Review

The alarming antimicrobial resistance in ESKAPEE pathogens: Can essential oils come to the rescue?

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ABSTRACT

Antibiotics, considered as a backbone of modern clinical-medicines, are facing serious threats from emerging antimicrobial-resistance (AMR) in several bacteria from nosocomial and community origins and is posing a serious human-health concern. Recent commitment by the Heads of States at the United Nations General Assembly (UNGA, 2016) for coordinated efforts to curb such infections illustrates the scale of this problem. Amongst the drug-resistant microbes, major threat is posed by the group named as ESKAPEE, an acronym for *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp., and *Escherichia coli,* comprising high to critical drug-resistant, World Health Organization Critical Priority I and II pathogens. The drying pipeline of effective and new antibiotics has worsened the situation with looming threat of heading to a 'post-antibiotic era'. This necessitates novel and effective approaches to combat this life-threatening issue. Medicinal and aromatic plants are hailed as the reservoir of bioactive compounds and can serve as a source of antimicrobial compounds, and some recent leads show that essential oils (EOs) may provide an effective solution for tackling AMR. EOs have shown wide-spectrum antimicrobial potentials via targeting the major determinants of pathogenicity, drug-resistance and its spread including cell membrane, drug efflux pumps, quorum sensing, biofilms and R-plasmids. Latest reports confirm the EOs having strong direct-killing or re-sensitizing potentials to replace or rejuvenate otherwise fading antibiotics arsenal. We discuss herein possibilities of using EOs directly for antimicrobial potentials or in combination with antibiotics to potentiate the later for combating AMR in ESKAPEE pathogens. The current understandings, success stories and challenges for translational success have also been discussed.

1. Introduction

Antimicrobial resistance (AMR) is a complicated phenomenon where microbes develop and exhibit resistance against commonly used antibiotics or antimicrobial drugs. AMR has exploded in recent years and is rightly considered as one of the greatest human health threats of 21st century [1,2], placed amongst top 10 urgent threats by the World Health Organization for the year 2019 [3]. Irrational use of commonly available antibiotics in human health, hygiene, agriculture, animal husbandry and food production sectors is one of the major factors leading to emergence and spread of AMR [4,5]. This issue has been further aggravated by the drying pipeline of antibiotics, with few new members in sight. Global AMR trends are highly alarming with complex

and dire threats but unfortunately with very few definite answers [6]. The deaths because of AMR infections globally are projected to reach 10 million mark by 2050, besides also leaving a tremendous economic loss, if nothing substantial is done to contain AMR and its causative agents [7]. Besides, these infections add significantly to the treatment costs [8,9]. Some of the most threatening drug-resistant microbes are the members of the group named as ESKAPEE, an acronym for *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp., and *Escherichia coli* pathogens. The members of this group have been reported as multidrug resistant (MDR), extensive drug resistant (XDR) and even pandrug-resistant (PDR) [10–12] rendering thus even the most effective drugs ineffective. Some members from this group are kept at first

priority (priority 1: critical) by the WHO [13] in its priority pathogens list that need controlling agents or urgent basis.

The limited treatment options against drug-resistant infections necessitate the new and more effective antibiotics, however, the pipeline for new antibiotics is drying, with only 30 new antibiotics approved for clinical use since 2000 [14] and around 40 in development phases [15]. Unfortunately, most of the new antibiotic members respond only to Gram-positive strains, and their responsiveness drastically get reduced against Gram-negative strains, and helping the later ones emerging as a greater threat to human health and survival. One of the main reasons for this limited success or rather failure is that greater emphasis has traditionally been placed on identifying targets and molecules that interact, with little emphasis on the actual ability of these molecules in permeating the bacterial cell walls/membranes, evading efflux pumps and mutational resistance, the major molecular determinants of AMR phenotypes [16]. Moreover, traditional antibiotics, especially the ones with single targets, are vulnerable to mutational resistance. Therefore, novel and effective strategies, keeping in view the holistic approach, for combating drug-resistant pathogens and their spread is an immediate need, and in this context natural products hold great significance. In recent years, novel approaches such as the combination or synergistic therapies are being suggested to control AMR, where non-antibiotics are incorporated to boost or potentiate the activities of otherwise ineffective antibiotics to combat such infections, in order to reclaim the effectiveness of current antibiotic arsenal.

The need for effective and novel antibacterial therapies have led to a resurgence in investigations directed at finding natural products as effective antimicrobials. Amongst the natural products, EOs hold significance because of their strong antimicrobial potencies and frequent use in folklores for prevention and control of microbial infections [17–21]. EOs are lipophilic, volatile phyto-products that can be extracted from different plant parts like leaves, roots, flowers, buds, fruits, stem, seeds and woods. Chemically the EOs are designated as secondary metabolites and are known for their antibacterial, antifungal, antiviral as well as insecticidal properties [22]. Such vital assets have made EOs a major source for pharmaceutical industries [23]. The key biological properties of EOs are due to the presence of terpenes and phenylpropenoids as their major components. Presence of such bioactive constituents possessing anti-pathogenic properties therefore make EOs as one of the prime component of bio-medicinal field [17]. EOs are seen as a reservoir of potent antimicrobial or drug-resistance-reversal agents against deadly microbes [24,25]. Interestingly, EOs have also found their applications as cleaning liquid for disinfecting the medical equipment and surfaces, effective in controlling the nosocomial infections [26] beside their uses as an aerosol in operating blocks and waiting rooms for air cleaning to limiting the contaminations [27]. Their pleasant smell provides a pleasant feeling of psychic comfort for patients [28].

Through this review, we present herein a current understanding and recent updates on AMR and its major determinants especially in ESKAPEE group of pathogens, use of EOs in combination with antibiotics as a novel and effective approach to potentiate the otherwise ineffective antibiotics for combating drug resistance in these microbes. Current trends, success stories and challenges for these approaches in their way to translational success have been discussed. Besides, the use of essential oils in combination with nanomaterials for their effective and targeted delivery and synergistic or potentiation effects have also been discussed.

2. Major mechanisms of AMR in ESKAPEE pathogens

To exert the antimicrobial effects, the potential antimicrobial molecule (drug) must reach and interact with the corresponding target sites. To nullify the effects of such antimicrobial agents the drug-target interaction is interrupted through various mechanisms in bacteria which lead to the ineffectiveness of antimicrobial agent and thus
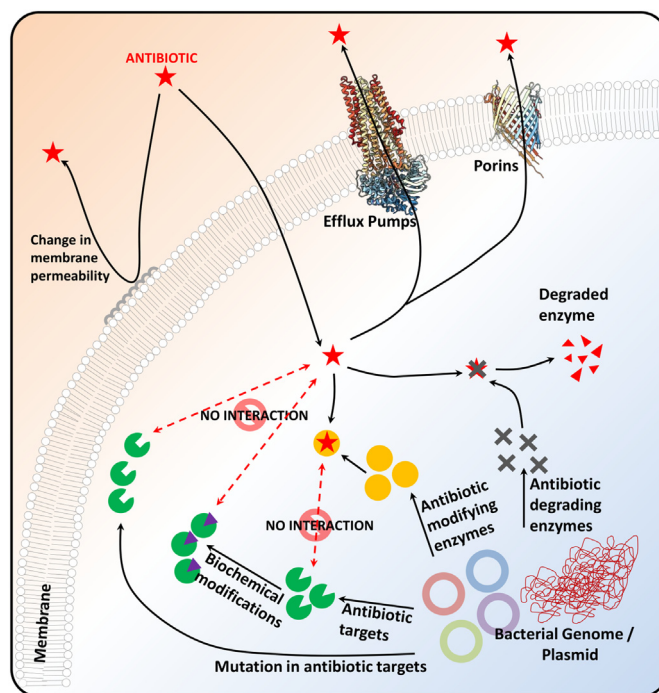

Fig. 1. Molecular mechanisms underlying antimicrobial resistance in microbes, especially the ESKAPEE pathogens.

development of resistance against that particular antimicrobial agent. Bactria have evolved multiple AMR mechanisms with emergence of new determinants [29,30]. These mechanisms may be of intrinsic and/or acquired nature and sometimes a combination of both making such phenotypes very difficult to treat. Moreover, these bacterial AMR systems can be transferred to different bacterial species in wide-ranging environments, as exemplified by the reports of drug-resistance spreading from nosocomial settings to the community environments [31]. Here we summarize major determinants in drug-resistant bacteria especially the members of ESKAPEE group (Fig. 1).

One of the important mechanisms imposing development of AMR involves hindrance in target accession by the antibiotic or drug molecule(s). Membrane permeability plays a vital role in acquiring the antibiotic resistance via blocking target access. Gram-negative bacteria are characteristically less permeable than Gram-positive bacteria because of permeability barrier formed by their outer membrane, and a major contributor to their strong AMR phenotypes and their recalcitrance to drugs [32,33]. Porins present on the outer bacterial membranes are key channels for diffusion of hydrophilic antibiotics across the membrane. To inhibit the access of porin-dependent antibiotics across the membrane, mutations in porins leading to the loss-of-function change is observed in bacteria. For instance, mutation/down regulation of porin gene OprD in *P. aerugenosa* results in prevention of the imipenem entry in bacterial periplasmic space [34]. Other examples of porin-mediated alteration in antibiotic susceptibility includes CarO porin from *Acinetobacter* spp. for carbapenems [35] and non-specific porin channels OmpF and OmpC present in *Enterobacteriaceae* [36].

Another important mechanism is active efflux pumps (EPs), which involves a reduction in antibiotic concentration inside the bacterial cell via extruding out the antibiotics (reviewed by Shriram et al. [2]). These pumps have sometimes narrow substrate specificity but most of them can transport a variety of structurally unlike substrates (drugs). Depending on their energy mechanisms, EPs are categorized in two classes. First class incorporates ATP-binding cassette (ABC) EPs whereas second class is named as proton motif force (PMF) EPs. PMF-EPs can be again distinguished in four types namely; resistance nodulation- cell division (RND) EPs, a major facilitator superfamily (MFS), small-MDR

(SMR) and multidrug and toxic compound extrusion (MATE) EPs family [37–39]. All the stated types of these EPs have been reported in many AMR strains from ESKAPEE group [2]. However, RND EPs, a tripartite complex assembly; are considered as the most potent and widely investigated efflux systems which confers resistance against vital antibiotics. RND pumps with utmost implicit knowledge include MexA-MexB-OprM system in *P. aeruginosa* and AcrA-AcrB-TolC system in *E. coli*. The EP assemblies are critical for bacterial pathogenesis, virulence, formation of biofilm and adaptive responses, hence higher levels of occurrence and expression of EPs related genes definitely confers greater resistance levels to attain AMR status in bacterial pathogens [40–44].

The next mechanism involves mutation in the antibiotic targets without disturbing the normal target function [30]. The gene encoding the targets are present in multiple copies and mutation in any one followed by the high-frequency homologous recombination can rapidly produce a population having a mutant allele [45,46]. Another tactic to acquire the target mutation is acquisition of homologous gene to the actual target [47,48]. Besides, biochemical changes can also modify the targets resulting in defunct target-drug interaction. For instance, enzymatic methylation of 16S rRNA have resulted in preventing the interaction between binding sites on 16S rRNAs with drugs such as macrolids, lincosamines/lincosamides, phenicols, pleuromutilins, oxazolidonones and streptogramins in *E. coli* and *S. aureus*. This enzymatic methylation is carried out by methylases (eg. erythromycin ribosome methylase; *erm*) or methyltransferases (e.g. chloramphenicol--florfenicol resistance methyltransferase; *cfr*) which are coded by genes present on the plasmids [49,50].

Apart from prevention of the entry of a drug molecule the resistance can be acquired by either destroying or modifying the drug molecules. Such type of inactivation of antibiotics can be achieved by enzyme-catalyzed hydrolysis of antibiotics. β-lactamases, extended spectrum β-lactamases, carbapenemases etc. are the prevalent enzymes identified in AMR strains of *K. pneumoniea, A. baumannii* and *P. aeruginosa* [51–53]. Another class of bacterial enzymes can also modify the antibiotics via addition of chemical groups (nucleotidyl, ribitoyl, phosphate, acyl etc.), resulting in prevention of binding of antibiotics to their respective targets [54]. These antibacterial enzymes generally belong to three main categories, acetyltransferases, phosphotransferases and nucleotidyltransferases [55].

Collectively, all these events confer the AMR abilities to the pathogens. Many of these events have been characterized at the molecular level; hence these finding are currently acting as a base in search and development of new antimicrobial agents.

3. Essential oils and their antimicrobial potentials

EOs comprise the mixture of 20–100 low molecular weight plant secondary metabolites. They are often volatile, naturally occurring fragrant liquids, spread in a limited number of plant families, and are extracted especially from leaves and flowers [56]. Chemically, EOs are derived from terpenes and terpenoids, and aromatic, aliphatic aldehydes and phenols [28]. Terpenes and their oxygenated derivatives, terpenoids are often major constituents of plant EOs, followed by phenylpropanoids and benzenoid compounds in terms of abundance [1,57]. In addition, the short-chain aliphatic hydrocarbon derivatives are another class of volatile compounds that constitute EOs [58]. Often, two or three constituents are major components (20–70%), whereas others are present in trace amounts [22]. For instance, the main constituent of clove (*Syzygium aromaticum*) EO is eugenol (68.52%) whereas α-caryophyllene (1.85%) is present as trace amounts [59]. Plants synthesize them through complex metabolic pathways for defence purposes against microbial pathogens.

The EOs are traditionally used for curing microbial infections. The bioactivities of EOs range from antimicrobial, antioxidant, antitumor and anti-inflammatory [60,61]. EOs have wide-spectrum applications

in cosmetics, food and drug industries [60]. The EOs can be classified on their geographical origin, botanical sources and on the basis of their applications [62]. Based on the applications, EOs can be classified as a) EOs used in cosmetics, perfumery and soap, b) EOs used in beverage and food industries (as flavouring agents and preservation additives), c) EOs as pesti−/fungi−/insecti-cides used in agriculture and d) EOs medical or alternative medico-therapeutic techniques [62]. The EOs discussed in current review are hence belong to the last category due to their application against pathogenic microbes.

Many EOs are reported to possess strong antibacterial activities against both Gram-positive and Gram-negative pathogens and therefore are seen as potent antimicrobial agents [16]. The EOs have been reported in recent years for both direct-killing (bactericidal) as well as sensitizing activities (re/sensitizing of drug-resistant strains with the help of adjuvants like EOs) against pathogenic microbes [63,64].

The therapeutic potential of EOs is supported by their assessment in regard to the stability, bioavailability, selectivity, biocompatibility and toxicity. An array of highly volatile and lipophilic compounds belonging to the various chemical classes represents the core composition of EOs. Hence the EOs are vulnerable to the conversion or degradation events. The stability of EOs is crucial to define their quality and pharmacological properties [58]. Determinants of EO stability include light, temperature, oxygen availability, interaction with metals, moisture content and chemical composition [58]. During administration, high bioavailability and stability of EOs results into effective treatment of a medical condition. Unfortunately, the records accessible for bioavailability of EOs with respect to human system are limited [65]. The available findings indicate that the dermal, oral or pulmonary administration of EOs results in rapid absorption. The EOs can cross the blood-brain barrier and then affect the relevant biological functions [65]. During the assessment of the anti-pathogenic potential of EOs, the dose-dependent selectivity of EO's activity was also observed [66]. Moreover, the EOs are usually considered safe for consumption and the biocompatibility investigations confirm EOs mostly safe for vital host tissues [67]. The non-toxic nature of EOs against normal cells has been demonstrated earlier [68–70].

In the early attempts for scientifically validating the antimicrobial potentials of plant EOs, Fournier et al. [71] reported strong antimicrobial activities of *Xylopia longifolia* EO against the *Staphylococcus aureus* and *E. coli*. Since then, several reports have reaffirmed EOs as strong antimicrobial agents that may provide a sustainable solution against drug-resistant microbes. Naveed et al. [72] screened EOs from a few Pakistani medicinally herbs for their antimicrobial potentials against MDR strains, and the authors reported that EOs of *Cinnamomum verum* barks exhibited excellent antimicrobial activities against MDR *S. typhi, E. coli* and *S. aureus* strains, with MIC ranging from 2.9 to 4.8 mg/mL. Similarly, a screening of antimicrobial activities of EOs of 18 plant species from Tajikistan by Sharopov et al. [73] revealed that the EOs of *Origanum tyttanthum* showed a strong antibacterial activity with both MIC and minimum bactericidal concentration (MBC) values of 625 μg/mL and 1250 μg/mL for MRSA, respectively, *Galagania fragrantissima* EOs were highly active against MRSA at concentrations as low as 39.1 μg/mL and 78.2 μg/mL for MIC and MBC, respectively. Likewise, there are several other reports confirming the strong antimicrobial potentials of EOs and representing them as alternative and/or adjuvants to the antibiotics.

The EOs of *Mentha piperita, Coriandrum sativum*, and *Pimpinella anisum*, for instance, exhibited antibacterial activities against the Gram-positive *S. aureus* and the Gram-negative *E. coli* [74]. *Petroselinum crispum* and *Ocimum basilicum* EOs showed strong antimicrobial activities against *Vibrio* strains [75]. EOs of *Pogostemon heyneanus* and *Cinnamomum tamala* displayed antibiofilm and antivirulent activities against MRSA strains [76]. Khalil and co-workers [77] tested antimicrobial effects of the EOs of ten Apiaceous fruits and out of that *Carum carvi, C. sativum, Cuminum cyminum* EOs showed strong antimicrobial activities against *E. coli* and *S. aureus* strains.

Buckova and group [78] investigated the antimicrobial activities of seven EOs of oregano, thyme, clove, arborvitae, cassia, lemongrass, tea tree against MDR *P. aeruginosa*, *E. coli*, *Enterobacter cloacae*, *Morganella morganii*, and *Proteus mirabilis* and the EOs exhibited strong activities as revealed by very low MIC (0.005% to 0.5%). More recently, Yang et al. [79] investigated the effects of additivity using a representative combination model involving *C. verum* bark EOs and meropenem and the observations through zeta potential measurements, outer membrane permeability and scanning electron microscopy confirmed that the synergistic/additive interactions of EOs caused bacterial membrane disruption.

In an interesting study, Benameur and co-workers [80] examined the susceptibility of *bla*ESBL producing Enterobacteriaceae to Slovakian *Thymus vulgaris* EOs with or without the antibiotic (cefotaxime). The authors reported the synergistic interaction of the EOs in combination with the antibiotic against blaSHV-12 producing MDR *E. coli* and an additive effect against ESBL producing MDR *Enterobacter cloacae* [80]. Likewise, Kwiatkowski et al. [81] reported that the peppermint oil showed synergistic effects when combined with gentamicin against ESBL-producing and NDM-1-producing *Klebsiella pneumoniae* isolates, while, Caraway EOs demonstrated synergy with gentamicin toward ESBL-producing and additionally gentamicin-resistant strains.

These and other recent reports strongly suggest and reaffirm the traditional antimicrobial usages of EOs for treating pathogenic infections and present the EOs as effective strategy to combat the wide spectrum drug-resistance in bacteria. However, most of the studies conducted so far for assessing the antimicrobial potentials of EOs through antagonistic/additive or synergistic effects against threatening microbes have been conducted using *in vitro* models and therefore *in vivo* studies are required to confirm and to further explore the EOs for therapeutic uses. Besides, more studies are required to identify the individual constituents of EOs responsible for the antimicrobial activities and the underlying drug-resistance mechanism targeted by the EOs for antimicrobial of drug-resistance reversal activities.

4. Targeting drug resistance and virulence mechanisms in ESKAPEE pathogens with essential oils

4.1. Disrupting cell wall and membrane, and membrane-permeabilization

Intactness of external cell envelope is must for bacterial survival as it guards inner cytoplasmic material from the external environment. Microbial cell wall makes up the first barrier for any antimicrobial agent which should be overcome for interaction of the agent with its target [82]. The membrane permeability is crucial for regulating and maintaining the inflow and intracellular concentrations of antimicrobials and therefore bacterial cell wall compounds are key targets of antimicrobial agents [82,83]. In presence of antibacterial agents, bacteria tend to alter the fatty acid- and membrane protein synthesis, which results in reformed membrane permeability against antibiotics [84,85]. The organization of cell membranes are even more dynamic and complex in Gram-negative microbes and are major determinants for their superior AMR. The hydrophobic nature of EOs and their components enable them to partition with the bacterial membrane lipids and mitochondria and thus rendering them more permeable by disturbing these cell structures [86]. The EOs with a high percentage of phenolics can penetrate the phospholipids of cell membrane and interact with the protein domains to block their regular function. Due to the lipophilic nature, the EOs and their major constituents affect the proportion and structural aspects of unsaturated fatty acids therein [22,87]. Therefore, bacterial cells often fail to control the leakage of critical molecules and ions when treated with EOs.

The cell membrane disruption (or enhancing the cell membrane permeability) is emerging as a key target for development of new antimicrobial agents and combating AMR [88]. However, Gram-positive bacteria are considered more susceptible to EOs than their negative

counterparts [89]. This may be due to the complex outer lipopolysaccharide-rich, rigid membrane in Gram-negative bacteria which limit the diffusion of hydrophobic compounds through it. This is absent in Gram-positive bacteria, where the membranes are surrounded by a thick peptidoglycan wall with not enough density to resist the small antimicrobial molecules and thus facilitating the access to the cell membrane [90]. Nevertheless, more and more reports are emerging on antimicrobial activities of plant EOs against both Gram-negative and Gram-positive microbes including members of ESKAPEE group, though few members are worked out with lesser extent than others.

For instance, *M. alternifolia* EO acted as membrane permeabilizer and led to the loss of chemiosmotic control in both Gram-positive and Gram-negative bacteria [91]. In an attempt to assess the antibacterial activities and decipher the targeted mechanisms of the EOs Wang et al. [92] used *Dodartia orientalis* EOs against *S. aureus*, *E. coli*, and *Salmonella enteritidis* and the authors attributed strong antibacterial activity to disruption of cell structure and resisting the biofilm formation. In the similar vein, Cinnamon EOs exhibited notable antimicrobial activities against *E. coli* and *Staphylococcus*, the changes in cell microstructure were observed under scanning electron microscope, besides, the cell permeability, membrane integrity and membrane potential were determined to elucidate the mechanism of action [93]. The Cinnamon EO induced the electrolytes leakage, causing rapid increase in the electric conductivity of samples at the first few hours and ultimately destroyed the cells [93]. Similarly, *Ocimum gratissimum* EOs exhibited antimicrobial potencies against *P. aeruginosa* and *S. aureus* via permeabilization of membranes [94]. Antimicrobial potential of coriander (*Coriandrum sativum*) EO against multidrug resistant uropathogenic *E. coli* was correlated with the disruption of membrane permeability [95]. The electron micrographs and propidium iodide assay confirmed the activity of EO on membrane permeability. This altered membrane permeability may negatively affect membrane potential, respiratory functioning and drug efflux efficiency to further damage the cell [95]. The treatment with 1,8-cineol (a major component of *Rosmarinus officinalis* EO) proved to be effective for changing membrane permeability of multidrug resistant *K. pneumoniae* [96].

In an interesting study, the activity of tea tree oil was tested against clinical strains of methicillin-resistant *S. aureus* (MRSA), extended-spectrum beta lactamases producer carbapenem-sensitive *K. pneumoniae* (ESBL-CS-Kp), carbapenem-resistant *K. pneumoniae* (CR-Kp), *Acinetobacter baumannii* (CR-Ab), and *P. aeruginosa* (CR-Pa) [97], and the oil exhibited potent bactericidal activities against all the tested microorganisms, besides, the EO in combination with reference antimicrobial (particularly oxacillin against MRSA) showed a high level of synergism at sub-inhibitory concentrations, the activities were apparently ascribed to the abilities of the EO in perturbation of cell membrane structural integrity and membrane permeabilization [97]. The results thus represent a promising option for local therapy of pneumonia caused by CR-Ab and this oil may further be explored in this direction. Further, *Cinnamomum verum* bark EO was used by Yang and co-workers [98] against drug-resistant *K. pneumonia* with an aim to identify the mode of action of the EO from a proteomic perspective by comparing the overall proteome profile of treated cells at their subinhibitory concentration (0.08%, *v*/v). Overall, 384 proteins were identified from the non-treated cells against 242 from treated ones and the pathway analysis confirmed the EO-induced oxidative stress in the bacterial cells as indicated by the abundance of oxidative stress regulator proteins. Further, EO-induced oxidative stress was attributed for apparent oxidation and disruption of the bacterial membrane as evidenced by the loss of major membrane proteins, and the authors concluded that cells exposed to EO underwent the oxidative stress that eventually disrupted the bacterial membrane possibly via interaction with the phospholipid bilayer [98]. Though more of such studies to bridge the missing link between antimicrobial activities and molecular mechanism underlying their activities are needed.

4.2. Targeting drug efflux pumps

Efflux pumps (EPs) have been identified by as vital components for development of AMR in Gram-negative as well as Gram-positive pathogens. These EPs are crucial for stress-adaptations, pathogenicity/virulence and transport of essential nutrients [99]. Therefore, molecules with EP-inhibitory activities are accomplishing great importance in the context of multi-drug resistance [100]. Many medicinal plants with antimicrobial potential have been reported to comprise EP inhibitors [101] and some of the EP inhibitors from plant origin include catechol, resveratrol, gingerol, capsaicin etc. [102]. On the similar line, some EOs or major components of EOs have been screened as a potential entity to block EPs in various pathogenic microbes. The EOs act on EPs as synergists for the antibacterials when used in combination.

Limaverde et al. [103] evaluated EP inhibition potentials of EOs and its main constituent α-Terpinene from *Chenopodium ambrosioides* against EP (TetK) harbouring strain of *S. aureus* (IS-58). Even though the MIC value of EOs for ethidium bromide was clinically irrelevant, in association with antibiotics; the EOs exhibited very high reduction in MIC values for ethidium bromide. As EPs are the only mechanisms to reduce the ethidium bromide toxicity, the MIC reduction for ethidium bromide indicates the inhibition due to EOs [103]. In another study, EOs from *Salvia fruticosa*, *S. officinalis* and *S. sclarea* were screened for their EP inhibitory effects in tetracyclin resistant *Staphylococcus epidermidis* [104]. The treatment with EOs displayed the reduced expression of tet(K) gene which can be correlated to the reduced efflux and MIC values for tetracyclin [104].

The *norA* EP (MFS family) is one of the well-studied pump in *Staphylococcus*, and is responsible for efflux of the antibiotics from class of fluoroquinolones [105]. The EOs from *Chenopodium ambrosioides* and its major component α-Terpinene were tested against the *norA* EPs in *S. aureus* (1199B/1199) [106]. The MICs of EOs and α-Terpinene were higher; however, in combination with antibacterial agent (tetracycline), EOs exhibited significant reduction in MIC for antibiotic as well as ethidium bromide [106]. In same context, Salehzadeh and co-workers [107] verified the anti-norA activity of *Thymus vulgaris* EOs against clinical isolates of ciprofloxacin resistant strains of *S. aureus*. At sub-MIC levels *norA* pump exhibited decrease in ethidium bromide efflux. The expression levels of *norA* gene also showed reduction in expression levels [107]. Anti-EP activity of EOs from two medicinal plants, namely *Thymus daenensis* and *Origanum vulgare* was evaluated against fluoroquinolone-resistant *Streptococcus pneumonia* [108]. The study revealed the synergistic activity of these EOs with ciprofloxacin and ethidium bromide. The study also confirmed significant reduction in expression levels of *pmrA* gene (MFS family) at sub-MIC concentrations of both EOs, hence confirming EP inhibiting action [108].

In another interesting study, EO from *Rosmarinus officinalis* and eucalyptol were assessed against MDR strains of *A. baumannii* and *P. aeruginosa* [109]. The study revealed the synergistic effect of *R. officinalis* EO and eucalyptol. Further the flow cytometry analysis indicated the mode of action of the EOs as efflux pump inhibition and membrane permeabilization [109]. EOs from Moroccan plants (*Thymus broussonetii, T. maroccanus, T. pallidus* and *R. officinalis*) were assessed against drug resistant Gram-negative strains by Fadli [110]. The EOs showed enhanced anti-EP activity in presence of EP inhibitor phenylalanine arginyl β-naphthylamide (PAβN) with significantly improved susceptibility of bacterial strains against chloramphenicol [110].

Even though the EOs and their major components have been emerged as potent inhibitors of EP activity, the incidence of such investigations are still infrequent. The investigation leading toward the various principal components of EOs and different classes of EPs hence can be can be targeted to find the potent EP inhibitors from EOs.

4.3. Targeting R-plasmids and resistance spread

Plasmids are known to mediate horizontal movement of plasmid-borne resistance genes and are accountable for global spread of resistance [111,112]. The EOs have shown antimicrobial and drug-resistance reversal potencies via curing or eliminating the plasmids conferring antibiotic resistance gene(s), though such investigations are again limited but reports confirm the potentials of EOs. In early such attempts, Schelz and co-workers [113] investigated the antimicrobial and anti-plasmid activities of EOs of orange, eucalyptus, fennel, geranium, juniper, peppermint, rosemary, thyme, Australian tea tree, purified turpentine oil and menthol (main component of peppermint oil) against *S. epidermidis* and *E. coli* F'lac K12 LE140. The peppermint oil inhibited the replication of the F'lac metabolic plasmid of *E. coli* by 37.5% at 0.54 mg/mL concentration, whereas, eucalyptus and rosemary oils caused a slight elimination with 0.2–0.5%, 3.1% inhibition, respectively, each at 1.09 mg/mL concentration [113]. Si and group [114] found that oregano EOs showed strong antibacterial activity against MDR ESBL *E. coli* strain, besides, the EO combined with amoxicillin, polymycin, and lincomycin exhibited an additive effect, with FIC ranging from 0.625 to 0.750. The antibacterial effects of EO in combination with fluoroquinolones, doxycycline, lincomycin, and maquindox florfenicol displayed synergism against *E. coli* (FIC- 0.375 to 0.500). The *E. coli* isolates were further confirmed for presence of plasmid-mediated activities of ESBL-TEM genes. Hence the activity of EO was positively claimed to be plasmid affecting. Yap et al. [115] reported the combinations of antibiotics and EOs of cinnamon (*Cinnamomum verum* (cort.)) bark, tea tree, peppermint (*Mentha piperita*), marjoram (*Origanum majorana*) and lavender (*Lavandula angustifolia*) successfully reduced the plasmid-conferred multidrug-resistance in *E. coli*. However, this should be confirmed in the next progenies to support these claims of targeting the drug resistance mechanism(s). Same group reported that the lavender (*L. angustifolia*) EOs successfully reversed the plasmid-mediated drug resistance in *E. coli* [88]. Interestingly, the lavender EOs resulted into the disruption of bacterial membrane and quorum sensing [88]. *Cuminum cyminum* seed EOs induced loss of plasmid integrity in *K. pneumoniae* strains and re-sensitized the strains against the used antibiotics [116]. In an important study, Skalicka-Woźniak [117] reported that *Thymus vulgaris* EOs, especially its constituent linalool, reduced the virulence and resistance spread of *E. coli* via interfering with its plasmid transfer abilities. Thus, though there are limited studies for a strong confirmation, EOs seem to offer solutions for controlling the spread of AMR in microbes, however, more investigations are needed.

4.4. Targeting quorum-sensing and biofilm mediated bacterial virulence

Considerable evidence supports the fact that even the unicellular microorganisms are capable of social behaviours and for this they require a coordinated response. This sophisticated cell-to-cell process of communication between microorganisms is known as quorum sensing and is an extremely important communication system for microorganisms. This system makes bacteria capable of measuring their concentration and to modulate gene expression in response to population density, which lead to the secretion of virulence factors, biofilm formation, competence, and bioluminescence [118,119]. Therefore, this coordinates the whole system of pathogenicity in bacteria [120]. Most of the members from ESKAPEE group are reported to be involved in biofilm formation and hence targeting their abilities to make biofilm and quorum sensing may be an effective approach for containing these pathogens.

Biofilm can be described as a structured microbial community organized inside the extra-polymeric substance (EPS). These communities are formed via multivalent physical, biological and chemical processes and are an adherent in nature, usually adhered to biotic/abiotic surface [121,122]. Formation of biofilm includes array of phases, which includes surface preconditioning, free-living cell transport, non-specific planktonic cells' adsorption on surface, irretrievable attachment of cells at surface, cellular communication (quorum sensing), substrate

Table 1

A summarized list of examples of EO-mediated antimicrobial activities against ESKAPEE pathogens and their mode of action.

Source of EO/ major component	Target pathogen	Mode of action	Reference
Disrupting cell wall and membrane, and membrane-permeabilization			
Dodartia orientalis	*S. aureus, E. coli*, and *Salmonella enteritidis*	Disruption of bacterial cell structure	[92]
Cinnamomum/ Cinnamaldehyde	*E. coli, Staphylococcus*	Induction of electrolytic leakage in cell membrane	[93]
Ocimum gratissimum	*P. aeruginosa* and *S. aureus*	Permeabilization of membranes	[94]
Coriandrum sativum	uropathogenic *E. coli*	Disruption of membrane permeability	[95]
Rosmarinus officinalis/1,8-cineol	multidrug resistant *K. pneumonia*	Chang in membrane permeability	[96]
Melaleuca alternifolia	methicillin-resistant *S. aureus*, carbapenem-resistant *K. pneumoniae, Acinetobacter baumannii*, and *P. aeruginosa*	Perturbation in cell membrane structural integrity and membrane permeabilization	[97]
Cinnamomum verum	Drug resistant *K. pneumoniae*	Induction of oxidative stress and oxidation/disruption of cell membrane	[98]
Targeting drug efflux pumps			
Chenopodium ambrosioides/ α-Terpinene	*S. aureus* (IS-58)	Inhibition of EPs (tetK)	[103]
Chenopodium ambrosioides/ α-Terpinene	*S. aureus* (1199B/1199)	Inhibition of EPs (norA)	[106]
Thymus vulgaris/ Thymol	ciprofloxacin resistant strains of *S. aureus*	Inhibition of EPs (norA)	[107]
Rosmarinus officinalis/ Eucalyptol	MDR *A. baumannii* and *P. aeruginosa*	Inhibition of EPs	[109]
Thymus daenensis/ Carvacrol	fluoroquinolone resistant *Streptococcus pneumonia*	Inhibition of EPs (pmrA)	[108]
Origanum vulgare/ Pulegone	fluoroquinolone resistant *Streptococcus pneumonia*	Inhibition of EPs (pmrA)	[108]
Salvia spp.	tetracyclin resistant *Staphylococcus epidermidis*	Inhibition of EPs (tetK)	[104]
Targeting R-plasmids and resistance spread			
Mentha piperita/Menthol	*E. coli* F'lac K12 LE140	Inhibition of replication of F'lac metabolic plasmid	[113]
Eucalyptus globulus, Rosmarinus officinalis	*E. coli* F'lac K12 LE140	Elimination of plasmid	[113]
Cuminum cyminum	*K. pneumoniae*	Loss of plasmid integrity	[116]
Thymus vulgaris/linalool	*E. coli*	Interference in plasmid-transfer abilities	[117]
Targeting microbial communications (quorum sensing and biofilm)			
Cinnamomum/ cinnamaldehyde	Carbapenem resistant *A. baumannii*	anti-biofilm	[137]
Baccharis psiadioides/ β-pinene	*E. faecalis*	anti-biofilm	[138]
Thymus vulgare/ Thymol	*P. fluorescens* KM121	anti-biofilm and anti-quorum sensing	[154]
Syzygium aromaticum/ Eugenol	Methicillin resistant *S. aureus* (MRSA)	anti-biofilm and anti-quorum sensing	[155]
Melaleuca alternifolia/ terpinen-4-ol	Methicillin resistant *S. aureus* (MRSA)	anti-biofilm and anti-quorum sensing	[156]
Thymus daenensis/ Thymol	*S. aureus*	anti-biofilm and anti-quorum sensing	[132]
Satureja hortensis/ Carvacrol	*S. aureus*	anti-biofilm and anti-quorum sensing	[132]

transportation and cell/EPS maintenance across the biofilm and finally the detachment [123,124]. Biofilm progression assigns alternate path for bacterial cell growth and hence multiple regulatory elements are active in the reorganization of microbial cells in the biofilm [124,125]. During these events, pathogens tend to produce signalling molecules to modulate the cellular density. This process involves differential expressions of genes which are considered vital during the quorum sensing [126]. As these genes are related to virulence, antibiotic production and biofilm formation; targeting quorum sensing to battle against multi-drug resistant pathogens is currently one of the widely studied approaches [126]. The eradication of biofilm is challenging as it exhibits great adaptability to survive under environmental stresses and antimicrobial agents [127]. As a result, the biofilm producing organisms are more difficult to eradicate.

Anti-biofilm and subsequent anti-quorum sensing activities of EOs and/or their principal component(s) have been evaluated on various occassions. For instance, Merghni [128] have evaluated anti-biofilm and anti-quorum sensing potential of EO from *Eucalyptus globulus* along with its main component 1,8-cineole (eucalyptol) against methicillin resistant *S. aureus*. The *Eucalyptus globulus* EO along with its major component represented a percent reduction in biofilm formation in the range 74.74 to 90.81%. Anti-quorum sensing properties of *Eucalyptus globulus* EO and major component was assessed using biomonitor strain *C. violaceum* ATCC12472 which revealed high anti-quorum sensing potential of *E. globulus* EO than that of the major component (1,8-cineole) [128]. The anti-biofilm efficacy of some constituents of EOs namely carvacrol, citral, and (+)-limonene was assessed against community-associated methicillin-resistant *S. aureus* (CA-MRSA) [129]. In another report, five strains of *S. aureus* were tested for their susceptibility levels against EOs from *Cymbopogon flexuosus* and *Citrus paradise* [130]. Out of these two EOs, authors concluded that the *C. flexuosus* EO

displayed the anti-biofilm potential at very low concentration (0.125%) and the exposure of *C. flexuosus* EO was also responsible for extensive disruption to the biofilm. The suggested mechanism for this disruption was damage to the extracellular matrix [130]. The *Plectranthus amboinicus* EOs, with Carvacrol as a major constituent have also showed strong anti-biofilm potential against oxacillin and vancomycin-resistant *S. aureus* strains [131]. Antibacterial, anti-quorum sensing and anti-biofilm characteristics of EOs from *T. daenensis* and *Satureja hortensis* were evaluated by Sharifi and co-workers [132] against *S. aureus* of clinical/dairy industry/food origin. The evaluation revealed the strong anti-biofilm and anti-quorum sensing activities of EOs along with a significant down-regulation in *hld* (RNAIII transcript encoding RNAIII effector molecule of *agr* locus; involved in quorum sensing) gene expression levels.

In another member of ESKAPEE group, *P. aeruginosa*; formation of biofilm and various virulence factors is governed by quorum sensing network which is mediated by pseudomonas quinolone signal (PQS) [133,134]. As per the study by Husain [135] papermint (*Mentha piperata*) oil (0.375–3%) have exhibited reduction in biofilm formation in a concentration dependent manner in *P. aeruginosa* PAO1. Anti-quorum sensing activity was also confirmed via violacein production assay in *C. violaceum* CVO26 by the authors. The quorum sensing regulated virulence factors including elastases, proteases, pycocyanins, chitinases, exopolymeric substances, swarming motility etc. have also showed degraded activities with an increase in the EO concentration. The GC analysis of *M. piperata* EO confirmed menthol as a major constituent which also showed anti-quorum sensing activity [135].

EOs from thyme and papermint were investigated for their anti-biofilm properties against pathogenic strains of *K. pneumonia* by Mohamed [136]. Both EOs exhibited very promising anti-biofilm potential as percent biofilm inhibition was up to 98% by both EOs at very
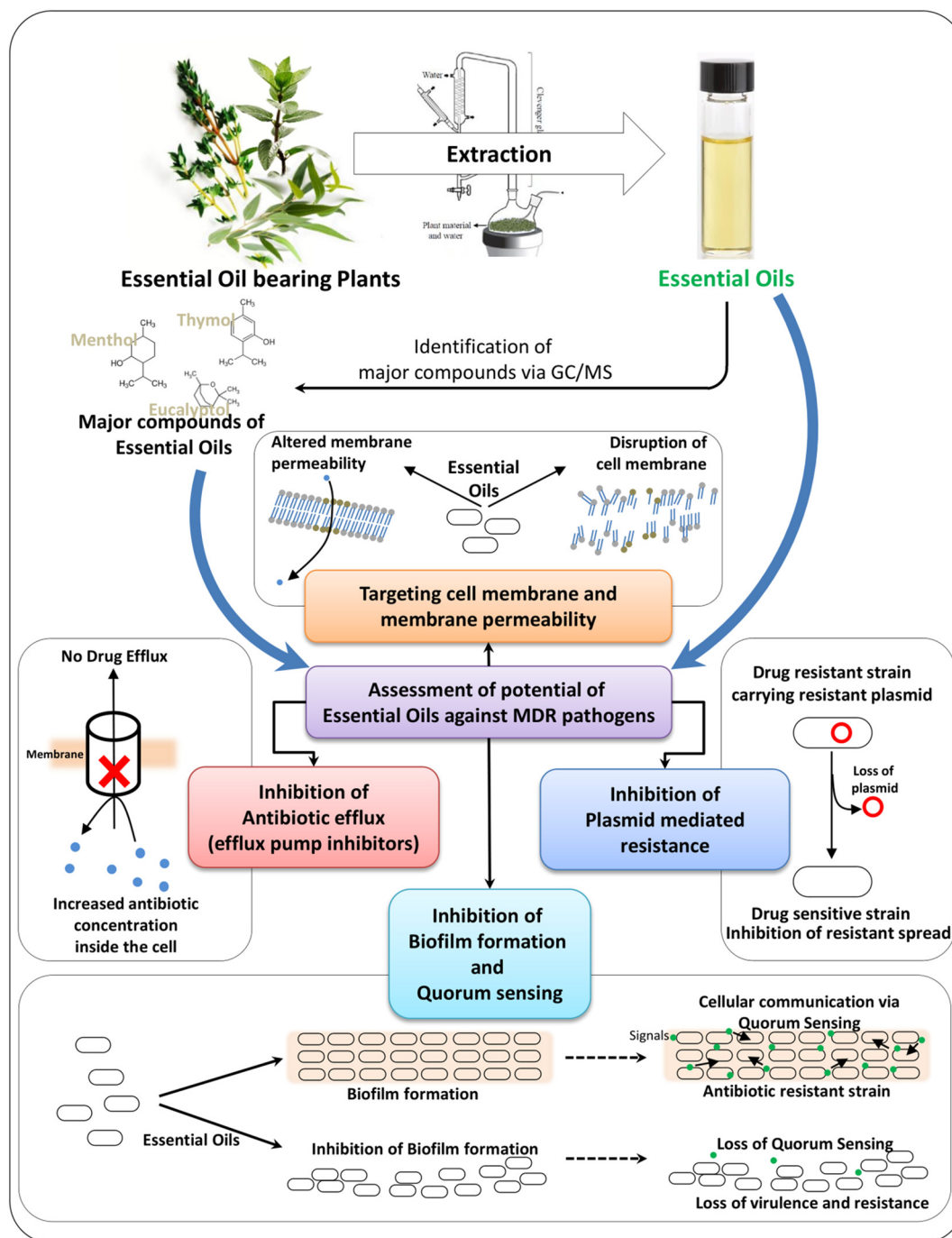
Fig. 2. Approaches for combating antimicrobial resistance in ESKAPEE pathogens using EOs.

low effective dose (5–10 μl/ml). After analysing the GC/MS profile of EOs, menthol and thymol were revealed as major constituents of papermint and thyme EOs, respectively. Both the principle components exhibited high anti-biofilm activity at very low concentration [136]. Cinnamaldehyde, a major constituent of EOs from cinnamon, have displayed anti-biofilm activities against carbapenem resistant *A. baumannii* [137]. A total of 23 clinical isolates were evaluated by the authors, in which inhibition of biofilm formation was observed at half of the MIC values with respect to cinnamaldehyde. The possible reason for strong anti-biofilm was suggested as reduction in quorum sensing and subsequent decrease in EPS formation [137]. EOs from *Baccharis psiadioides* was assessed for its antimicrobial and anti-biofilm potential against antibiotic resistant *E. faecalis* [138]. The *Baccharis psiadioides* EO (major component as β-pinene, a monoterpene) did not show

complete disruption of the biofilm however, the EO significantly lowered the microbial adherence to the surface and viability of the cell [138]. Examples of EO mediated antimicrobial activities against ES-KAPEE pathogens and their mode of action are summarized in Table 1 and Fig. 2.

5. Antimicrobial potential of essential oils in combination with nanomaterials

Recent years have witnessed an emergence of nanomaterials (NMs) as an effective means for combatting AMR in microbial pathogens [56]. Several types of NMs ranging from silver and gold to copper, iron, zinc, chitosan, and carbon nanotubes and others are being assessed regularly for their antimicrobial potential including evaluating their synergistic

effects with EOs [139–143]. There are several studies on EO-mediated biosynthesis and/or encapsulation of different nanoparticles with essential oils from the medicinal and aromatic plants. The NMs have also emerged as excellent delivery agents of drugs and are known for targeted delivery of drug molecules including EOs.

Peppermint EOs and cinnamaldehyde were used in the core part by Duncan [144] to synthesize capsules which were stabilized by NPs encapsulation. Similarly, Paula and co-workers [145] prepared chitosan-gum NPs loaded with thymol containing EO of *Lippia sidoides*. In an interesting study, Bravo Cadena [146] reported that the encapsulation of EOs with mesoporous silica nanoparticles helped to protect EOs from evaporation and degradation and significantly enhanced their antimicrobial activity against bacterial phytopathogens. This reaffirms the potentials of EOs in controlling pathogens of different sources and types. In another attempt, Hosseini and group [147] developed the combination of chitosan NPs and oregano EO to evaluate their antimicrobial potentials and the releasing-pattern of EO particles adsorbed onto the NPs. Similarly, the nano-encapsulation of thymol by zein-sodium caseinate NPs resulted into the enhanced antimicrobial potentials of thymol [148].

Some of the most frequently used EOs for their encapsulation with NMs in order to boost their antimicrobial potentials have been reported from the plants including members of *Eucalyptus* species, tea tree (*Melaleuca alternifolia*) and *Thymus daenensis*. Various conjugates of NMs and EOs have been formulated, mainly for exploring NMs as drug molecule carries employing mainly three categories of nano-carries including polymer-based NPs, lipid-based NPs and molecular complexes [56] (Table 2). However, though there are some reports against strains of *E. coli, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* there are very few or no reports against *Enterococcus faecium* and *Enterobactor* and necessitates further investigations in this direction. Table 2 summarizes important case studies from recent years on combinations of nanoparticles and essential oils (and their constituents) effectively used for antimicrobial uses.

6. Challenges for the translational success

There are several reports highlighting or confirming the antimicrobial potentials of EOs against a wide-spectrum drug-resistant microbes with direct bactericidal and synergistic effects (as adjuvants for resistance-reversal). The sensitivity of microbes against EOs is traditionally assessed by *in vitro* agar well diffusion method. The zone of inhibition obtained via this method is a measure of sensitivity against the EOs. Another classic *in vitro* method for antimicrobial assessment is micro-dilution assay which determines the MIC values for particular EOs. The comprehensive information regarding the methodology for *in vitro* antimicrobial assessment can be obtained in a review by Balouiri et al. [149]. However, most of the investigations are conducted using *in vitro* models, and only a few reports are on *in vivo* activities, where activities are assessed using animal models. The animal models are subjected to the induced microbial infection via administration of pathogen inoculum through different routes. The efficacy of the EOs against pathogen is then assessed in infected animals by examining their survival and recovery. *in vivo* EO studies using similar approaches are conducted by using different animal models including mice [150,151] and silver catfish [152].

The number of such *in vivo* investigations to confirm the antimicrobial potential of EO are however very less. Further, the clinical trials involving extensive pre-clinical studies that yield preliminary efficacy, toxicity, pharmacokinetic and safety information to decide whether a particular EO or its component(s) is/are ready for clinical trials are even less and necessitates more such investigations. Nonetheless, there are some recent attempts on examining the activities in vivo. Lu and co-workers [150] investigated effectiveness of oregano EO against a panel of MDR bacteria isolated from combat casualties and the results confirmed efficacy of oregano oil to treat burn infections in

Table 2
A list of combinations of nanoparticles and essential oils (and their constituents) effectively used for antimicrobial uses against ESKAPEE pathogens.

Source/constituents of Essential oil	Nanoparticles	Type of combination	Antimicrobial activity	References
Cinnamaldehyde	Mesoporous silica	Encapsulation	Synergistic antimicrobial activities against phytothogens	[146]
Thymus vulgaris	Nanoarchaeosomes and nanoliposomes	Nanovesicles	Synergistic antimicrobial activities against methicillin-resistant *S. aureus*	[157]
Melaleuca alternifolia	Silver	Encapsulation	Synergistic Antimicrobial activities against *P. aeruginosa, S. aureus*	[158]
Melaleuca alternifolia	Nanoemulsions of tree tea oil	Nanoemulsion	Synergistic antimicrobial activities against *E. coli, A. baumannii, K. pneumoniae, S. aureus*	[159]
Allyl isothiocyanate, carvacrol, cinnamaldehyde, diallyl disulphide, eugenol and thymol	Montmorillonite nanoclay	Encapsulation	Synergistic antimicrobial activities against *S. aureus*	[160]
Eucalyptus globulus and *Melaleuca alternifolia*	Diastearoyl phosphatidylcholine and diastearoyl phosphatidylethanolamine liposomes	Encapsulation	Synergistic antimicrobial activities	[161]
Carvacrol, thymol, *p*-cymene, and γ-terpinene from *Origanum dictamnus*	phosphatidyl choline-based liposomes	Encapsulation	Synergistic antimicrobial activities against *S. aureus, S. epidermidis, S. mutans, S. viridans, P. aeruginosa, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae*	[162]
Eugenol	Whey protein or soy lecithin	Encapsulation	Enhanced antimicrobial activity against *E. coli*	[163]
Eucalyptus citriodora oil	Nanoliposomes	Encapsulation	Species specific antimicrobial activity of encapsulated EO against *S. aureus*	[164]
Cinnamon oil	Liposome	Encapsulation	Anti-biofilm activities against methicillin-resistant *Staphylococcus aureus*	[165]
Thymol, carvacrol and thymol/carvacrol	Liposomes	Encapsulation	Antimicrobial activities against *Staphylococcus aureus* or *Salmonella enterica*	[166]
Thymus daenensis essential oil	Essential oil nanoemulsion	Nanoemulsification	Enhanced antimicrobial activity against *E. coli*	[167]

mice. Importantly, the authors reported that the strains could not re-gain the resistance even up to 20 passages in the presence of sub-lethal concentrations of oregano oil, besides, no side-effects were seen in mouse skin treated with the oil, and thus this oil may prove to be a potential candidate for pre/clinical phases. Preuss [151], observed that *S. aureus* killed all 14 untreated mice within a week, against over one third survival for thirty days when given oral Origanum oil daily (6/14) and > 60% of mice survived when receiving a daily combination of Origanum oil and monolaurin (5/8). In the similar vein, Yang et al. [153] reported strong *in vivo* antibacterial activities of *Artemisia vestita* EOs against respiratory infection-causing bacterial strains with no no-ticeable side-effects in mice up to an intake of 100 µg/mouse once or twice each day for 9 days [153].

One of the biggest advantages is that out of around 3000 well-re-cognized EOs, 300 belongs to the category generally recognized as safe (GRAS) to humans by the U.S. FDA [150]. These volatiles having sev-eral bioactivities, are considered as green antimicrobials owing to their low-cost, biocompatible, antimicrobial and resistance-reversal poten-tials, no or less toxic to eukaryotic cells and environment [150] and therefore are looked upon as an effective solution for tackling AMR in bacterial strains including ESKAPEE members. However, some im-portant questions still need to be answered about the stability, se-lectivity, bio-availability, biocompatibility or any possible non-target or toxic effects on human body or any type of allergy to selective in-dividuals before translational success of EOs, and more studies should be designed in these directions so that these potent natural products can come to the rescue from life-threatening issue of AMR.

7. Concluding remarks

Recent investigations scientifically validate the traditional claims and usages of EOs from medicinal and aromatic plants for tackling human pathogens. Several reports as discussed in this review represent essential oils as effective antimicrobials against wide-spectrum patho-gens including threatening ESKAPEE members. Owing to the ever-in-creasing antimicrobial resistance in ESKAPEE members and drying pi-pelines of effective antibiotics against them necessitates the novel, safe and cost-effective approaches to fight these menacing pathogens. Essential oils qualify on these parameters and very rightly looked as a new treatment modality to contain drug-resistant pathogens. However, in spite of several reports confirming their antimicrobial potentials with both direct as well as adjuvant actions (in combinations with anti-biotics), *in vivo* confirmations are a must, and more such studies needed to be undertaken followed by pre-clinical and clinical studies which will eventually translate these potent natural antimicrobial agents into the drugs for clinical applications. Additionally, high-throughput screening will add to the pool of potent essential oils that can be turned into lead molecules in drug discovery/development programs. Nevertheless, the recent promising leads will positively hasten the process and we can hopefully expect drug discovery from these potent agents soon.

Declaration of Competing Interest

Authors have no conflict of interest to declare.

Acknowledgements

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