB, ultraviolet B; MMP, matrix metallopeptidase.

TABLE 9 In vivo memory enhancement effects of rosemary extracts and its major constituents

Extract/ compound	Doses	Route of administration	Model	Effect	Reference
Rosmarinic acid	0.25 mg/kg	Intraperitoneal administration	Memory impairment in a mouse model induced by acute ICV injection of Abeta (25–35)	Prevents memory impairments	(Alkam, Nitta, Mizoguchi, Itoh, & Nabeshima, 2007)
Rosmarinic acid	16 and 32 mg/kg	Oral administration	Scopolamine-induced cognitive dysfunction in male Wistar rats	Restored learning and scopolamine-induced memory deficits	(Hasanein & Mahtaj, 2015)
Water-ethanol (1:1) extract of rosemary Rosmarinic acid	200 mg/kg 10 mg/kg	Oral administration	Scopolamine-induced cognitive dysfunction in male rats	Inhibit acetylcholinesterase activity and promote butyrylcholinesterase activity in the hippocampus and frontal cortex	(Ozarowski et al., 2013)
Rosemary essential oil		Inhalation in classroom	Secondary school students	Increased numbers memorization	(Filiptsova et al., 2018)
Rosemary essential oil		Inhalation in classroom	Secondary school students	Significantly increased image memory and numbers memorization compared with controls	(Filiptsova et al., 2017)
SRM extract	Equivalent to a daily dose of 5 g of plant material in a single dose for 2-weeks	Oral administration	A double-blind, randomized, placebo-controlled pilot study	Supported verbal episodic memory in healthy subjects having ages under 63 years	(Perry et al., 2018)

Abbreviation: ICV, intracerebroventricular injection; SRM, Salvia officinalis L., Rosmarinus officinalis L. and Melissa officinalis L.

The most often observed mechanisms of action include acetylcholinesterase activity inhibition and butyrylcholinesterase activity stimulation in the hippocampus and frontal cortex and mRNA butyrylcholinesterase expression decrease in the cortex and a simultaneous increase in the hippocampus (Ozarowski et al., 2013). The antiamnesic effects of rosmarinic acid have also been reported as deriving from its ability to decrease acetylcholinesterase and improve central cholinergic neurotransmission as a main regulatory mechanism in learning and memory processes (Alkam et al., 2007; Hasanein & Mahtaj, 2015; Iuvone, De Filippis, Esposito, D'Amico, & Izzo, 2006).

5.7 | Antidiabetic effect

Rosemary extracts have shown marked antidiabetogenic effects (Table 12), mostly through lowering blood glucose and increasing serum insulin levels in diabetic rabbits (Bakirel, Bakirel, Keles, Ulgen, & Yardibi, 2008). It also present a remarkable ability to reduce lipid peroxidation; activate serum antioxidant enzymes, such as SOD and catalase (Bakirel et al., 2008); and even reduce total cholesterol (TC) and triglycerides (TG) and enhance serum high-density lipoprotein-c and decrease low-density lipoprotein-c, besides to markedly improve glucose tolerance and insulin sensitivity in a dose-dependent manner in mice (Wang et al., 2011; Xie et al., 2016). Also, rosemary oil has also shown to prevent alloxan-induced weight loss and liver and kidney weight increase, besides to promote glucose level reduction, liver and kidney function, and reverse lipoperoxidation and the decrease in catalase, SOD, Cu/Zn-SOD, Mn-SOD, and Fe-SOD (Selmi et al., 2017). Given this insight, and because sterol regulatory-element binding proteins (SREBPs) are master regulators in fatty acids, TG and TC biosyntheses (Goldstein, DeBose-Boyd, & Brown, 2006), there would be beneficial effects in lipid homeostasis after SREBPs inhibition, either by gene silencing (Liang et al., 2002) or small chemical inhibitors (Tang et al., 2011; Zhao et al., 2014). Indeed, rosemary can inhibit SREBP-1c and SREBP-2, as well as their target genes in a dose-dependent manner in liver tissues. Inhibitory effects have also been stated in α-amylase (Funke & Melzig, 2006), pancreatic lipase, hormone-sensitive lipase (Bustanji et al., 2010), and dipeptidyl

TABLE 10 In vivo antidiabetic effects of rosemary extracts and its major constituents

Extract/ compound	Doses	Route of administration	Model	Effect	Reference
Ethanolic extract of the rosemary leaves	200 mg/kg	Oral administration	Alloxan-diabetic rabbits	Lowered blood glucose level and increased serum insulin concentration	(Bakirel et al., 2008)
Rosemary petroleum ether fraction	75 and 150 mg/kg per day	Orally administered	C57bl/6 mice western type diet	Reduced elevated fasting blood glucose, total cholesterol, and triglycerides	(Xie et al., 2016)
Rosemary EO	(30 mg/kg) for 15 consecutive days	Intraperitoneal administration	Alloxan-induced diabetes rats	Prevented weight loss and reduced glucose level, reversed lipoperoxidation, and reestablished liver and kidney functions	(Selmi et al., 2017)
Rosemary aqueous extract and EO	Rosemary aqueous extract: Intraperitoneal injection of 0.2 ml at a dose of 10% for 3 days and EO: Topical application of 25 ul/excision wound, twice a day for 3 days.	Topical application	Alloxan-induced diabetic Balb/c mice having two full-thickness round wounds created in the dorsal area of each mouse	Healing diabetic wounds	(Abu-Al-Basal, 2010)
Rosmarinic acid	100 or 200 mg/kg per day for 8 weeks	Oral administration	Uninephrectomized diabetic rats	Ameliorated diabetic nephropathy	(Tavafi et al., 2011)
Carnosic acid	15 mg/kg per d and 30 mg/kg per day for 14 weeks	Oral administration (gavage)	*db/db* mice (having nephropathy due to long-term hyperglycemia)	Reduced water uptake and urine volume, attenuated diabetes-induced albuminuria, increased urine creatinine, and improved glomerular sclerosis and mesangial expansion	(Xie et al., 2018)

Abbreviation: EO, essential oil.

peptidase IV and protein tyrosine phosphatase 1B (Bower, Real Hernandez, Berhow, & de Mejia, 2014) activities. Rosemary extract is also able to promote hepatocyte (HepG2) glucose consumption and glycolytic rate in a dose-dependent manner and decrease the cellular glycogen content (Prudente et al., 2013).

Concerning diabetic complications (Table 10), the topical application of rosemary EO has revealed high activity in healing diabetic wounds more than oral aqueous extract (Abu-Al-Basal, 2010). Moreover, rosmarinic acid can ameliorate diabetic nephropathy, thus reducing glomerular hypertrophy and number loss and glomerulosclerosis (Tavafi, Khalatbari, & Tamjidipoor, 2011). On the other hand, carnosic acid showed to be able to attenuate diabetes-induced albuminuria, increase urine creatinine, and then improving glomerular sclerosis and mesangial expansion in *db/db* mice. Similarly, it also was shown to improve kidney damage, inhibit the expression of profibrotic factors (e.g., transforming growth factor-β1, fibronectin, and E-cadherin), and promote glucose-lowering effects.

The rosmarinic acids antiglycation effects are also highly prominent, suggesting that besides its clear antidiabetic action, it could confer hepatoprotection in diabetic conditions (Wen & Yin, 2017) and as a muscle glucose homeostasis regulator (Selmi et al., 2017; Vlavcheski, Naimi, Murphy, Hudlicky, & Tsiani, 2017). Rosmarinic and carnosic acids, given together, also confer clear anti-inflammatory and protective effects against tissue damage, for example, abdominal aorta (Ou, Huang, Zhao, Du, & Wang, 2018; Samarghandian, Borji, & Farkhondeh, 2017). Also, it is worth to note that the pharmacological effects of rosemary and its isolated compounds have been tackled in metabolic syndrome (Hassani, Shirani, & Hosseinzadeh, 2016); thus, their mechanisms in this plethora of health conditions should be very well-documented by in vitro and in vivo but mostly clinical studies.

5.8 | Antilipidemic effect

As highlighted, remarkable antilipidemic effects have been attributed to rosemary (Table 11).

The inhibition of weight and fat mass gain, the stimulation of fecal lipid excretion, and reduction of liver TG and TC contents are among

TABLE 11 In vivo antilipidemic effects of rosemary extracts and its major constituents

Extract/compound	Doses	Route of administration	Model	Effect	Reference
RE	0.25% in the diet	Supplemented in diet	HFD mice	Inhibited weight gain, inhibited fat mass gain, induced higher fecal lipid excretion, and reduced liver triglycerides content	(Harach et al., 2010)
Standardized RE	0.5% in the diet	Supplemented in diet	HFD-fed male C57BL/6J mice	Reduced plasma cholesterol levels	(Ibarra et al., 2011)
RE enriched with 40% carnosic acid	0.5% of the diet	Supplemented in standard chow diet	Obese (fa/fa) and lean (fa/+) female Zucker rats	Inhibit lipase activity in the stomach	(Romo Vaquero et al., 2012)
Rosemary water-soluble extract	100 mg/kg	Oral administration	Female Balb/c mice	Reduced plasma total cholesterol, low-density lipoprotein cholesterol, and triglycerides levels	(Al Sheyab, Abuharfeil, Salloum, Bani Hani, & Awad, 2012)
Rosemary water-soluble extract contains 1.87% rosmarinic acid (Afonso et al., 2013)	70 and 140 mg/kg	Gavage	Diet-induced	hypercholesterolemic rats	Significantly reduced total serum cholesterol and non-HDL-c levels
Carnosic acid	20 mg/kg	Oral administration	HFD-fed mouse model	Prevent weight gain and accumulation of epididymal fat. Lower serum triglyceride reduction	(Ninomiya et al., 2004)
	0.05%, w/w	Added in standard chow diet	Male *ob/ob* mice (obese leptin-deficient mice)	Inhibited weight gain and visceral adiposity, reduced serum triglyceride and cholesterol levels, and significantly improved glucose tolerance	(Wang et al., 2011)

Abbreviations: HDL, high-density lipoprotein; HFD, high-fat diet; RE, rosemary extract.

TABLE 12 In vivo gastroprotective effects of rosemary extracts and its major constituents

Extract/ compound	Doses	Route of administration	Model	Effect	Reference
Rosemary leaves aqueous extract	10 ml/kg daily 30 min before acrylamide administration for 4 weeks	Oral administration	Acrylamide-induced gastric toxicity of adult male albino rats	Gastro-protective effect through reducing oxidative stress, apoptosis and inflammation as well as accelerating the healing process	(El-Mehi & El-Sherif, 2015)
70% rosemary ethanol extract	500 and 1,000 mg/kg	Oral administration	Ethanol-induced gastric ulcers in rats	Induced high gastroprotective effects	(Dias et al., 2000)

the most prominent, directly attributed to its ability to inhibit both gastric and pancreatic lipases, thus limiting lipid absorption (Al Sheyab et al., 2012; Harach et al., 2010; Ibarra et al., 2011). These effects have been mostly attributed to carnosic acid and carnosol (Romo Vaquero et al., 2012) and even to phenolic compounds acting as strong antioxidants (Afonso et al., 2013; Ninomiya et al., 2004). Also, and specifically to carnosic acid, besides being able to inhibit weight gain, it displays a marked inhibition of hepatic and visceral fat accumulation, improves glucose tolerance, and even decreases the serum alanine aminotransferase levels and adipocyte size, thus inhibiting adipocyte hypertrophy (Wang et al., 2011).

5.9 | Anti-inflammatory effect

Rosemary and its components, especially rosmarinic acid, have also been reported as good neuroinflammatory modulators and, thus, may be potential candidates in neuropathic pain therapy and different inflammation-associated neurological disorders. These aspects sustain the antinociceptive properties of rosmarinic acid (Rahbardar, Amin, Mehri, Mirnajafi-Zadeh, & Hosseinzadeh, 2018; Rocha et al., 2015). The levels of some spinal inflammatory markers, such as COX-2, prostaglandin E2, IL-1β, MMP-2, NF-κB, mitogen-activated protein kinases, iNOS expression, TNF-α, myeloperoxidase activity, and nitric oxide (NO) production were already assessed in several animal models of neuropathic pain. Beyond rosmarinic acid, carnosol, carnosic, betulinic, and ursolic acids have been directly linked to the anti-inflammatory effects of rosemary (Altinier et al., 2007; Arranz et al., 2015; Bai et al., 2010; Beninca, Dalmarco, Pizzolatti, & Fröde, 2011). To flavonoids, remarkable effects such as spasmolytic, arthritic, and on gout affections have been stated (Gomez-Coronado, Ibanez, Ruperez, & Barbas, 2004). The volatile aroma compounds (e.g., 1,8-cineole, borneol, and camphor) seem also to be the determinant to the anti-inflammatory activity (Ehrnhofer-Ressler et al., 2013). Specifically, carnosol and rosemary oil inhibited the adhesion of TNF-α-induced monocytes to endothelial cells and suppressed the expression of intercellular adhesion molecule at the transcriptional level in vitro (Lian et al., 2010).

5.10 | Gastroprotective effect or antiulcerogenic effect

Rosemary is also able to inhibit the ulcerative lesion, as it acts as a gastroprotective agent (Table 12), exerting a potent anti-inflammatory activity in the gastric mucosa, thus reducing swelling and preventing the inflammatory cells infiltration (Amaral et al., 2013; Dias, Foglio, Possenti, & de Carvalho, 2000). Among other rosemary constituents, carnosic and rosmarinic acids have been pointed as responsible for this effect by distinct mechanisms (Amaral et al., 2013; Asokkumar, Sen, Umamaheswari, Sivashanmugam, & Subhadradevi, 2014; Dias et al., 2000). However, some minor constituents may also contribute synergistically to the antiulcerogenic activity (Amaral et al., 2013).

5.11 | Hepatoprotective effect

The hepatoprotective effects of rosemary and its diterpene carnosic acid have also been reported (Table 13).

As most pronounced effects, they can improve the liver detoxication enzymes, such as glutathione S-transferase, UDP-glucuronosyltransferase, particularly UGT1A6, and NAD(P)H-quinone reductase activities (Debersac et al., 2001; Singletary et al., 1996), to modulate cytochrome P450 (CYP), decrease the DNA damages, and even decline the increased aspartate transaminase, alanine transaminase, and alkaline phosphatase activities and restore the reduced levels of TC and TG. Also, it decreases lipid peroxidation, increases the liver/body weight ratio, and exerts strong free radicals scavenging effects in all tissues, except in heart and kidney tissues, also avoiding physiological and histopathological changes (Al-Attar & Shawush, 2015).

5.12 | Miscellaneous activities

Besides to the abovementioned remarkable effects of rosemary, some studies have also shown that it displays interesting antiviral (Aruoma et al., 1996; Nasr-Eldin et al., 2017), insecticidal (Isman, 2016), anthelmintic (Zoral, Futami, Endo, Maita, & Katagiri, 2017), antivenom (Salama, Abdel-Aty, & Fahmy, 2018), reproductive

TABLE 13 In vivo hepatoprotective effects of rosemary extracts and its major constituents

Extract/compound	Doses	Route of administration	Model	Effect	Reference
RE and its diterpene Carnosic acid (Car)	RE: 0.25 to 1.0%, w/w Car: Car at 0.01–1.0%, w/w RE: 200 mg/kg Car: 100–400 mg/kg	Supplied in diet Intraperitoneal	Female rats	Enhance liver GST and QR activities	(Singletary et al., 1996)
DL, EO, and DCM WE	0.5% (w/w)	Supplied in diet	Male Wistar rats	EO had induced CYP, particularly CYP2B; and WE enhanced both CYP and detoxication enzymes. DCM acted as a monofunctional inducer, inducing GST, NAD(P)H: QR and UGT, particularly UGT1A6	(Debersac et al., 2001)
Rosemary EO	0.125%, 0.25% and 0.5%	Supplied in drinking water	DNA damage induced in rat hepatocytes by genotoxins	Free radical-scavenging activity	(Horváthová, Slameňová, & Navarová, 2010)
Ground rosemary leaves	1% w/w	Supplied in diet	CCl_4 induced hepatotoxicity in Wistar rats	Prevent the increased AST, ALT, and ALP activities and restoring of the reduced levels of serum cholesterol and triacylglycerides	(Botsoglou et al., 2010)
Rosemary leaves aqueous extracts in combination with olive leaves aqueous extract	200 mg/kg body weight per day for 12 weeks	Oral administration	TAA-induced liver in Wistar male rats	Antioxidant activity through inhibition of physiological and histopathological changes induced by TAA	(Al-Attar & Shawush, 2015)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DCM, dichloromethane extract; DL, dried leaves; EO, essential oil; GST, glutathione S-transferase; QR, quinone reductase; RE, rosemary extract; TAA, thioacetamide; UGT, UDP-glucuronosyltransferase; WE, water-soluble extract.

promotion (Attia et al., 2017; Heidari-Vala et al., 2013; Nusier, Bataineh, & Daradkah, 2007), radioprotective (Ghoneim & Arafat, 2016), bone protective (Putnam, Scutt, Bicknell, Priestley, & Williamson, 2007), myogenic (Şengül, Çelebİ, Gelen, & Çinar, 2017), antinociceptive (Gonzalez-Trujano et al., 2007; Martinez, Gonzalez-Trujano, Chavez, & Pellicer, 2012), antidepressant (Machado et al., 2009; Machado et al., 2012; Sasaki, El Omri, Kondo, Han, & Isoda, 2013), and antithrombotic (Naemura, Ura, Yamashita, Arai, & Yamamoto, 2008; Yamamoto, Yamada, Naemura, Yamashita, & Arai, 2005) effects (Table 14).

6 | CLINICAL EFFECTIVENESS OF ROSMARINUS PLANTS IN HUMANS

The above-summarized preclinical studies reflect the innumerable potentialities of rosemary extracts and its isolated components, especially diterpenes, flavonoids, and phenolic acids. Antioxidant, antimicrobial, antitumor, anti-inflammatory, skin protective, hypolipidemic, hypoglycemic, and neuroprotective effects comprise the most prominent and deepened ones. Also, and considering that rosemary is easily absorbed through the gastrointestinal tract, it has been subjecting to a large array of clinical studies, with the most important ones detailed herein. There are several completed performed on several diseases using rosemary extract/compounds (Table 15). The clinical trials that had compounds where rosemary was used as flavoring were not included.

6.1 | Antimicrobial effect

Dental caries remains the most prevalent and costly oral infectious disease worldwide. The use of EOs and their isolated constituents with potential antibacterial activity have been employed to prevent this biofilm-dependent disease. *R. officinalis* is among the most promising species with antibacterial potential against cariogenic bacteria, thus opening new paths for further clinical studies using the EOs and their isolated constituents (Freires, Denny, Benso, de Alencar, & Rosalen, 2015). Gingivitis is a highly prevalent periodontal disease resulting from microbial infection and its subsequent inflammation. A randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy of a polyherbal mouthwash containing hydroalcoholic extracts of

TABLE 14 In vivo miscellaneous effects of rosemary extracts and its major constituents

Extract/compound	Doses	Route of administration	Model	Effect	Reference
Aqueous rosemary extract	5-, 10-, 15-, 20-, 40-, 60-, 80-, and 100-ml/100 g feed	Supplemented in fish diet	Anthelmintic against monogenean (*Dactylogyrusminutus*)	Prevention and control of monogenean infection	(Zoral et al., 2017)
Rosemary leaves aqueous extract	(1:5, 1:10, 1:20, and 1:40)	Injected dorsally and intradermally	Mice injected with Egyptian *Cerastes cerastes* (Cc) viper venom	Antivenom effect through reduction of lethality, hemorrhage, edema, muscle, and liver toxicities induced by Cc venom	(Salama et al., 2018)
Rosemary leaves	5 g/kg	Supplied in diet	Rabbit bucks	Improved semen quality and fertility	(Attia et al., 2017)
Rosemary leaves	500 mg/kg	Oral administration	Adult Sprague–Dawley male rats	Reduced fertility in female rats and declined spermatogenesis in male rats	(Nusier et al., 2007)
Rosemary leaves aqueous extract	220 mg/10 ml	Oral administration	Rats exposed to mobile phone	Protective role against this harmful effect and structural changes at the level of light and electron microscopic examination	(Ghoneim & Arafat, 2016)
Rosemary ethanol extract (aerial parts)	10–300 mg/kg	Oral administration	Acetic acid-induced writhing in mice	The antinociceptive effect through reduction of the number of writhing movements	(Gonzalez-Trujano et al., 2007)
The hydroalcoholic extract of rosemary stems and leaves	10 mg/kg	Oral administration	Mice	Exerted antidepressant activity	(Machado et al., 2009)
Rosemary tea	(2%, w/w)	Oral administration	Adult male mice	Reduced anxiety	(Ferlemi et al., 2015)
Rosemary essential oil	Sachets	Oral administration	Human	Reduced anxiety	(McCaffrey, Thomas, & Kinzelman, 2009)
Rosemary dried leaves	5% and 0.5%	Supplemented in diet	C57BL/6 mice	Inhibited arterial thrombus formation	(Naemura et al., 2008)

TABLE 15 Main clinical trials performed on Rosemary essential oils, extracts or components

Drug	Administration route	Dose	Disease	Outcome	Reference
Polyherbal mouthwash containing hydroalcoholic extracts of *Zingiber officinale*, *Rosmarinus officinalis* and *Calendula officinalis* (5%, v/w)	Mouthwash	Mouthwash twice a day (after breakfast and dinner) for 30 s for a period of 2 weeks	Gingivitis	Treat gingivitis with efficacy comparable with that of chlorhexidine mouthwash	(Mahyari et al., 2016)
1:1 combination of rosemary (phenolic content of 57.16 gallic acid equivalent per 100-g dry weight) and citrus extracts (22.57 gallic acid equivalent per 100-g dry weight)	Oral	Daily oral consumption of 250 mg for 8–12 weeks	Skin photoprotection	Photoprotection	(Perez-Sanchez et al., 2014)
Meta050, a patented mix of reduced iso-alpha-acids from hops, rosemary extract, and oleanolic acid	Oral	440 mg and three times per day	Pain	Pain relief in patients with rheumatic disease	(Lukaczer et al., 2005)
NG440, a mix of rho iso-alpha acids from hops, rosemary, and oleanolic acid	Oral	Less than or equal to 250 mg/kg per day for 21 days	Pain	Reduce pain in patients with joint discomfort through lowering inflammatory cytokine releasing, including PGE-2 generation	(Minich et al., 2007)
Rosemary essential oil	Aerosol	10× and 1,000× dilution with odorless propylene glycol	Salivary FRSA	Enhance FRSA and decrease the stress hormone, cortisol, which protects the body from oxidative stress	(Atsumi & Tonosaki, 2007)
A supplement containing 0.02% rosemary extract, 0.001% vitamin E, and 0.3% omega-3 polyunsaturated fatty acids	Oral	Meat products (100 g per day, 3 days a week) for a 12-month treatment	Type 1 diabetic children	Restore glycine catabolism-related metabolites (guanidinoacetate and creatinine) and increase in diabetics due to insulin impairment	(Balderas et al., 2010)
R. officinalis essential oil	Oral	Dropping 1 ml every 8 hr on sugar for 72 weeks	Hypertension	Both blood pressure variables of systolic and diastolic blood pressure levels reflect the clinically significant antihypotensive effect	(Fernandez et al., 2014)
Rosemary extracts: Consisting of active substances carnosol (0.97 mg), carnosic (8.60 mg), and rosmarinic acid (10.30 mg).	Oral	77.7 mg for 3 weeks	Atherosclerosis	Decreased endothelial dysfunction and level of serum plasminogen activator inhibitor-1	(Sinkovic et al., 2011)
Rosemary scent/ medicine flower rosemary Spain (10-ml bottle)	Aerosol	Three drops of diluted rosemary essential oil (five drops aromatherapy per 30-ml distilled water)	Physiology and mood state following an anxiety-provoking task	Moderate different aspects of mood	(Burnett et al., 2004)
100% powdered rosemary (*R. officinalis* L.)	Oral	Daily received a single 16-oz (458 ml) drink of reduced	Cognitive function	Improve cognitive function in an elderly population	(Pengelly et al., 2012)

(Continues)

TABLE 15 (Continued)

Drug	Administration route	Dose	Disease	Outcome	Reference
		sodium tomato juice 750-mg dose			
Capsules containing rosemary (1.7 g)	Oral	Single administration	Attention and cognitive tasks	Enhanced attention and improved cognitive tasks	(Lindheimer et al., 2013)
Rosemary essential oil	Aerosol	Four drops of the oil were applied to a diffuser pad for a "Tisserand aroma-stream"	The olfactory impact	Objective effects on cognitive performance and subjective effects on mood	(Moss et al., 2003)
Rosemary essential oil	Aerosol (the oils were placed on a piece of gauze in diffusers with an electric fan)	0.08-ml rosemary essential oil in the morning from 9 to 11 hr for 28 days	Dementia in Alzheimer's disease	Nonpharmacological effective therapy for dementia with potential for improving cognitive function, especially in Alzheimer's disease patients	(Jimbo et al., 2009)
Rosemary essential oil	Massage	Aromatherapy massage for 6 weeks	Anxiety and depression	Decreased anxiety and/or depression	(Wilkinson et al., 2007)
Rosemary essential oil	Inhalation	3 min of aromatherapy	Mood and anxiety	Decreased frontal alpha and beta power and increased alertness.	(Diego et al., 1998)
Rosemary essential oil (15 ml tap water and 10 drops of the essential oil)	Inhalation	Spread oil particles in the room for 10 min	Short-term memory	Increase the image memory and the numbers memorization	(Filiptsova et al., 2017; Filiptsova et al., 2018)
Combination of sage, rosemary and melissa (*Salvia officinalis* L., *R. officinalis* L., and *Melissa officinalis* L.; SRM)	Oral	5-ml SRM ethanol extract diluted in warm water, 2x per day for 2 weeks	Memory and brain function	Improved delayed word recall in the under 63-year age group	(Perry et al., 2018)
Essential oils (thyme, rosemary, lavender, and cedarwood) in a mixture of carrier oils (jojoba and grapeseed)	Massage scalp	Daily for 7 months	Alopecia aerates	Effectively treat 44% of patients	(Hay et al., 1998)

Abbreviations: FRSA, free radicals scavenging activity; PGE-2, prostaglandin E2.

Zingiber officinale, *R. officinalis*, and *Calendula officinalis* (5%, v/w) compared with chlorhexidine and placebo mouthwashes in 60 subjects with gingivitis. Polyherbal mouthwash was effective in the gingivitis treatment, no adverse reactions were reported, and its efficacy was comparable with the standard chlorhexidine mouthwash (Mahyari et al., 2016).

6.2 | Skin diseases protective effect

UV radiation is the major cause of photoaging and skin cancers. A diet enriched in certain plants may significantly contribute to lifelong protection of skin health against excessive sun UV exposure. A 1:1 combination of rosemary (phenolic content of 57.16 gallic acid equivalent per 100-g dry weight) and citrus extracts (22.57 gallic acid equivalent per 100-g dry weight) was used to inhibit UV harmful effects in human volunteers after oral intake. Daily oral consumption of 250 mg of the combination by human volunteers revealed a significant minimal erythema dose increase after 8 weeks (34%). Stronger protection was achieved after 12 weeks (56%). Thus the combination may be considered as an oral photoprotection ingredient (Perez-Sanchez et al., 2014). Thus the oral administration of citrus flavonoids, rosemary polyphenols, and diterpenes has strong potency for skin photoprotection (Perez-Sanchez et al., 2014). As previously stated, skin photodamage upon UV exposure is followed by the upregulation of MMP-1. Using a 3-D skin model exposed to solar simulated radiation, anti-MMP-1 activity was confirmed together with a photoprotective effect at the morphological level. Thus, from the molecular to the tissue level, these results illustrate the ability of *R. officinalis* extract to inhibit UV-induced MMP-1 and prevent skin photodamage (Martin et al., 2008).

6.3 | Inflammation and oxidative stress

R. officinalis has been used in folk medicine to alleviate rheumatic pain, stomachache, and dysmenorrhea. In a related study on humans, the bioavailability of some herbs and spices after consumption was assessed by analyzing their antioxidant potential upon human lymphocytes and their effect on inflammatory biomarkers expression in activated THP-1 cells (human leukemic monocytes). Thus, blood was drawn from subjects before and after (1 hr) herbs consumption. Subjects' serums were analyzed for antioxidant capacity of ingested herbs, and human peripheral blood mononuclear cells were tested for DNA strand breaks. THP-1 cells were treated with subject serum, and relative quantities of the inflammatory cytokines (TNF-α, IL-1α, and IL-6) mRNAs were analyzed. Among the herbs that protected human peripheral blood mononuclear cells against DNA strand breaks was rosemary, which significantly reduced oxidized low-density lipoprotein-induced expression of TNF-α in THP-1 cells. These data support the rosemary antioxidant and anti-inflammatory capacities (Percival et al., 2012). The effects of several EOs, including rosemary, were tested upon pain induced by contact heat, pressure, and pain. The individuals indicated that pain intensity and unpleasantness were reduced after lavender and slightly reduced after rosemary application. The author stated that aroma therapy probably does not install a direct analgesic effect but alters the effective assessment of pain experience (Gedney, Glover, & Fillingim, 2004). Moreover, a Meta050, a patented mix of reduced iso-alpha-acids from hops, rosemary extract, and oleanolic acid, was subject to an observational trial for analyzing its efficacy on pain relief in patients with rheumatic disease. A significant decrease in pain of 50% and 40% was observed in arthritis subjects following treatment correlated with a marked decrease in C-reactive protein. These data have suggested that Meta050 administrated according to a precise scheme (440 mg and three times per day) has antipain effects in arthritis subjects (Lukaczer et al., 2005). Another formula, NG440, representing a mix of rho iso-alpha acids from hops, rosemary, and oleanolic acid, was tackled for pain relief in joint illness. Data from a multicenter trial indicated that NG440 reduces pain in patients with joint discomfort, as measured by visual analog scale method, and these effects may be owed to a lowered inflammatory cytokine release, including prostaglandin E2 generation (Minich et al., 2007). However, in rheumatoid arthritis (RA), the search for novel powerful drugs in preventing inflammation and joint destruction with fewer undesirable effects is still a tremendous challenge. Carnosic acid is highly endorsed for its antioxidant and antimicrobial properties, but its effects on RA have not been clarified yet. The effects of carnosic acid were in vitro investigated on osteoclasts and fibroblast-like synoviocytes and in vivo on a collagen-induced arthritis model in Wistar rats. Results showed that carnosic acid suppressed the expression of the proinflammatory marker, including TNF-α, IL-1β, IL-6, IL-8, IL-17, and MMP-3, and decreased the receptor activator of NF-κB ligand expression. Also, carnosic acid was able to inhibit in vitro osteoclastogenesis and bone resorption and protect in vivo against joint damage. All these findings provide not also the evidence that carnosic acid is a promising therapeutic compound for RA treatment but endow with data related to the molecular foundation of its activity (Liu et al., 2018).

On the other hand, a study measuring the total salivary free radicals scavenging activity (FRSA) induced after the smelling of lavender and rosemary EOs found that cortisol, secretory IgA, and α-amylase levels were correlated with aroma-induced FRSA. These results indicate that certain phytocompounds, such as lavender and rosemary, augment FRSA system and diminish the stress hormone, cortisol, protecting the body from oxidative stress (Atsumi & Tonosaki, 2007).

6.4 | Diabetes

As a key strategy to reduce the oxidative damage in diabetes, which contributes to severe complications, interest has grown for natural antioxidants, such as rosemary. In a pilot study enrolling Type 1 diabetic children, the effect of a supplement containing rosemary extract, vitamin E, and omega-3 polyunsaturated fatty acids given in children's diet was investigated. Through a complex metabolomic approach, certain metabolites associated with Type 1 diabetes were detected, such

as guanidinoacetate, creatinine, urea, phenyllactate, p-OH-phenyllactate, phenaceturate, and benzoate, thus allowing to depict a pattern of metabolites before and after rosemary mix treatment. From all the parameters measured at the beginning of the study, that is, glucose, glycosylated hemoglobin (HbA1c), TC, high-density lipoprotein-c, total proteins, TG, creatinine, uric acid, vitamin E, and microalbumin, only glucose and HbA1 were higher in diabetics, and uric acid and total proteins were significantly lower. After a 12-month treatment, the complex analysis revealed some changes in guanidinoacetate, and creatinine, known as glycine catabolism-related metabolites, increased in diabetic patients due to insulin impairment. Thus accumulation of guanidinoacetate observed in diabetic children without diet prevailed over, and catabolism could be restored when supplemented diet was given. It is also important to mention that some metabolites with aromatic ring (phenyllactate, p-OH-phenyllactate, phenaceturate, and benzoate) were significantly changed due to diabetes and/or treatment (Balderas et al., 2010).

6.5 | Cardiovascular diseases

In cardiovascular disease domain, various rosemary extracts have been studied. Heart failure and arrhythmia are symptoms associated with cardiomyocyte hypertrophy and fibrosis (Kong, Christia, & Frangogiannis, 2014), and there are reports on rosmarinic acid as angiotensin-converting enzyme regulator (Li et al., 2008) or as an endothelium-dependent vasodilator (Ersoy et al., 2008). In 2012, Yang et al. (2012) proved that rosmarinic acid could activate peroxisome proliferator-activated receptor gamma inducing an antifibrotic effect. Peroxisome proliferator-activated receptor gamma agonists can activate 5′adenosine monophosphate-activated protein kinase-alpha that have a cardioprotective effect (Konrad et al., 2005; Osman & Segar, 2016). Thus, in 2018, it was shown that rosmarinic acid activates 5′adenosine monophosphate-activated protein kinase-alpha and inhibits Smad3, inducing a positive effect against cardiac hypertrophy and fibrosis (Zhang et al., 2018). In another study, with 72-week length, around 30 patients with diagnosed hypotension were subjected to rosemary oil treatment, and several parameters were investigated: systolic blood pressure, diastolic blood pressure, and scores from physical and mental summary components. Rosemary oil showed marked antihypotensive effects, especially on physical summary component and mental summary component parameters. This prospective study has shown a significant improvement in patients' quality of life, clearly based on the long-term antihypotensive effect displayed by rosemary oil therapy (Fernandez, Palomino, & Frutos, 2014). On healthy volunteers, oral rosemary extracts (77.7 mg) were given for 3 weeks, and various atherosclerotic parameters were studied. After the study period, endothelial dysfunction decreased significantly and was correlated with a decreased level of serum plasminogen activator inhibitor-1 (Sinkovic et al., 2011). In 2004, Burnet et al. (2004) reported that in over 70 individuals, physiological alterations in temperature and heart rate did not differ when evaluating different scents, including rosemary, whereas mood ratings differ following an anxiety-provoking task.

6.6 | Neurological disorders

The plant extract was proven in ancient history to have cognition-enhancing properties. In 2011, a randomized, double-blinded crossover study was performed on around 30 individuals (75 years old) using 750- to 6,000-mg rosemary extract. Memory speed increased significantly using the low dose of rosemary extract, and the highest dose had an impairing effect. Memory speed is correlated with cognitive function during aging, and, remarkably, the culinary dose had the best effect. Thus, this study points out to investigate the long-term effect on cognitive functions (Pengelly et al., 2012). In young adults, a single dose of rosemary was tested for enhanced attention and improved cognitive tasks. In 40 young adults, sustained 16-min dual-task attention was measured. Rosemary induced small, transient reductions in false alarm errors and mental fatigue but not consistent improvements in sustained attention at short term (Lindheimer, Loy, & O, 2013). In infants and adults subjected to various oils, the rosemary group compared with lavender oils had a left frontal electroencephalographic (EEG) shifting in both adults and infants that had greater baselines compared with the right frontal EEG activation (Sanders et al., 2002). In over 140 individuals, the Cognitive Drug Research was performed using lavender and rosemary oils. Lavender decreased the working memory, whereas rosemary significantly enhanced overall memory quality but decreased memory speed. The olfactory properties of the tested EOs can improve cognitive performance, along with a significant influence on overall mood (Moss, Cook, Wesnes, & Duckett, 2003). In Alzheimer's disease patient, aromatherapy was done for 28 days using rosemary and lemon EOs in the morning and lavender and orange EOs in the evening. Patients were assessed in dynamics using various assessment scales and had improved personal orientation on the tested standards. This study confirmed that rosemary extract improved cognitive functions (Jimbo, Kimura, Taniguchi, Inoue, & Urakami, 2009). Also, rosemary oil sachets lowered test anxiety measure, personal statements, and pulse rates (McCaffrey et al., 2009). For anxiety and depression, common symptoms in cancer patients, aromatherapy massages were tested in almost 300 patients. In comparison with usual supportive care, patients receiving aromatherapy massage for 6 weeks decreased significant anxiety and depression and reported an improvement in self-reported anxiety (Wilkinson et al., 2007). Clinical trials for mood and anxiety started in the 1990s, where 40 adults were treated with lavender or rosemary oils; the group that received rosemary displayed decreased frontal alpha and beta power as registered on EEG, signifying increased alertness. This group was also less anxious, more alert, and relaxed and faster in testing their math computations (Diego et al., 1998).

6.7 | Memory enhancement effect

Filiptsova et al. (2017, 2018) studied the effect inhalation of the EOs of rosemary on human short-term memory and compared their effect with a control untreated group. The study was conducted on 79 secondary school students (34 boys and 45 girls and 13–17 years). The

tested EO in each case was placed in a standard Petri dish in the four corners of the class whose volume is 120 m (Ribeiro-Santos et al., 2015). Each Petri dish was filled at the bottom with 15-ml tap water and 10 drops of the tested EO. The time between pouring the EO and the time of the experiment was about 10 min, being enough for spreading the oil particles in the room, and all windows were close to prevent leakage of EO evaporations. It was found that rosemary EOs significantly increase the image memory compared with the control. Rosemary oil still increased the numbers memorization linked to its stimulant effect (Filiptsova et al., 2018). These results were consistent to those obtained in 53 secondary school students (24 boys and 29 girls and 13–15 years), who were exposed in the same manner to rosemary EO, where they found that inhalation of rosemary oil triggered a significant increase in image memory and numbers memorization compared with control (Filiptsova et al., 2017; Filiptsova et al., 2018).

A double-blind, randomized, placebo-controlled pilot study was performed to evaluate the effects of SRM extract, consisting of *Salvia officinalis* L. (sage), *R. officinalis*, and *Melissa officinalis* L. (Melissa) extracts on 44 normal healthy subjects (61 years). Memory was evaluated by assessing the immediate and delayed word recall after SRM extract or placebo (*Myrrhisodorata* [L.] Scop. ethanol extract, not known to affect brain function) administration. The results indicated that the oral administration of SRM extract in a single dose for 2 weeks is more effective than a placebo in supporting verbal episodic memory. Short- and long-term supplementation with SRM extract merits more robust investigation as an adjunctive treatment for Alzheimer's disease patients and in all aging problems (Perry et al., 2018).

6.8 | Hair loss or alopecia aerates

One of the first trials was at the end of the 90 decades on skin disease, alopecia aerates. For 7 months, over 80 patients were subjected to EOs massage (thyme, rosemary, lavender, and cedarwood) and compared with the placebo group. About 44% of patients had significant improvement when compared with 15% in the control group (Hay, Jamieson, & Ormerod, 1998).

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

In short, the use of rosemary oil for both food and biotechnological purposes seems to be promising. In addition, their application in foodstuff is considered safe at the effectively used levels; thus, it may represent a key alternative to synthetic antioxidants/preservatives, often associated to severe side effects and related toxicity, besides to help in avoiding huge economic losses due to the foodstuffs spoilage along with infections/intoxications that might result from this spoilage. As well, rosemary extracts and several of its components have been tested in recent years due to their potent antioxidant, anti-inflammatory, antiproliferative, and antimicrobial effects. The potential of various dietary agents, like spices and their components, can aid classic drugs in inflammatory pathways suppression, in both cancer prevention and therapy and even other chronic diseases. In the specific case of rosemary, although it has received a Generally Recognized as Safe status, a special attention should still be given to their neurotoxic potential, especially due to its rich content in camphor, verbenone, and α-pinene. These components, although safe when used at recommended doses, may be harmful both in children or in infants and even in sensitive individuals. Adverse skin reactions and acute toxicity may also occur, although rare, and as most of studies did not refer/specify which chemotype was used, the extrapolation and conclusion about the real toxicity of rosemary cannot be definitively stablished here. Thus, as a future perspective, rosemary alone or its isolated active components should be tested in a more in-depth manner, and its antiviral therapeutic approach should also be addressed, given that terpenes-type compounds (e.g., ursolic acid) have been proposed as favorable candidates for anti-HIV agents.

ACKNOWLEDGEMENTS

Martins N. would like to thank the Portuguese Foundation for Science and Technology (FCT–Portugal) for the Strategic Project Reference UID/BIM/04293/2013 and "NORTE 2020—Programa Operacional Regional do Norte" (NORTE-01-0145-FEDER-000012).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work. J.S.-R., P.V.T.F., and N.M. critically reviewed the manuscript. All the authors read and approved the final manuscript.

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How to cite this article: Sharifi-Rad J, Ezzat SM, El Bishbishy MH, et al. *Rosmarinus* plants: Key farm concepts towards food applications. *Phytotherapy Research*. 2020;34: 1474–1518. https://doi.org/10.1002/ptr.6622