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Rosmarinus officinalis L.: A Source of Potential Antimicrobial Agents for Combating Antimicrobial Resistance

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Abstract: Antimicrobial resistance is a global concern that is levying a great economic burden on the global population. Therefore, more studies are needed from the mechanistic point of view to understand and combat antimicrobial resistance. *Rosmarinus officinalis* L. is a perennial shrub belonging to the Lamiaceae family, globally cultivated, and widely used in folk medicine for various ailments. Essential oil from *Rosmarinus officinalis* has been found to be useful in the food processing industries due to its potent antioxidant and antimicrobial properties. Essential oil, phenolics, and diterpenes constitute the major phytoconstituents of *Rosmarinus officinalis*. Furthermore, the major phytoconstituents such as carnosol, carnosic acid, rosmarinic acid, and essential oil exhibit potent antibacterial action against various pathogens and clinical isolates via targeting cell membrane proteins and efflux pumps.. Thus, this review encompasses the various resistance mechanisms equipped by the pathogens and provides an extensive review of the antimicrobial potential of *R. officinalis* extracts and its significant phytoconstituents like essential oil, phenolic diterpenes (carnosol and carnosic acid) and phenolic acid (rosmarinic acid).

Keywords: *Rosmarinus officinalis;* antimicrobial resistance; essential oil; rosmarinic acid; carnosic acid; carnosol.

1. Introduction

The World Health Organization (WHO) has recognized antimicrobial resistance (AMR) as a threatening global concern, and numerous measures have been taken to combat AMR [1]. AMR is the ability of a microorganism to resist and evade the action of antimicrobial agents from inhibiting or killing them. Thus, it renders conventional treatments ineffective, compromising chemotherapy and surgical procedures and levying huge economic and social burdens [1]. The WHO has published a list of 12 bacterial families that need critical attention and has been categorized as medium, critical, and high priority based on the requirement of novel antimicrobials [2]. Among them, the critical group exhibits different patterns of resistance, i.e., multidrug resistance (MDR), extensively drug-resistant (EDR), and pan-drug resistant (PDR) bacterial strains, which could cause critical life-threatening infection with

prolonged illness and hospitalization [3]. According to the Centers for Disease Control and Prevention (CDC) reports, about 2 million people get infected, and 23,000 people die yearly in the USA [4]. It is emphasized that the number of AMR-related deaths could increase by 50 million by 2050 [5]. A greater economic burden of about 100 trillion was levied over Asia and Africa due to AMR-related deaths [6,7]. Thus, these pathogens have evolved to acquire AMR due to various factors such as personal hygiene, food, environmental factors, antibiotics misuse, and poor or insufficient healthcare facilities, which makes AMR a serious concern worldwide [2].

Among the pathogenic organisms, MDR microbes such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Klebsiella pneumoniae*, causing diseases such as meningitis, pneumonia, gonorrhea, have resistant to antimicrobial drugs [8]. Among them, MRSA from clinical samples exhibits increased resistance. Thus, potent antimicrobial agents are necessary to combat the catastrophic effects of AMR in pathogenic microbes.

Rosmarinus officinalis L. (*R. officinalis*), belonging to the Lamiaceae family, is a globally cultivated perennial shrub widely found in Western countries and extensively used in the Mediterranean region [9]. *R. officinalis* has been used as a folk medicine with established antiseptic, anti-inflammatory, antirheumatic, antimicrobial, antioxidant, and antispasmodic activities [10,11]. In addition, the rosemary extracts cause relaxation of smooth muscles and possess hepatoprotective and antitumorigenic activity [12]. Furthermore, due to its antioxidant properties, it has been used as a food preservative and flavoring agent [13]. The review aims to provide insights into the antimicrobial potential of *R. officinalis* and its main constituents and various mechanisms involved in developing antimicrobial resistance.

2. Botanical Description

Rosemary is a woody, perennial shrub with a strong aromatic fragrance, needle-like evergreen leaves, and flowers in different colors like white, purple, pink, or blue. It has various forms that vary from upright to prostrate with multiple stems. The leaves are 2-4 cm long and 2-5 mm broad, with a green-white gradient, and leaves with dense, short woolly hairs. The flowers are purplish white with two long-exerted (protruding) stamens. The fruit consists of four dry nutlets (one-seeded section). The leaves are opposite, with 4-6 leaves grouped in a single axil. The stem is square and woody. There are more than 20 varieties of rosemary plants. These plants are of excellent ornamental and culinary value. This plant grows to cover about 12 inches but rarely gets over six inches tall [14].

3. Traditional uses

In ancient days, rosemary was used as folk medicine. It has been used as an antispasmodic, antiepileptic, antibacterial, analgesic, antirheumatic, carminative, cholagogue, diuretic, expectorant, treatment of dysmenorrhea, relieving respiratory disorders and had improvising effects on human fertility [15]. Orally, it is used to treat dyspeptic complaints.

Externally, it is used as a rubefacient to stimulate hair growth and treat scalp eczema, rheumatic complaints, circulatory disorders, boils, and wounds [12,16]. Essential oils of *R. officinalis* are volatile aromatic oils obtained by steam distillation from fresh leaves and flowering tops of the plant. It is a colorless or pale-yellow liquid having a characteristic odor of the plant and used as an ingredient in cosmetics such as Eau-de-cologne, hair lotion, cold creams, carminative, rubefacient, stimulants, inhalers, soaps, and the leaves are used for flavoring foods as a condiment [17].

4. Bioactive Phytoconstituents

R. officinalis leaves are one of the richest sources of essential oils, and their chemical composition greatly varies based on their geographical location and climatic conditions [18–20]. However, the major and common phytoconstituents include camphor (5-31%), 1,8-cineole (15-55%), α-pinene (9-26%), borneol (1.5-5.0%), camphene (2.5-12.0%), β-pinene (2.0-9.0%), limonene (1.5-5.0%), verbenone (2.2-11.1%), caryophyllene (1.8-5.1%) and myrcene (0.9-4.5%) [21,22]. The plant is also rich in phenolics and terpenes. The terpenic compounds in *R. officinalis* can be classified into phenolic diterpenes and pentacyclic triterpenes.[23] The composition of major secondary metabolites explored in *R. officinalis* is as follows: diterpenes (up to 4.6%): carnosic acid, carnosol, isorosmanol, rosmadiol, rosmaridiphenol, rosmanol, rosmariquinone, triacetylrosmanol, dimethylrosmanol; triterpenes: oleanolic acid (10%), ursolic acid (2-5%), α-amyrin, β-amyrin, epi-α-amyrin, 19-α-ursolic acid, 2-β-hydroxy oleanolic acid, betulin; phenolic acids (2-3%): rosmarinic acid (3.5%), chlorogenic acid, neo-chlorogenic acid, caffeic acid, labiatic acid; flavonoids: luteolin, genkwanin (7-O-methlylapigenin), diosmetin, diosmin, genkwanin-4'-methyl ether, 6-methoxygenkwanin, 6-methyoxyluteolin, 6-methoxyluteolin-7-glucoside, 6-methoxyluteolin-7-methyl ether, hispidulin, apigenin - corresponding glycosides [13,24]. The chemical structures of various chemical constituents of *R. officinalis* are shown in Figure 1.

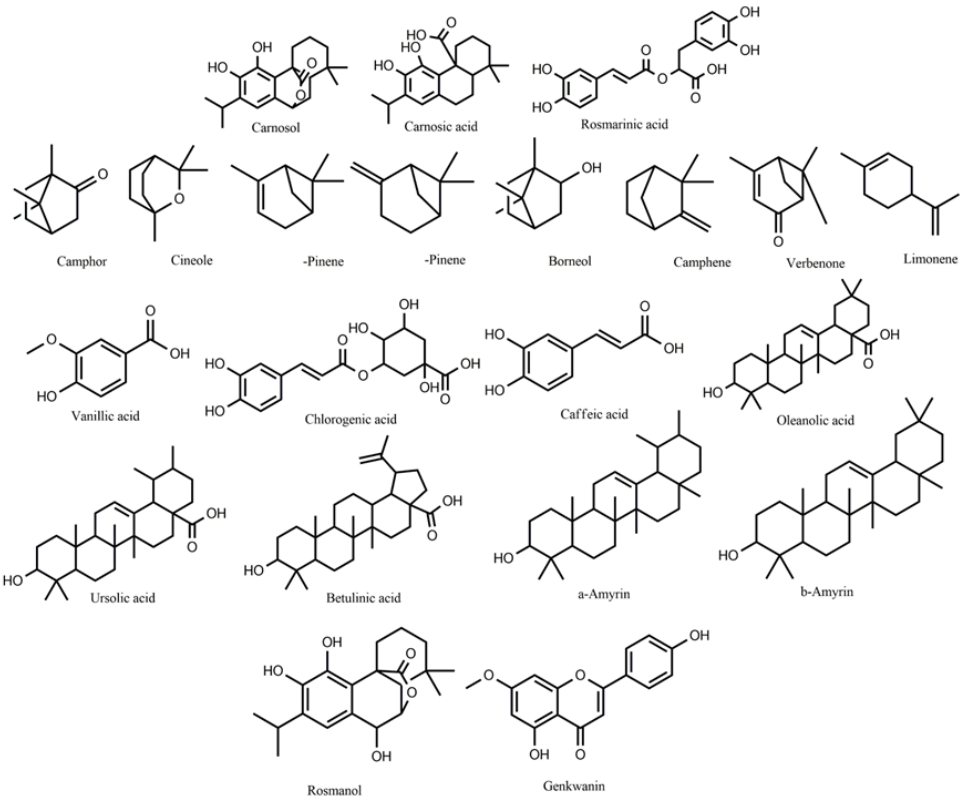

Figure 1. Chemical structure of phytoconstituents from *Rosmarinus officinalis.*

5. Pharmacological activities

A review on the pharmacology of rosemary was published in the year 1999 in which the listed pharmacological actions of rosemary were bronchodilator, smooth muscle relaxant, anti-inflammatory, antioxidant, and anticancer activities [12], as represented in Table 1. Until 2000, there were no reports on the antimicrobial activity of rosemary or its phytoconstituents.

Later, the rosemary extract and its bioactive phytoconstituents were explored for their efficacy as an antimicrobial agent against various pathogens.

Table 1. Pharmacological activities of *R. officinalis* and its bioactive constituents.

S.No	Activity studied for	Pharmacological activity	References
1	Essential oils	Antibacterial	[25–30]
		Antimicrobial	[31–35]
		Anti-inflammatory	[36]
		Antinociceptive	
		Cytotoxicity	[34]
		Colitis	[37]
		Antiproliferative	[25]
		Antioxidant	[38]
		Antilisterial	[39]
2	Carnosic acid	Antimicrobial activity	[40–42]
		Antibacterial	[9,43]
		Antioxidant	[40,41]
		Anti-neuronal stress	[44]
		Anxiolytic	[45]
		Antiulcer	[46]
3	Carnosol	Antimicrobial	[41,47]
		Antioxidant	
		Antibacterial	[9,43]
		Anti-inflammatory Antinociceptive	[48]
		Antiulcer	[46]
		Neuroprotective	[39]
4	Rosmarinic acid	Antimicrobial	[40,41]
		Antibacterial	[43,49]
		Antioxidant	[40,41]
		Neuroprotective	[39]
		Anti-neuronal stress	[50]
5	Eugenol, Farnesol, Benzoic acid, Cinnamic acid	Antimicrobial	
		Neuroprotective	
6	Ursolic acid	Neuroprotective	
7	Salvigenin, Rosmanol and Cirsimaritin	Antidepressant	[51]
		Anxiolytic	
		Antinociceptive	
8	Extract	Antimicrobial	[52]
		Anti-inflammatory and antinociceptive	[48]
		Anti-tumor	[53,54]
		Antioxidant	[52,54–57]
		Antibacterial	[56]
		Anti-diabetic	[57]
		Nephrotoxicity	[58]
		Colitis	[37]
		Antifertility	[59]
		Neuroprotective	[39]
		Antidepressant	[60]
9	Diterpenes	Alzheimer's	[61]
		Hepatoprotective	[62]
10	Total phenolics	Antimicrobial	[63,64]
		Antioxidant	

The present review discusses the antimicrobial studies conducted on rosemary and the mechanistic action of its phytoconstituents against various pathogens.

6. Resistance mechanisms equipped by pathogens

Generally, antimicrobial agents inhibit or disrupt cell wall synthesis, cell membrane function, ribosome or protein synthesis, nucleic acid synthesis, and folate metabolism [65,66]. On the other hand, pathogens acquire or become resistant to antimicrobial agents *via* various evasion mechanisms and techniques. The various mechanisms that are equipped by pathogenic bacteria are represented in Figure 2.

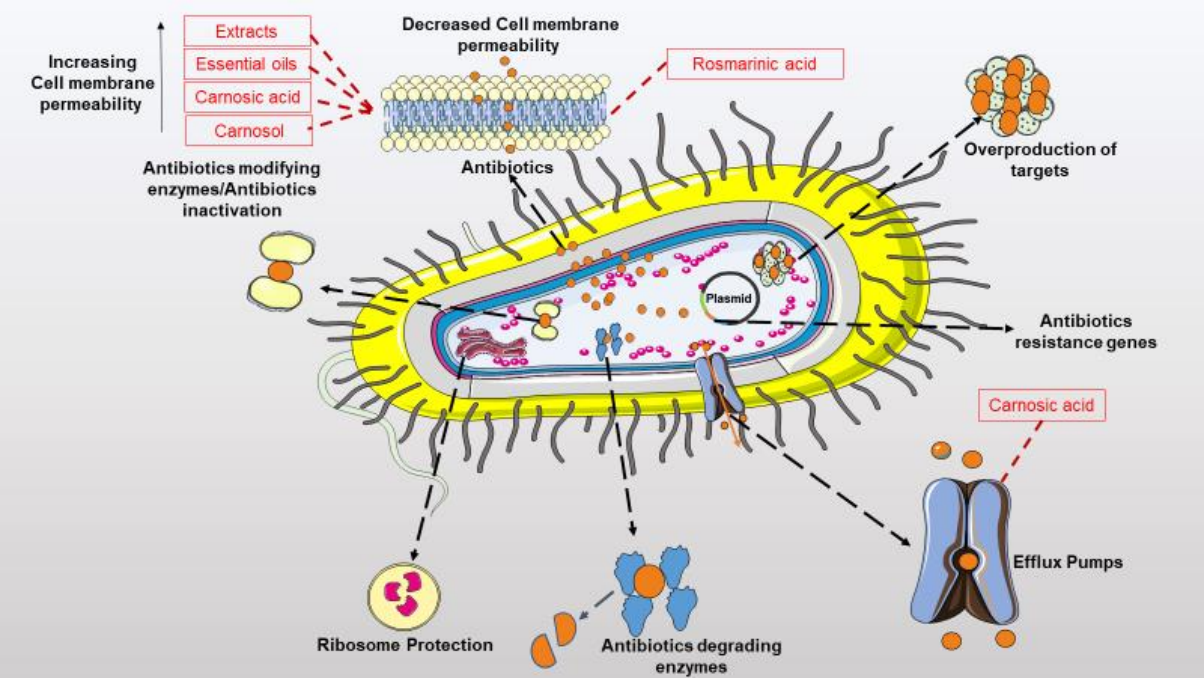

Figure 2. Effect of *Rosmarinus officinalis* extracts, essential oil, and phytoconstituents against antimicrobial resistance mechanisms equipped by pathogens. The extracts, essential oil, and phytoconstituents of *Rosmarinus officinalis* extracts have been shown to inflict antimicrobial action by increasing the cell permeability of the bacterial cell and inhibiting the efflux pump in the pathogens as a mechanism of action.

6.1. Antimicrobial's inactivation or destruction.

Certain pathogenic organisms render the β-lactam antibiotics inactive, acquiring resistance by synthesizing and producing β-lactamases, which breaks the β-lactam ring. Thus, the microbes produce enzymes such as transferases, which disrupt the chemical structure of the antibiotics, and over 1000 β-lactamase enzymes have been isolated till now [67,68]. B-lactamases induce significant antimicrobial resistance to their respective hosts by disrupting the amide bond of β-lactam rings by hydrolysis in antibiotics such as penicillin, Amoxicillin, ampicillin, and ceftazidime. In addition, the resistance to β-lactams is acquired by modulating the penicillin-binding protein (PBP) and modifying the cellular permeability [65,69]. Furthermore, the spread of the β-lactamases gene has facilitated the integration of the resistant genes into the bacteria (Plasmids and transposons) and the rapid transfer between the bacteria [70]. Predominantly, gram-negative bacteria synthesize β-lactamases, a threatening antimicrobial mechanism against β-lactam antibiotics [71,72]. When a molecule with the β-lactam ring comes into use, a new resistance mechanism against the introduced β-lactam drug is discovered. For instance, when the new third-generation cephalosporins were introduced, a plasmid-encoded β-lactamase known as Extendeyyd-Spectrum β-Lactamases (ESBLs) capable of hydrolyzing the drugs were discovered [73,74]. In gram-negative bacteria, β-lactamases of clinical importance include ESBLs and AmpC enzymes, which confer resistance to penicillins

and cephalosporins, not cephamycin and carbapenems [75,76]. Finally, carbapenemases confer resistance to the carbapenems and β-lactams (hydrolyzable) [77]. Thus, novel antimicrobial molecules that can evade the β-lactamases are necessary to overcome the setbacks of AMR.

6.2. Limitation of drug uptake.

Bacteria intrinsically have a difference in the uptake of antimicrobial drugs. The Lipopolysaccharide (LPS) in the cell wall of gram-negative bacteria provides additional resistance to certain molecules compared to gram-positive bacteria. Thus, it imparts a natural resistance to the antimicrobial agents wherein, in the case of bacteria with high lipid content in the outer membrane, it gives easier access to hydrophobic drugs such as fluoroquinolones [78–81]. Certain bacteria, such as mycoplasma, lack cell walls, making them intrinsically resistant to the molecules targeting the cell wall, such as β-lactams and glycopeptides [82]. As known, gram-positive bacteria possess a weak cell wall without an outer membrane that allows the passage of hydrophilic molecules, so restricting access to the drug molecule is not widely common. However, enterococci exhibit resistance against the polar molecules that cross the cell wall, thereby developing an intrinsic aminoglycoside resistance. *S. aureus*, a gram-positive organism, developed resistance against vancomycin, where the mechanism is unknown. Yet, it develops a thickened cell wall that imparts difficulty in transporting drugs across the cell wall. These particular strains were designated as Vancomycin-intermediate *Staphylococcus aureus* (VISA) strains [80,83,84].

Generally, porins facilitate the influx of substances to the cells in bacteria with the larger outer membrane; predominantly, gram-negative bacteria utilize the porins to transport hydrophilic substances [78,83,85]. The type and number of porins affect the organism's susceptibility to antimicrobial drugs [86]. Drug resistance or a decrease in drug uptake can be inflicted by reducing the number of porins and inducing mutation, which can change the porin channel selectivity [79]. Mutations in the porins lead to changes in the molecular structure, size, conductivity, and expression of channels. However, porin changes are considered low-level resistance, but the effect changes when they coexist in synergy with other resistance mechanisms [86]. Reduction in the number of porin channels and mutations in the porin channels have been observed in the members of the *Enterobacteriaceae* and *E. aerogenes*, respectively, and they became resistant to carbapenems, imipenem, and cephalosporins [87]. Thus, limiting the drug uptake by modulating cell permeability and porins plays a crucial role in developing drug resistance.

6.3. Extrusion of drugs using efflux pumps.

Various pathogenic bacterial strains possess efflux pump mechanisms that potentially nullify the antimicrobial effects of drugs. Efflux mechanisms are chromosome-coded or plasmid-coded to the bacteria genes, providing intrinsic resistance to the antimicrobial drugs. The efflux pumps are cytoplasmic energy-dependent channels the bacteria employ to expel the toxic substances from inside the cells. After acquiring the resistance, it expels the antimicrobial agent, nullifying its effects [88].

Levy *et al*. first identified the active efflux of antimicrobials in pBR322 plasmid containing *Escherichia coli* against tetracyclines [89,90]. Over time, various plasmid, chromosome-coded, class-specific, agent-specific, and MDR efflux pumps have been identified, becoming a critical factor of AMR [91]. Several studies confirm that pathogens have

utilized efflux pumps to expel most antimicrobial agents [92]. The efflux pumps that are capable of expelling the antimicrobials are broadly classified into ATP (adenosine triphosphate)- binding cassette (ABC) family, the major facilitator superfamily (MFS), small multidrug resistance (SMR) family, the resistance-nodulation-division (RND) family, and the multidrug and toxic compound extrusion (MATE) family [91,93]. Efflux pumps can expel the antimicrobial agents or compounds without any change or deterioration identified by non-drug-specific proteins, resulting in multidrug resistance [79,94]. Furthermore, it reduces the concentration of the antibiotics below its inhibitory concentration, reducing its effect on the pathogen.

Most efflux pumps are predominantly single-component systems supporting the transportation of substrates across the cytoplasmic membrane. In contrast, RND is a multi-component system that facilitates substrate transportation across the entire cell envelope. In certain instances, in gram-negative bacteria and cellular components, some efflux pumps function as multi-component systems. For example, MacB, which belongs to the ABC superfamily, acts as a tripartite pump in the extrusion of macrolides [95]. MATE and MFS are known to efflux fluoroquinolones in gram-positive bacteria, inflicting inherent resistance against therapeutic antimicrobials [96–98]. In addition, specific efflux transporters such as TetK and MsrA export tetracyclines and macrolides, inducing antimicrobial resistance [9]. Figure 3 shows the structure of different efflux pumps equipped with pathogens.

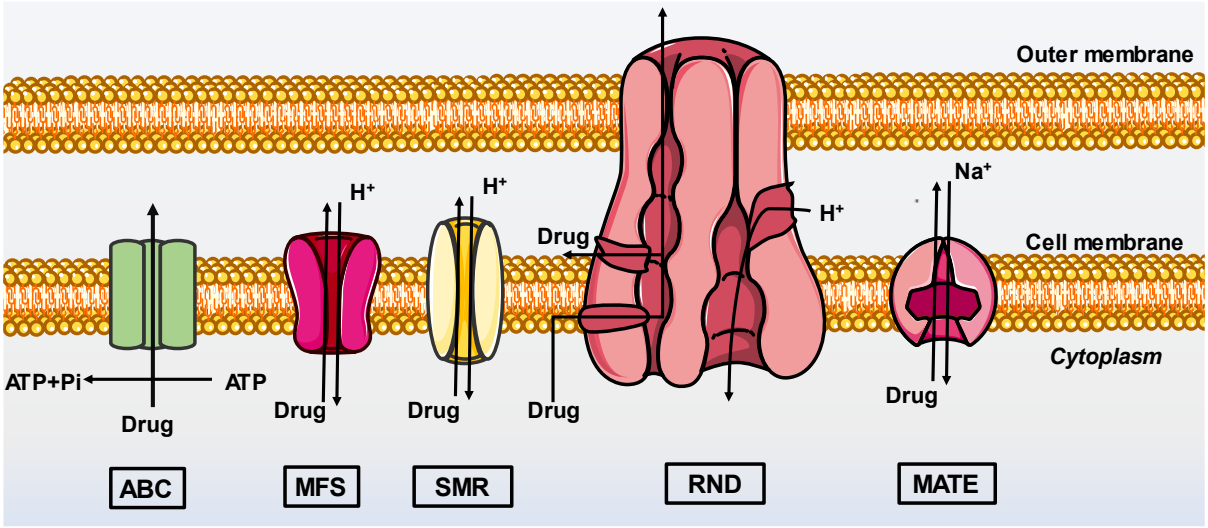

Figure 3. Various types of antimicrobial-resistant efflux pumps. ATP (adenosine triphosphate)- binding cassette (ABC) family, the major facilitator superfamily (MFS), small multidrug resistance (SMR) family, the resistance-nodulation-division (RND) family, and the multidrug and toxic compound extrusion (MATE) efflux pumps.

6.4. Target site alteration.

Drug target site alteration is one of the resistance mechanisms used by the pathogens to counteract the antibiotics by altering the site of action either by mutation of the responsible gene or enzymes, thus rendering the antibiotics inactive or disabling them [99,100]. It can also be said that the targ*et al*teration or modification can also result from the enzymes produced by the bacteria, which are either inductive or constitutive. For instance, the *Streptococcus* sp evades the MLSB (macrolides, lincosamide, and streptogramin B) action via post-transcriptional modification of 23S rRNA, i.e., methylation of N6 amino group in the adenine residue of 23s rRNA, of the 50s ribosomal subunit, thereby blocking protein synthesis [101]. Likewise, erythromycin-resistant bacteria alter the enzyme peptidyl transferase in addition to

efflux pumps as a resistance mechanism against antibiotics. Though the protein synthesis is not affected even after the methylation at the specific amino acid residue but impairs the affinity of antibiotics towards the target site, a key resistant approach exhibited from the clinical isolates of *S. aureus* [102].

6.5. Target site protection.

Ribosome protection proteins (RPPs) confer protection to the ribosomal subunits from the tetracyclines, implicated in both gram-positive and gram-negative bacteria [103–105]. Quinolone resistance is inflicted by Qnr proteins (chromosome or plasmid-mediated), reducing the interaction of topoisomerase IV and bacterial gyrase with DNA by acting as a DNA template, thereby reducing the binding site for quinolones [106]. RPP belongs to the cytoplasmic protein that confers the modification of ribosomal conformation that affects the binding of tetracycline to the ribosome, thereby affecting the drug action of tetracyclines such as minocycline and doxycycline, inducing much more resistance than with bacteria equipped with tetracycline efflux pumps [65]. Even though certain members of the Streptomyces species are gram-positive, they are highly penicillin-resistant due to either overproduction of low-affinity PBPs or PBP [107].

6.6. Overproduction of drug targets.

Overproduction of drug targets can overwhelm the antibiotic concentration, rendering it below its therapeutic doses. Resistance to the sulfonamides is mediated by the drug-resistant forms of the enzyme dihydropteroate synthase (DHPS). The enzymatic action of dihydrofolate reductase (DHFR) is an important factor in the synthesis of dihydrofolic acid, an essential component in amino acid and nucleic acid synthesis, generally inhibited by their analog trimethoprim. Thus, overproduction of DHFR renders the drug ineffective against pathogens [65,88].

6.7. Biofilm formation and quorum sensing.

Biofilm is a community-based microbial resistance against antimicrobial agents, where they get attached and encased in an extracellular matrix of microbial origin. Quorum sensing facilitates the formation of biofilm and communication between bacteria through extracellular signaling molecules known as autoinducers, enhancing cell density and imparting antibiotic resistance that corresponds to the bacteria's population. The formed biofilm inhibits the penetration of antimicrobial drugs through the biofilm matrix, efflux pump, and quorum sensing. The efflux pump further facilitates the resistance in the biofilm by blocking membrane channels and preventing multi-component channels [6,108,109]. A schematic representation of biofilm is shown in Figure 4.

Till now, several auto-inducers have been found; gram-positive and gram-negative bacteria usually use small peptides and acyl homoserine lactone (AHL) for signaling, respectively. Quorum sensing tends to influence biofilm architecture; many streptococcal species use an autoinducer called competence stimulating peptide (CSP). CSP-deficient *Streptococcus mutans* could not form biofilm compared to their wild counterparts. Thus, quorum sensing plays a vital role in forming biofilm in certain species [108,110]. Among the bacterial population, a small subpopulation of cells tends to coexist along with bacteria known as persister cells.

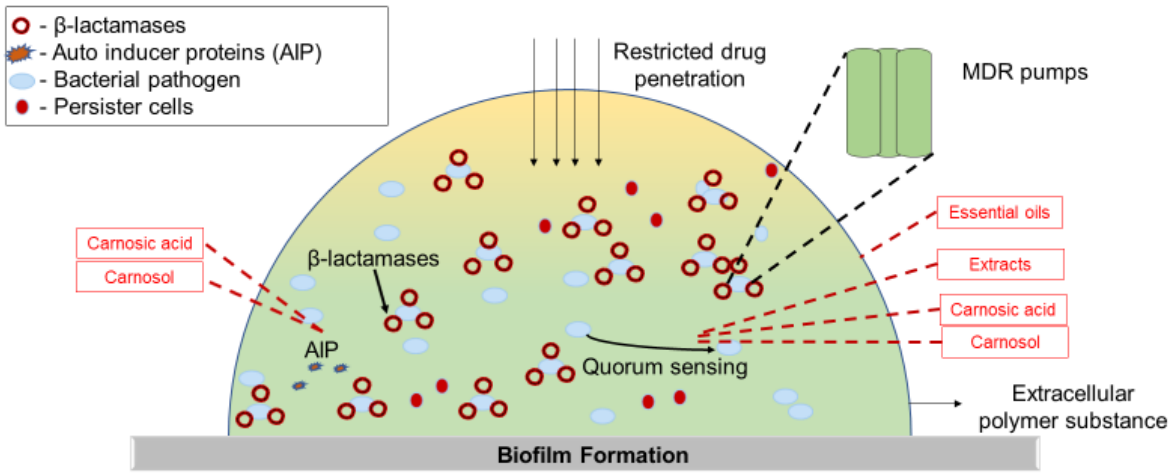

Figure 4. Effect of *Rosmarinus officinalis* extracts, essential oil, and phytoconstituents biofilm formation and quorum sensing in pathogens. The extracellular polymeric substance restricts the entry of antimicrobials within the biofilm. β – lactamases were secreted by the biofilm-inhabited bacteria into its surroundings, thereby increasing the expression of multidrug resistance (MDR) pumps. The quorum sensing activation between the bacteria and the gradients of nutrients and metabolic wastes, makes a significant contribution to the development of antimicrobial resistance. The persistent cells that coexist with bacterial clusters highly contribute to intractable biofilm infection by imparting resistance against antimicrobial agents. Rosemary extracts comprising carnosic acid as primary constituent inhibited quorum sensing in pathogens via inhibiting agr – pathway. The essential oil has been shown to exhibit antibiofilm activity against *S. aureus* MU47 strain. Carnosol and carnosic acid downregulated RNAIII and psmα gene expression, inhibiting autoinducing peptide (AIP) expression, subsequently inhibiting the quorum sensing in *S. aureus* strain.

The persister cells are specialized cells that seize to grow by entering a dormancy phase, allowing them to survive extreme conditions and evade death, as most antibiotics inhibit cell growth. Even under extreme conditions and increased antibiotic concentration, the cells tend to survive. The antibiotic resistance of persister cells did not rise due to mutation, but rather, they are the clonal population of phenotypical wild-type variants that are genetically identical [111,112].

From the various reports, the postulated targets for combating microbial resistance by the active constituents are as follows: Phytochemicals tend to donate free radicals that form irreversible complexes with transporter proteins inhibiting the transport of substances across the cell membrane.[113] Disruption or altering of the cell membrane proteins causes leakage of substances from the bacterial cell, altering the cell adhesion and polypeptides for active binding of drug molecules. Competitive inhibition of the proteins governing the efflux pumps inhibits the uptake/efflux of molecules through the channel. Suppression of ATPase activity thereby inhibits ATP's hydrolysis to ADP+P_i energy conversion, causing energy deficiency for the active transport of substances, leading to increased accumulation inside the cell causing cell rupture. The genes coding to synthesize efflux pump channel proteins often linked with a regulatory gene tend to be activators or repressors. Downregulation of the genes coding to synthesize efflux pump channel proteins can be a viable strategy to combat the multifaceted efflux pumps inducing AMR [113–115].

7. Antimicrobial activity *R. officinalis* extracts

The antimicrobial potential of *R. officinalis* extracts was extensively studied, and their Minimum inhibitory concentration (MIC) and Minimum Bactericidal Concentration (MBC)

values were used to determine their antimicrobial efficacy. Various rosemary extracts and their activity against different strains with their MIC and MBC values are listed in Table 2.

Table 2. Antimicrobial activity of *R. officinalis* extracts.

S. No	Type of extract	Tested against microbial strains	MIC/MBC	References
1	Methanolic extract	*S. aureus* and *E. faecalis* *E. coli, E. cloacae, P. mirabilis, P.aeruginosa, M. morganii, P. stuartii*	MIC 60-200 µg/mL 400-1600 µg/mL	[43]
		M. luteus, *S. aureus,* *B. subtilis,* *K. pneumoniae,* *P. aeruginosa* *E. coli*	MIC 1.56 mg/mL 1.56 mg/mL 3.13 mg/mL 1.56 mg/mL 3.13 mg/mL 3.13 mg/mL	[116]
		L. mesenteroides and *L. delbruekii*	MIC 1.25 - 1.5 mg/mL	[64]
		S.cerevisia and *I. orientalis*	2.25 - 2.5 mg/mL	
		E. coli, K. pneumoniae and P. mirabilis *X. campestris*	MIC 2 -15 mg/mL 2 - 60 mg/mL	[41]
		Yeast	MIC - 4 mg/mL	
2	Alcoholic extract	*S. aureus, B. cereus, L. monocytogenes, C. jejuni, S. infantis* and *E. coli*	MIC 0.02 - 1.03 mg/mL	[46]
3	Carbon dioxide/ Isopropyl alcohol extract	29 aerobic and anaerobic bacteria	MIC 1 – 100 µg/mL	[55]
		yeasts (*C. albicans* (ATCC 90028) and *C. krusei* (ATCC 6258))	MIC -20 µg/mL and MBC - 100 µg/mL	
4	Extracts i)VivOX 20 ii)VivOX 40	Against different species of *Listeria*	MIC i)625–5000 g/mL ii)312.5-2500 µg/mL and MBC-15.63 - 98.5 µg/mL	[42]
5	Ethyl acetate fraction from the crude extract	*E. coli* and *K. pneumonia*	MIC 5 – 10 µg/mL	[117]
6	Supercritical fluid extract	*S. aureus, B. cereus, E. coli* and *P. aeruginosa*	MIC 0.1- 0.5 mg/mL	[118]

Moreno *et al*. 2006 demonstrated the antimicrobial activity of various extracts (methanol, acetone, and water) of *R. officinalis* against gram-positive and gram-negative bacteria using disk diffusion and broth dilution techniques. Compared to other extracts, methanolic extract comprising carnosic acid (30%), carnosol (16%), and rosmarinic acid (5%) exhibited potent antimicrobial activity with lower MIC values. Thus, the results showed that the antimicrobial activity was attributed to the phenolic compounds present in the extracts.[41] When the antimicrobial efficacy of the aqueous extract was compared with the methanolic extract against the gram-positive (*Micrococcus luteus, Staphylococcus aureus*, and *Bacillus subtilis*) and gram-negative bacteria (*Klebsiella pneumonia, Pseudomonas aeruginosa* and *Escherichia coli*), the methanolic extract exhibited pronounced antimicrobial action against both the type of strains. The methanolic extract exhibited a lower MIC value of 1.56, 1.56, 3.13, 1.56, 3.13, and 3.13mg/ml against *Micrococcus luteus, S. aureus, B. subtilis, K.pneumoniae, P. aeruginosa*, and *E. coli*, respectively than the aqueous extract (6.25 mg/ml).

It was emphasized that the exerted antimicrobial activity might be due to the ability of bioactive components to alter the membrane permeability, facilitating the antibiotic influx and intoxicating the bacteria [116]. The polar fractions of rosemary extracts exhibited more potent antimicrobial action against *B.subtilis* than the Gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA), Gram-negative *P. aeruginosa*, and *E. coli* [119]. In addition, commercially available rosemary extract formulations exhibited potent antioxidant and antimicrobial properties against both gram-positive and gram-negative pathogens including *Bacillus cereus* WSBC 10530 (clinical isolate), *Staphylococcus aureus* ATCC 25923, *Campylobacter jejuni* ATCC 33560, and *Salmonella infantis* ZM9. Still, gram-positive bacteria (*Bacillus cereus* and *S.aureus*) were more susceptible to antimicrobial action than gram-negative bacteria (*Campylobacter* and *Salmonella*) due to their dense lipopolysaccharide membrane, where the phenolic constituents, i.e., carnosic acid in the soluble oil extracts majorly contributed to its antimicrobial activity [120].

The methanolic extracts were more effective against the bacterial strains (*Leuconostoc mesenteroides* and *Lactobacillus delbruekii*) compared to the yeast strains (*Saccharomyces cerevisiae* and *Candida krusei*), exhibiting its efficacy against bacteria than yeast [64]. The methanolic extract showed good antibacterial activity against MDR 37 nosocomial strains such as *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis*, *Morganella morganii*, and *Providencia stuartii*. The extracts exhibited a 2-fold increase in the MIC value for gram-negative strains than the concentration used for gram-positive strains. Besides, rosemary extract and carnosic acid inhibited MRSA, gentamicin, and streptomycin-resistant *Enterococcus faecalis* with MIC values of 60 µg/mL and 200 µg/mL, respectively [43]. Hence the MDR strains such as MRSA and gentamicin and streptomycin-resistant *Enterococcus faecalis* were highly susceptible to the antimicrobial action of *Rosmarinus officinalis*. Furthermore, the alcoholic extracts of *R. officinalis* and *V. vinifera's* antimicrobial efficacy were evaluated and correlated with phenolic constituents present in the extract. Rosemary extracts exhibited potent antimicrobial activity compared to vine extracts. The results showed that the antimicrobial potential against the pathogens (*S.aureus*, *B.cereus*, *Listeria monocytogenes*, and *Campylobacter jejuni*) was also due to the phenolic phytoconstituents [52]. Thus, various reports suggested that the phenolic phytoconstituents in extracts may have contributed to its antimicrobial effects. On the contrary, a study reported that the essential oil possessed more potent antimicrobial activity than the methanolic extracts when evaluated against the pathogens *S.aureus* and *E.coli*. Both *S.aureus* and *E.coli* were highly susceptible to the antimicrobial action of essential oil and methanolic extract. [121] Hence, it opens a broad window of opportunity for *R. officinalis* to be used as a potent antimicrobial agent to combat AMR.

Besides phenolic compounds, few reports proposed that the antimicrobial activity is mainly due to another major secondary metabolite, i.e., diterpenes. Rožman & Jeršek 2009 evaluated the antibacterial effect of two different types of Rosemary extracts containing different levels of carnosic acid (VivOX 20:22.04 % and VivOX 40:40.49 %) against different species of Listeria by using the disc diffusion method and broth dilution method. However, both VivOX 20 and VivOX 40 showed effective antibacterial activity against pathogenic Listeria, showing that rosemary extracts' activity depended on the extract type and concentration. [42] Similarly, the potent antioxidant and antimicrobial activity of *R. officinalis* extract against *S. aureus* and *L. monocytogenes* depended on the number of phytoconstituents in the extract. About 27 methanolic extracts of 27 rosemary plants collected in the various

altitudes of the province of Murcia, comprising various concentrations of phytochemicals (carnosol, carnosic acid, and rosmarinic acid) were evaluated against *S. aureus* and *L. monocytogenes*. With respect to antimicrobial efficacy, the presence of the diterpene compound carnosol played a significant role in augmenting the antimicrobial efficacy of the extracts [40]. Also, rosemary extracts consisting of carnosic acid specifically inhibited the expression of the agr virulence factor in *S. aureus,* thereby inhibiting the quorum sensing agr pathway [122].

Compared with the extracts, the solvent fractions (Petroleum ether, dichloromethane, ethyl acetate, and aqueous fraction) obtained from the extracts of *R. officinalis* exhibited increased antimicrobial effects. Ethyl acetate fraction of *R. officinalis* leaves with the MIC between 1.25 and 80 µg/µL exhibited antimicrobial activity against Extended-Spectrum Beta-Lactamase (ESBL) synthesizing bacteria, i.e., *Escherichia coli* and *Klebsiella pneumonia*.[117] The rosemary leaf extract obtained through the supercritical fluid extraction (SFE) technique demonstrated potent antimicrobial activity against gram-positive bacteria than gram-negative bacteria with larger MIC values. The antimicrobial activity exhibited by the leaf extract obtained using SFE was due to the presence of essential oils in the extract.[118] . Similarly, the extract obtained by SFE, containing 116 µg mg−1 of carnosic acid content and 60.6 µg mg−1 of carnosol content, exhibited potent antimicrobial action against *Bacillus subtilis* among the other bacterial strains, i.e., *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* [123]. On the contrary, the nonvolatile phenolic fraction of rosemary showed potent antibacterial activity against gram-positive (*S.aureus* and *S.epidermidis*) and gram-negative (*E.coli* and *P.aeruginosa*) pathogenic bacteria. In addition, the results showed that the flavonoid fraction of rosemary leaves did not contribute to its antimicrobial effects. Hence, it was evident that the antimicrobial property was due to the high concentration of nonvolatile terpenoid contents [124]. Due to the wide spectrum of biological activities, the different solvent fractions obtained from the rosemary extracts, including Dichloromethane (DCM), Ethyl acetate (EA), and butanol (BuOH), were evaluated for their antibacterial and antioxidant properties. The results suggested that DCM exerted efficient antibacterial activity against *S.aureus* (ATCC®25923TM), *S.epidermidis* (ATCC®12228TM), *P.aeruginosa* (ATCC®27853TM), and *Bacillus cereus* compared to other fractions and extracts. Carnosic acid and Rosmarinic acid were found to be the major constituents of DCM; hence, antimicrobial action was due to the high phenolic composition of DCM fraction [125].

8. Antimicrobial activity of bioactive constituents of *R. officinalis*

Essential oils, carnosol, carnosic acid, and Rosmarinic acid constitute the major bioactive constituents *R. officinalis,* and their respective exhibited antimicrobial activities are shown in Table 3.

Table 3. Antimicrobial activity of bioactive phytoconstituents of *R. officinalis.*

S.No	Bioactive constituents	Tested against microbial strains	MIC/MBC	References
1	Essential oil	*S. aureus*, *B. cereus*, *B. subtilis*, *B. pumilis* (wild type), *P. aeruginosa*, *S. poona*, *E. coli* and ampicillin resistant *E. coli*	MIC 0.20-0.48 mg /mL	[25]
		L. garvieae	MIC-15.6 µg / mL MBC-31.2 µg / mL	[30]
		E. coli, *P. aeruginosa*, *S. aureus*, *K. pneumonia*, *S. typhi*, *S. intermedius*, *B. subtilis*, *S. mutans*, *M. luteus*, and *P. mirabilis*	4 – 40 µg/mL	[26]
		M. luteus	5.8 mg/mL	[126]
		E. coli	18-20 µL/mL	[127]

S.No	Bioactive constituents	Tested against microbial strains	MIC/MBC	References
		B. cereus *P. aeruginosa*	32 µg/mL 64 µg/mL	[32]
		E. coli and *S. aureus*	25 µl/ mL and 5 µl/mL	[128]
		C. albicans	MIC 2 µl/mL and MBC 4 µg/mL	[129]
		B. cinerea, F. solani, P. digitatum, A. niger	90 - 180 µg/mL	[130]
2	Carnosic acid	*E. coli, K. pneumonia* *X. campestris*	MIC 1 µg/mL and MBC 60 mg/mL	[41]
		S. aureus and *E. faecalis*	60 µg/mL	[43]
		MDR-*K. pneumonia* (KpGM1, KpGM2, KpGM3, Kp010, Kp013, NNKp), MRSA (GM20, GM31, GM1977)	>100, >200, >200, nt, nt, >100 µg/mL 12, 24, 32 µg/mL	[131]
		S. cerevisiae, B. subtilis	2 µg/mL	[41,123]
		E. faecalis, S. salivarius, S. sanguinis, S. mitis, S. mutans and *S. sobrinus*	70, 30, 50, 15, 30, 40 µg/mL	[35]
3	Rosmarinic acid	*S. aureus, S. epidermidis, E. coli, P. aeruginosa*	600, 600, 400, 400 µg/mL	[124]
4	Carnosol	*B.subtilis, E. faecalis, S. salivarius, S. sanguinis, S. mitis, S. mutans* and *S. sobrinus*	100, 35, 35, 35, 75, 50 µg/mL	[35,123]

8.1. Essential oil.

Essential oils are a mixture of volatile constituents plants produce as a secondary metabolite for protection against predators and microorganisms [132]. In rosemary extract, the essential oil composition (1, 8-cineol, camphor, α-pinene, limonene, camphene, and linalool) varies widely with respect to its geographical locations and climatic conditions [20,130,133]. The essential oils obtained from the rosemary collected from different locations were explored and reported to have potent antimicrobial activity. The essential oil obtained from the leaves of *R. officinalis* collected from Pakistan during the winter season was studied for antibacterial, antioxidant, and antiproliferative activities. The antibacterial activity of essential oil was studied against *S. aureus, Bacillus cereus, B. subtilis, Bacillus pumilis, Pseudomonas aeruginosa, Salmonella poona, Escherichia coli,* and *ampicillin*-resistant *Escherichia coli*. The essential oils exhibited MIC values of about 0.20-0.48 mg mL^{-1} and 1.16-1.72 mg mL^{-1} against gram-positive and gram-negative bacteria, respectively. The essential oils have been shown to have more potent antimicrobial activity than 1,8-cineol, and α-pinene primary phytoconstituent of *R. officinalis* essential oil has been shown to exhibit potent inhibitory action against *C.albicans* via inducing ROS-dependent lethality [134]. The essential oil collected from Pakistan had shown potent antimicrobial activity against the tested pathogens, which might be due to the varied chemical composition of the *R. officinalis* essential oil native to its geographic location [25]. The antibacterial activity of essential oil of *R. officinalis* collected from Morocco was studied against the strains *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumonia, Salmonella typhi, Staphylococcus intermedius, Bacillus subtilis, Streptococcus mutans, Micrococcus luteus,* and *Proteus mirabilis* by disk diffusion method and the MIC of essential oil was calculated to be ranged from 4 – 48.2 µg/mL. Further, the results suggested that the activity was due to the presence of monoterpenes as the major constituents in the essential oil [26].

Mattazi *et al*. evaluated the antibacterial effect of essential oils obtained from the leaves of *Rosmarinus officinalis, Mentha piperita,* and *Salvia officinalis* cultivated in Agadir

(Morocco). It was observed that the essential oil was more highly active against gram-positive bacteria than gram-negative, as because gram-negative bacteria possess a hydrophilic barrier, the compounds could not easily diffuse through it. It was also proposed that the possible mechanism of essential oils was due to their direct contact with the bacterial cell membrane [126]. The major constituents of essential oil of *R. officinalis* cultivated in South-west Tunisia was found to be 1,8- cineole, followed by trans-caryophyllene, borneol, camphor, α-pinene and α-thujene and its antibacterial efficacy was evaluated against the pathogens. It was apparent that the antibacterial activity exhibited by the essential oil against *S.aureus,* followed by *S.epidermidis* and *S.aureus* 25923, was due to the presence of the phytoconstituents such as terpenes and phenols in th

e essential oil. However, the essential oils' terpenes and phenolic hydroxyl groups could form hydrogen bonds with the active site of target enzymes, contributing to their antimicrobial effect. The terpenes tend to alter the permeability of the cell membrane, disrupting the function and causing the leakage of cellular components [34]. A similar effect was reported when rosemary essential oils were produced using different extraction methods and examined for antimicrobial efficacy against Staphylococcus aureus, Bacillus subtilis, E. coli, and *Klebsiella pneumoniae*. The rosemary extract obtained via solvent-free microwave extraction (SFME) showed higher antimicrobial activity against the pathogens than the hydrodistillation (HD), especially against the gram-positive bacteria. It is emphasized that the higher antimicrobial action was due to oxygenated monoterpenes in oil produced by microwave-assisted extraction. The possible mechanism was the disruption of cell membrane integrity in bacterial cells [28].

The biological effectiveness of rosemary essential oil obtained from the leaves of *R. officinalis* collected from Baghdad was evaluated for their antimicrobial activity against three types of bacteria (*E.coli, B. aureus,* and *Pseudomonas*), and MIC was found to be 37 µg/mL, 20 µg/mL, and 69 µg/mL respectively [135]. Similarly, the essential oil obtained from *R. officinalis* collected from Brazil was evaluated for antimicrobial activity against 18 isolates of *Staphylococcus pseudintermedius* isolated from dogs, in which the essential oil had shown effective activity against *S. pseudintermedius* [136]. On comparing the antimicrobial activity of *R. officinalis* essential oil with different main phytoconstituents 1, 8-cineole, α-pinene, and β-pinene, it was found that the essential oil has shown better activity against tested pathogens (both gram-positive and gram-negative bacteria) than the main components. Also, the activity was mainly related to its concentrations [29,33].

The essential oil obtained from *R. officinalis* was evaluated against *E.coli* and *S.aureus;* the MBC and MIC values were 2.5, 25 µL mL^{-1}, and 1.25 and 5 µL mL^{-1} for the two strains, respectively. Randomly amplified polymorphic DNA (RAPD) analysis was used to evaluate its potential on the change in DNA pattern, which indicated marked changes in the essential oil-exposed DNA of *E.coli* and *S aureus* [128]. Biofilm formation is a major concern in antibiotic resistance. So, the antibiofilm formation activity of essential oils extracted from *R. officinalis* was evaluated against pathogenic gram-positive and gram-negative organisms. The essential oils exerted increased antibiofilm activity against gram-positive bacteria than the gram-negative bacteria, especially in the *S. aureus MU47* strain, reducing the biofilm formation from 60.76% to 48.14%. MBC and sub-inhibitory essential oil concentrations exhibited limited anti-biofilm activity [137].

The synergistic action of essential oils with current antimicrobial agents was also studied. Rasool. 2013 investigated the antibacterial activity of essential oils of *Rosmarinus officinalis, Syzygium aromaticus, Cuminum cyminum, and Zingiber officinale* against *E.coli,*

and it was found that the essential oils combined with tetracycline were more effective than tetracycline alone [138]. Similarly, the essential oils showed marked antifungal activity against *Aspergillus flavus* compared to gentamicin; the antimicrobial effect was due to the presence of α-pinene, a monoterpene, as the main constituent [130,139,140]. They were also highly effective against *C. albicans* and *C. dubliniensis*, exhibiting marked inhibitory action. Aside from antibacterial activity, the essential oil obtained from *R. officinalis* has exhibited potent antifungal activity against the selected strains of *Candida*, confirming its antifungal potential [141].

8.2 Carnosic acid and Carnosol.

Carnosic acid was first discovered in *Salvia officinalis* [142], whereas later, it was found that carnosic acid was abundant in the leaves of *Rosmarinus officinalis* [143]. Carnosic acid and carnosol are naturally occurring phenolic diterpenes found in rosemary and are widely studied for their antimicrobial activity. Both carnosol and carnosic acid isolated from *Rosmarinus officinalis* exhibited potent antibacterial activity against drug-resistant pathogens. Carnosol and carnosic acid inhibited the efflux pump MDR proteins in different *S.aureus*, strains XU212 (TetK), RN4220 (MsrA) and SA-1199B (NorA). Both the phytoconstituents exhibited synergistically potentiated antimicrobial efficacy of erythromycin, tetracycline, and norfloxacin. Additionally, even at the concentration of 10 μg/mL, both carnosic acid and carnosol potentiated erythromycin activity by a factor of 32 and 16-fold against the strain that can efflux erythromycin. Finally, the results suggested that carnosic acid can be a potent efflux pump inhibitor [9]. In addition, Horiuchi *et al*. 2007 also demonstrated the antimicrobial activity of Carnosol and Carnosic acid against Vancomycin-resistant enterococci (VRE) and evaluated their synergistic action with aminoglycosides. Carnosol and Carnosic acid alone did not show any promising activity against VRE, but these compounds increased the activity of aminoglycosides by increasing the cell membrane permeability of VRE. [144] In addition, carnosic acid and carnosol inhibited the agr (accessory gene regulator) expression in *S. aureus* strains associated with atopic dermatitis. It also inhibited autoinducing peptide (AIP) induced RNAIII and psmα gene expression, thereby inhibiting quorum sensing in *S. aureus* [122].

Owing to its importance, these compounds were also evaluated for their activity against oral pathogens. The results suggested that carnosol and carnosic acid had shown better activity against the cariogenic bacteria with moderate MIC values than rosmarinic acid [35]. In addition, carnosic acid also inflicted good antimicrobial efficacy against foodborne pathogens, including *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Salmonella Paratyphi A*, and *Yersinia enterocolitica*) following kaempferol [145].

Carnosic acid is considered the most potent antimicrobial constituent of its other counterparts from *R. officinalis*, and when complexed with cyclic glucans, the antimicrobial activity of carnosic acid was increased. All of the complexes exhibited potent antimicrobial activity against *B. subtilis subsp. spizizenii* ATCC 6633, among them cycloamylose (CA) exhibited a reduction in the MIC of carnosic acid [146]. Carnosic acid was also reported to be effective against MDR-Klebsiella pneumonia and methicillin-resistant *Staphylococcus aureus* (MRSA) with the MIC values of >100, >200, >200, nt, nt, >100 μg/mL against MDR-K.pneumonia strains (KpGM1, KpGM2, KpGM3, Kp010, Kp013, NNKp). About 100% inhibition in bacterial growth was observed in the MRSA strains, including GM20, GM31, and GM1977 treated with 12, 24, and 32 μg/mL of carnosic acid, respectively. Thus carnosic acid has a potent antimicrobial effect against *S.aureus* strains resistant to 8 antimicrobials growing

in the planktonic state [43,131]. In addition, Carnosic acid showed potent antifungal activity against *Cryptococcus neoformans* at the concentration of 50 µg/ml and provided a synergistic effect against the pathogen when mixed with propolis extract in the ratio of 4:1 [147] similar to the results against *C.albicans* [148]. Thus, carnosol and carnosic acid are potential candidates that need further exploration on the mechanical approach to use them as antimicrobial agents.

8.3 Rosmarinic acid

Rosmarinic acid (RA), an ester of caffeic acid and 3, 4-dihydro phenyl lactic acid, is a naturally occurring polyphenol commonly found in herbs of the lamiaceae family. The compound is extensively studied for various pharmacological activities, whereas its antioxidant, anti-inflammatory, and anticancer properties make it a worthwhile polyphenol to explore its antimicrobial potential. The MIC values of various bioactive constituents of *R. officinalis* against gram-positive and gram-negative pathogens are tabulated [Table 2].

Zampini *et al*. 2013 observed that Rosmarinic acid could show a narrow spectrum of action against a few gram-negative clinical isolates like *Proteus mirabilis* and *Pseudomonas aeruginosa* compared to rosemary extract and carnosic acid. Rosmarinic acid was ineffective even at a high 480 µg/mL concentration against MRSA, *Enterococcus faecalis, Escherichia coli,* and *Enterobacter cloacae*.[43] In another study, Petrolini *et al*. 2014 also reported a similar result, stating that the fractions and the pure compound rosmarinic acid did not yield promising results for gram-positive and gram-negative bacteria up to 400 µg/mL.[49] On the contrary, rosmarinic acid was reported to synergize with various antibiotics like Amoxicillin, ofloxacin, and vancomycin against *Staphylococcus aureus* and MRSA. However, its MIC was found to be quite higher, i.e., 0.8 and 10 mg/mL. It was concluded that further studies on increasing the efficacy of rosmarinic acid could develop it as an adjuvant for antibiotics [149]. Besides, rosmarinic acid showed a potent antimicrobial effect against 11 candida strains along with 13 bacterial pathogens. It inhibited the biofilm activity by reducing exopolysaccharide production [150]. Besides, in order to expand the activity spectrum of rosmarinic acid, it was modified via esterification using methyl (me), propyl (pro), and hexyl (hex) alcohols. Among them, rosmarinic acid–propyl derivatives exhibited potent antimicrobial activity against *P. chibensis, S. warneri,* and *B. cereus*. It was noted that the antimicrobial activity was not only from the enhancement of cell membrane permeability but also the length of the alkyl group, which influenced the antimicrobial potential of rosmarinic acid [151]. In the case of foodborne pathogens, *Listeria monocytogenes,* which is resistant to streptomycin and erythromycin, showed a 50.1% reduction in their count when treated with 1% of rosmarinic acid [152]. Restricting iron intake by pathogenic bacteria is a viable method to inhibit their growth. Rosmarinic acid and sodium citrate synergistically inhibited the binding of ferric ion-binding protein (FbpA) utilizing food components in the *Vibrio* bacterial species. Further, they inhibited *V. metschnikovii, V. vulnificus,* and *V. parahaemolyticus*, at 100/100 µM, 100/100 µM and 1000/100 µM, respectively, without affecting the gut microbiota [153]

Hu *et al*. 2015 reported the bactericidal effect of Rosmarinic acid against acne-causing pathogens, i.e., *Staphylococcus aureus, S. epidermidis,* and *Propionibacterium acne*s. The bactericidal activity was due to the membrane-damaging effect inflicted on microbes by RA [154]. Rosmarinic acid-loaded niosomes were highly effective as an antimicrobial agent against *Staphylococcus aureus* and *Propionibacterium acne.* The study results showed that drug-loaded niosomes dispersed in the gelling agent were an effective delivery system for the

treatment of acne vulgaris [155]. Similar antibacterial action was exhibited by rosmarinic acid against MRSA [156]. Rosmarinic acid also attenuated MRSA-induced pneumonia in mice by triggering nuclear factor erythroid 2–related factor 2 (Nrf-2) translocation, which further initiated autophagy and macrophage-mediated bactericidal activity [157]. When incorporated with poly(lactic-co-glycolic acid) (PLGA) microparticles, it showed marked antibacterial activity against *S. aureus* and *P. aeruginosa.* Due to the lack of a thick cell wall, S. aureus was more susceptible to the action of rosmarinic acid than *P. aeruginosa* [158]. Thus, it is evident that rosmarinic acid is a potent antimicrobial molecule that must be studied extensively to combat antimicrobial resistance.

9. Conclusions

An extensive analysis of the literature conveys that *Rosmarinus officinalis* can be exploited for its potent antimicrobial properties, among the various phytoconstituents of *Rosmarinus officinalis,* essential oils, carnosic acid, rosmarinic acid, and carnosol exhibited marked antimicrobial properties. Both essential oils and carnosic acid have been shown to exhibit potent antimicrobial efficacy against pathogens among the phytoconstituents. The efficacy of *Rosmarinus officinalis* and its phytoconstituents against various resistance mechanisms should be studied to understand the extent of its antimicrobial efficacy. Considering the application of novel technologies such as nanotechnology [159] and CRISPR-CAS9 [160] to understand the antimicrobial mechanisms and genetic variation may aid in combating antimicrobial resistance. Together, more studies are needed to understand the underlying mechanisms and to assess the safety profile of the drug candidates from *R. officinalis* to develop plant-based antimicrobial therapeutics. Studies from the point of view of mechanistic approaches are needed to combat and evade the development of antimicrobial resistance.

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Conflicts of Interest

The authors declare no conflict of interest.

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