

Nanoemulsion as an Effective Inhibitor of Biofilm-forming Bacterial Associated Drug Resistance: An Insight into COVID Based Nosocomial Infections

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Abstract Antibiotic overuse has resulted in the microevolution of drug-tolerant bacteria. Understandably it has become one of the most significant obstacles of the current century for scientists and researchers to overcome. Bacteria have a tendency to form biofilm as a survival mechanism. Biofilm producing microorganism become far more resistant to antimicrobial agents and their tolerance to drugs also increases. Prevention of biofilm development and curbing the virulence factors of these multi drug resistant or tolerant bacterial pathogens is a newly recognised tactic for overcoming the challenges associated with such bacterial infections and has become a niche to be addressed. In order to inhibit virulence and biofilm from planktonic bacteria such as, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and others, stable nanoemulsions (NEs) of essential oils (EOs) and their bioactive compounds prove to be an interesting solution. These NEs demonstrated significantly greater anti-biofilm and anti-virulence activity than commercial antibiotics. The EO reduces disease-causing gene expression, which is required for pathogenicity, biofilm formation and attachment to the surfaces. Essential NE and NE-loaded hydrogel surface coatings demonstrates superior antibiofilm activity which can be employed in healthcare-related equipments like glass, plastic, and metal chairs, hospital beds, ventilators, catheters, and tools used in intensive care units. Thus, anti-virulence and anti-

biofilm forming strategies based on NEs-loaded hydrogel may be used as coatings to combat biofilm-mediated infection on solid surfaces.

Keywords: drug-resistant bacteria, microevolution, COVID-19, nanoemulsions, anti-biofilm, essential oils

1. Introduction

With the discovery of antibiotics like penicillin in the early nineteen twenties and the multitude of antibiotics being commercialised since then, a notion of all cures has been taken for granted. The use of these on a large scale has led to the microevolution of multidrug-resistant bacteria. The development of resistance or tolerance to any therapeutic agent compromises the successful use of that particular drug from the very first time of its use. This stands true for any treatment whether bacterial, fungal, parasitic, or even viral infection. Various physiological or biochemical mechanisms could be responsible for the growing tolerance. Specifically, in regards to antimicrobial agents, lack of adequate knowledge and the complexity of the process of developing tolerance itself are leading causes that there has been no significant accomplishment in preventing or controlling drug resistance. There are several recommendations in literature advocating resolutions but to no avail. The microevolution of drug resistance is inevitable [1]. Some bacterial strains are now resistant to essentially all commonly available antibiotics, for a case, methicillin resistant *Staphylococcus aureus*, has developed tolerance to not only methicillin but also various agents like macrolides, aminoglycosides, lincosamides and chloramphenicol and some kinds of disinfectants. Such strain that become

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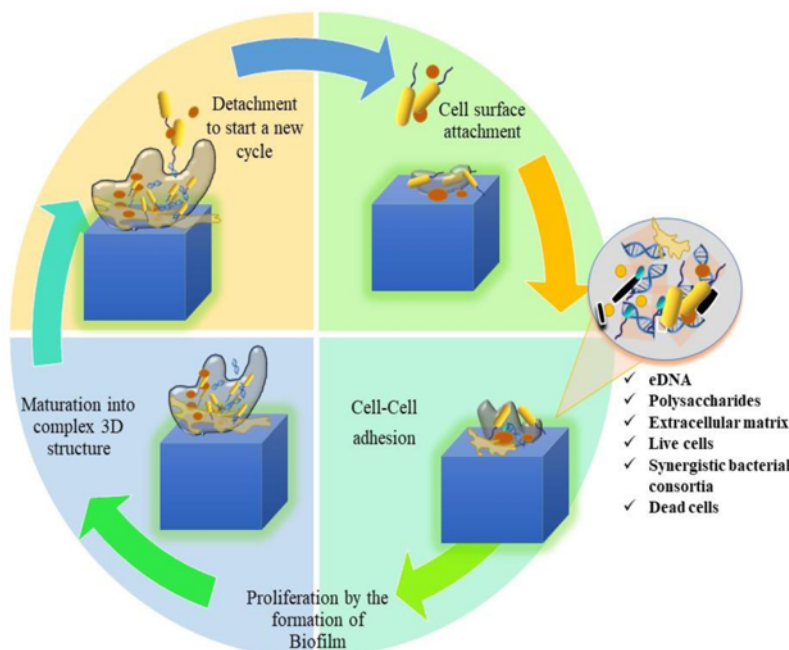


Fig. 1. Schematic representation of biofilm formation on static surface. 3D: three-dimensional, eDNA: environmental DNA.

resistant to even disinfectants contribute a majority of source for nosocomial infections also known as hospital acquired infections (HAIs), the overall schematic of the biofilm forming bacteria and its inhibitory mechanism using nanoemulsion (NE) is demonstrated in the Fig. 1. [2]. This raising concern affects not only humans in general but also animal care and health care industry as a whole.

An even more deadly threat could be considered as the emergence of Gram-negative pathogens that tolerate almost all of the available antimicrobial agents. “Pan-resistant” a term relating to resistance developed for all available antimicrobial agent [3], particularly belonging to the strains *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, [4] are now causing a high concern in recent times owing to that fact that pharmaceutical industries have not developed any new generation antibacterial agent that is effective against these strains, which have a low permeable barrier in the outer membrane and a range of efficient multidrug-resistant efflux pumps that work in sync with scores of specific resistance mechanisms. According to World Health Organization (WHO) reports [5], nosocomial infections affects a vast number of patients worldwide with great mortality rate and cause significant economic disturbance. In a prevalence survey undertaken by WHO in fifty-five hospitals in panning over 14 countries showed an average 8.7% of hospitalized patients readmitted due to nosocomial infection [6]. Approximately 15% of all patients who are hospitalised get readmitted with these infections. Neonatal cases have upto 18% mortality rate [7]. The occurrences of

overall such infections in developing countries is three times higher than in developed countries [8].

2. Burdens of Nosocomial Infections

The major types of nosocomial infection include Catheter-Associated Urinary Tract Infections (CAUTI), infections associated with bloodstream and the central line (CLABSI), pneumonia infection associated with ventilators (VAP), and surgical site infections (SSI) [9].

2.1. Central line associated bloodstream infections

CLABSI are lethal nosocomial infections with mortality rates of 12% to 25%. Catheters are inserted into the intravenous lines near the centre of the body to provide fluid and medicines, but prolonged use causes serious bloodstream infections which can result in compromised health and in some cases even death [9].

2.2. Catheters-associated urinary tract infection

CAUTI is one of the frequently occurring nosocomial infections globally. They are primarily caused by endogenous microflora of the patients. Catheters placed inside the urinary tract serve as an entry point of bacteria and imperfectly drained catheters retain some number of bacteria which provides a very conducive environment for the bacteria to thrive. CAUTI can lead to severe complications like epididymitis, prostatitis, cystitis, meningitis leading to mortality.

2.3. Surgical site infection

Surgical site infections are found in 2% to 5% of patients who have undergone surgeries. These are also one of the most commonly acquired nosocomial infections primarily caused by *S. aureus* which can cause compromised health leading to prolonged hospitalisation or in some cases death. These also arise from the endogenous microflora of patients [10].

2.4. Ventilator associated pneumonia

VAP accounts for 9% to 27% of HAIs in patients who are mechanically assisted in breathing using ventilators. It is usually detected within 48 h of tracheal intubation. Close to 90% of nosocomial pneumonia is related to ventilator use. Commonly found symptoms of VAP include raging fever, leukopenia, and wheezing sounds.

3. Emergence of Opportunistic Pathogens

The wake of the emerging pandemic COVID-19, a novel SARS-CoV-2 Coronavirus, brought devastation on a global scale, multitudes of people were hospitalised and treated and with this, the uproar of HAIs was also heard even louder. The viral respiratory infections predisposes patients with bacterial infections, these co infections were using spread through the use of contaminated glass, plastic, and metal chairs, hospital beds, ventilators, catheters, and COVID emergency tools used in intensive care units (ICUs) in a retrospective study [10], it was found that in ICUs almost all the microbiological investigations conducted in COVID-19 related cases, 28% of bacterial coinfection rates, that is, the patients were simultaneously infected by other pathogens like *S. aureus*, *Enterobacteriaceae*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

These categorical pathogens promote virulence and evade the already compromised immune response of the host by producing biofilm, and by inducing virulence factors like hemolysins, adhesins cytokines, pneumolysin

and acquisition of iron from host, besides other virulence factors of particular interest is biofilm formation as shown in Fig. 2. Prevention of biofilm from forming and curbing the virulence factors of pathogenic bacteria is a newly recognised tactic for addressing the challenges associated with bacterial infections.

3.1. Complex mechanism of biofilm formation

Biofilm is a complex syntropic consortium of the planktonic bacteria [11]. They form colonies within an extracellular matrix which is composed of environmental DNA, polysaccharides, extracellular polymeric substance and some protein produced by the consortium. The microbial cells adhere to each other and onto a living or non-living static surface. Biofilms of bacteria being pathogenic, in the scenario of healthcare environment causes nosocomial infections.

The National Institute of Health confers the formation of complex biofilms are related to 80% of the chronic infections. There are many steps involved in the formation of biofilm. It starts with the adherence to a static surface which then leads to the formation of a micro-colony. These microcolonies form three dimensional structures and finally detach themselves after maturation as visualised. During this process, several bacterial species are found to communicate among themselves using quorum sensing. These biofilms essentially make the bacteria highly resistant to the antibiotics the human immune system as well as disinfectants, this causes great concern over surface related and medical device related infections in the case of immunocompromised individuals such as COVID-19 patients.

Prevention of biofilm from forming and restriction of the virulence factors of bacterial pathogens is a newly recognised tactic for addressing the challenges associated with bacterial infections and thus it is of utmost importance that new agents with anti-biofilm activities are employed for such tasks.

In this regard, nanotechnology provides a viable solution by providing targeted drug delivery, which enhances the effectiveness of therapeutic agents and the provides protection

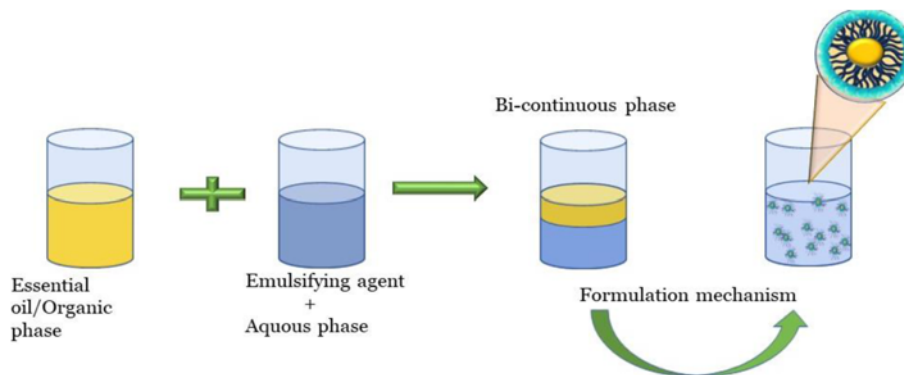


Fig. 2. General overview of nanoemulsion formulation.

to medical devices against biofouling. The emerging concept of green nanotechnology has provided a paradigm shift in development of eco-friendly, non-hazardous and highly efficient nanomaterials which proves to be an armoured asset in the battle against nosocomial infections [12,13].

Table 1 consists of conventional antibiotics currently used for the inhibition of biofilms, although in some cases they are effective, bacteria soon become resistant and in an attempt to reduce harsh harmful chemicals, green alternative therapeutic agents have been studied extensively [14-19]. It is of common knowledge since age untold that, medicinal and aromatic plants (MAPs) have antimicrobial properties, thus inclining towards them only seems like the natural course [20-24].

Oils from these MAPs are essential oils (EOs) that are obtained from MAPs are highly aromatic due to the presence of multifarious chemical substances such as terpenes, phenols, aldehydes, ketones, ethers and alcohols [25,26]. EOs in MAPs are mostly accumulated in the secretory cavities or canals, in their epidermal cells and in their glandular trichomes [27].

The chemical constituents of the EOs exhibit more

bioactivity when they are exposed to oxygenated form as they become more bioactive. The biochemical composition of EOs is very complex and they have about 20 to 60 different bioactive components. Monolaurin with Tween 20 and Tween 80 and Tween 40 have been reported to be upto 92% inhibition in diluted NE and undiluted NE completely inhibits *S. aureus* and *Escherichia coli* cells in under 1 min [28].

Table 2 summarizes some MAPs with their bioactive agents and the bacterial strains they are effective against [29-98]. The most common methods of extraction are steam distillation, cold press extraction, carbon dioxide extraction, solvent extraction, water distillation, and enfleurage, maceration. Out of these methods suitable methods can be selected for the particular EO based on the part of the plant used, for instance, the cold press methods are best suited for extraction of oils from citrus peels as the peels need to be pierced and squeezed.

In order to enhance and to augment the efficiency of these EOs, complexing it with more advanced nanotechnology accentuates the anti-biofilm activity of these EOs. But the constraints and limitation arise due to the rapid releasing of

Table 1. Conventional antibiotics against biofilms

Antibiotics	Species	Consequence on bacterial biofilm	References
B-Lactams	Methicillin resistant <i>Staphylococcus aureus</i>	Anti-biofilm activity per subsequent exposure and induction of biofilm formation at subinhibitory concentrations	[14]
Ciprofloxacin	<i>Escherichia coli</i>	Inhibited the forming of biofilm expression levels of the virulence genes were also suppressed	[15]
Rifampicin	<i>Pseudomonas aeruginosa</i>	Unaided antibiofilm activity or synergistically with other agents	[16]
Vancomycin	<i>S. aureus</i>	Inhibiting release of eDNA at subinhibitory concentrations leading to decrease in biofilm formation	[17]
Daptomycin	<i>Staphylococcus epidermidis</i>	Anti-biofilm effect by penetrating cluster and decrease the viability	[18]
Fosfomycin	<i>E. coli</i>	Anti-biofilm activity per subsequent exposure and induction of biofilm formation at subinhibitory concentrations synergistically with other agents	[19]

eDNA: environmental DNA.

Table 2. Various essential oils, their bioactive chemical constituents, and its antibacterial activity

Medicinal and aromatic plants	Inhibited bacterial species	Bioactive chemical constituents	References
<i>Achillea clavennae</i>	<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>	Camphor, 1,8-cineole, geranyl acetate, β -caryophyllene, linalool, myrcene	[29]
<i>Achillea fragrantissima</i>	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Staphylococcus epidermidis</i>	Thujone, 1,8-cineole, artemisia alcohol, Yomogi alcohol	[30]
<i>Artemisia absinthium</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i>	Myrcene, transsabinyl acetate, transthujone	[31]
<i>Artemisia biennis</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i>	Derivatives of beta-farnesene, beta-ocimene, acetylenes, En-yn-dicycloether	[31]
<i>Artemisia cana</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i>	Santolina triene, camphene, alpha-pinene	[31]
<i>Artemisia dracunculoides</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i> , <i>Brochothrix thermosphacta</i> , <i>Listeria innocua</i> , <i>Shewanella putrefaciens</i>	Methylchavicol, terpinolene, beta-phellandrene, methyl eugenol	[31,32]
<i>Artemisia longifolia</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i>	Camphene, Alpha-pinene, 1,8-cineole	[31]
<i>Artemisia frigida</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i>	1,8-Cineole, camphor, methylchavicol	[33,34]

Table 2. Continued

Medicinal and aromatic plants	Inhibited bacterial species	Bioactive chemical constituents	References
<i>Cinnamomum zeylancium</i>	<i>Enterobacteriaceae</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i> , <i>Staphylococcus pyogenes</i> , <i>Enterococcus faecalis</i> , <i>Escherichia faecium</i> , <i>Bacillus cereus</i> , <i>Enterococcus</i> spp.	Cinnamaldehyde	[35,36]
<i>Copaifera officinalis</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	δ -cadinene, β -Caryophyllene, β -bisabolene, germacrene B, α -copaene, α -humulene, germacrene D	[37]
<i>Coriandrum sativum</i>	<i>Salmonella typhi</i> , <i>Bacillus subtilis</i> , <i>S. aureus</i> , <i>E. coli</i>	2E-Decenal, n-decanol, decanal, 2E-decen-1-ol	[38,39]
<i>Cuminum cyminum</i>	<i>Salmonella typhimurium</i> , <i>S. aureus</i> , <i>E. coli</i>	Cuminaldehyde, γ -terpinene, γ -Terpin-7-al, β -pinene	[40]
<i>Cyperus longus</i>	<i>S. aureus</i> , <i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>Enterococcus faecium</i> , <i>Salmonella enteritidis</i> , <i>P. aeruginosa</i>	α -humulene, β -Himachalene, γ -himachalene	[41]
<i>Daucus littoralis</i>	<i>S. aureus</i> , <i>E. coli</i>	Germacrene D, acorenone B	[42]
<i>Dracocephalum foetidum</i>	<i>Micrococcus luteus</i> , <i>Enterococcus hirae</i> , <i>Staphylococcus mutans</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i>	Geranial, 8-dien-10-al, n-Mentha-1, limonene	[43-45]
<i>Eremanthus erythropappus</i>	<i>S. epidermidis</i>	Caryophyllene, γ -terpinene, germacrene D, p-cymene, viridiflorol	[46]
<i>Eugenia caryophyllata</i>	<i>S. epidermidis</i>	Phenylpropanoids, cinnamaldehyde, eugenol, carvacrol, thymol	[47]
<i>Euphrasia rostkoviana</i>	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. faecalis</i> , <i>P. aeruginosa</i>	Thymol, myristic acid, linalool, n-Hexadecanoic acid	[48]
<i>Foeniculum vulgare</i>	<i>S. typhimurium</i> , <i>E. coli</i>	Trans-anethole, methylchavicol, limonene	[49]
<i>Fortunella margarita</i>	<i>S. aureus</i> , <i>B. subtilis</i> , <i>S. faecalis</i> , <i>Sarcina lutea</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	Gurjunene, eudesmol, murolene	[49,50]
<i>Juniperus phoenicea</i>	<i>L. monocytogenes</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>S. aureus</i>	α -Pinene, β -phellandrene, α -terpinyl acetate	[41]
<i>Laurus nobilis</i>	<i>Mycobacterium smegmatis</i> , <i>E. coli</i>	Eucalyptol (1,8-cineole), linalool	[41,51,52]
<i>Lavandula x intermedia</i> Provence (Blue Lavandin)	<i>M. smegmatis</i> , <i>E. coli</i>	Camphor, α -pinene, eucalyptol (1,8-cineole), linalool, β -pinene	[53]
<i>Juniperus excelsa</i>	<i>S. aureus</i>	α -Pinene, α -cedrol, δ -car-3-ene	[54,55]
<i>Lippia sidoides</i>	<i>Streptococcus mutans</i> , <i>Streptococcus sanguis</i> , <i>Streptococcus mitis</i> , <i>Streptococcus salivarius</i>	Thymol and carvacrol	[56,57]
<i>Mentha pulegium</i>	<i>E. faecium</i> , <i>S. epidermidis</i> , <i>B. cereus</i> , <i>S. enteritidis</i> , <i>S. aureus</i> , <i>L. monocytogenes</i> , <i>Vibrio cholerae</i> , <i>E. coli</i> , <i>S. typhimurium</i>	Piperitenone, pulegone, α -terpineol, Piperitone	[41]
<i>Mentha suaveolens</i>	<i>Lactococcus lactis</i>	Piperidones, cis-cis-p-menthenolide, Pulegone, limonene germacrene	[58-60]
<i>Melaleuca alternifolia</i> (tea tree oil)	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. pyogenes</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i> , <i>Mycobacterium avium</i>	Terpinen-4-ol, terpinolene, 1,8-cineole, α -terpinenes, γ -terpinene	[61-64]
<i>Momordica charantia</i>	<i>S. aureus</i> , <i>E. coli</i>	Apiole, Trans-nerolidol, cis-dihydrocarve, ol germacrene D	[65]
<i>Myrtus communis</i>	<i>B. subtilis</i> , <i>K. pneumoniae</i> , subsp. <i>paratuberculosis</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>Enterobacter cloacae</i> , <i>Mycobacterium tuberculosis</i> , <i>Enterococcus durans</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>M. avium</i> , <i>L. monocytogenes</i>	α -terpineol, γ -terpinene, eugenol	[66,67]
<i>Nigella sativa</i>	<i>P. aeruginosa</i> , <i>B. cereus</i> , <i>S. aureus</i> , <i>E. coli</i>	Thymoquinone, longifolene, p-cymene, thymohydroquinone, α -thujene	[68-70]
<i>Ocimum gratissimum</i>	<i>S. typhi</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Bacillus</i> spp., <i>Proteus mirabilis</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>E. cloacae</i>	Eugenol, cis-ocimene, trans-ocimene, methyl eugenol, α -pinene, camphor	[71,72]

Table 2. Continued

Medicinal and aromatic plants	Inhibited bacterial species	Bioactive chemical constituents	References
<i>Ocimum kilimandscharicum</i>	<i>E. coli</i> , <i>B. subtilis</i> , <i>Klebsiella</i> spp., <i>S. aureus</i> , <i>Proteus</i> spp., <i>Citrobacter youngae</i> , <i>Pseudomonas</i> spp., <i>Micrococcus</i> spp., <i>Salmonella</i> spp.	Eugenol, borneol, linalool, methyl eugenol	[73]
<i>Ocimum basilicum</i>	<i>B. thermosphacta</i> , <i>E. coli</i> , <i>L. monocytogenes</i> , <i>L. innocua</i> , <i>S. typhimurium</i> , <i>Micrococcus flavus</i> , <i>Pseudomonas putida</i> , <i>S. putrefaciens</i>	γ -Terpinene, methylchavicol	[73-75]
<i>Petroselinum sativum</i>	<i>S. putrefaciens</i> , <i>S. typhimurium</i> , <i>L. innocua</i> , <i>E. coli</i> , <i>P. putida</i> , <i>B. thermosphacta</i> , <i>L. monocytogenes</i>	1-4-tetramethoxy-5-(2-propenyl)-benzene, Myristicin, apiol	[23]
<i>Piper nigrum</i>	<i>S. aureus</i> , <i>E. coli</i>	Paracymene, linalool, terpinen-4-ol, camphene, α -copaene, eugenol, 1,8 cineole, α -pinene, β -caryophyllene, Limonene, δ -3-carene, α -felandeno, myrcene, β -pinene, sabinene, safrole, terpinolene, β -selinene, α -terpinene, α -humulene	[76,77]
<i>Pimpinella anisum</i>	<i>S. typhimurium</i> , <i>E. coli</i>	Trans-anethole	[78-80]
<i>Plectranthus neochilus</i>	<i>S. mitis</i> , <i>Streptococcus sobrinus</i> , <i>E. faecalis</i> , <i>Streptococcus sanguinis</i> , <i>Listeria casei</i> , <i>S. mutans</i> , <i>S. salivarius</i>	α -Pinene, trans-caryophyllene, β -pinene, caryophyllene oxide	[81]
<i>Pogostemon cablin</i>	<i>K. pneumonia</i> , <i>E. faecalis</i> , <i>P. aeruginosa</i> , <i>Helicobacter pylori</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i>	δ -guaieeno; gurjunene- α , α -guaiene, aromadendrene, β -patchoulene, Patchoulol	[82]
<i>Rosmarinus officinalis</i>	<i>Streptococcus agalactiae</i> , <i>S. putrefaciens</i> , <i>L. innocua</i> , <i>E. faecalis</i> , <i>P. putida</i> , <i>L. monocytogenes</i> , <i>B. subtilis</i> , <i>S. typhimurium</i> , <i>P. aeruginosa</i> , <i>Proteus vulgaris</i> , <i>B. thermosphacta</i> , <i>K. pneumonia</i> , <i>B. cereus</i> , <i>M. smegmatis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. typhimurium</i> , <i>S. epidermidis</i>	Camphor, camphene, limonene, geraniol, myrcene, linalool benzoylacetate, linalool, α -pinene, α -terpinolene, bornyl acetate, borneol	[83,84]
<i>Salvia sclarea</i>	<i>S. agalactiae</i> , <i>S. epidermis</i> , <i>E. faecalis</i> , <i>B. subtilis</i> , <i>K. pneumonia</i> , <i>P. aeruginosa</i> , <i>Bacillus pumilus</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , <i>P. vulgaris</i> , <i>E. coli</i>	β -ocimene acetate, Linalool, caryophyllene oxide, linalyl acetate, geranyl acetate	[85,86]
<i>Salvia officinalis</i>	<i>Shigella sonnei</i> , <i>S. aureus</i> , <i>Providencia stuartii</i> , <i>E. coli</i> , <i>L. innocua</i> , <i>M. flavus</i> , <i>B. thermosphacta</i> , <i>L. monocytogenes</i> , <i>S. lutea</i>	1,8-cineole, α -pinene α -Thujone, camphor	[87,88]
<i>Salvia lavandulifolia</i>	<i>P. vulgaris</i> , <i>E. faecalis</i> , <i>P. aeruginosa</i> , <i>K. pneumonia</i>	Camphor, beta-thujone, α -thujone, camphene, terpineol, α -pinene	[89]
<i>Satureja cuneifolia</i>	<i>E. coli</i> , <i>S. enteritidis</i> , <i>Campylobacter jejuni</i> , <i>S. sonnei</i> , <i>P. aeruginosa</i> , <i>B. cereus</i> , <i>S. aureus</i> , <i>L. monocytogenes</i>	Carvacrol and p-cymene	[90,91]
<i>Struchium sparganophora</i>	<i>B. cereus</i> , <i>S. typhi</i> , <i>P. aeruginosa</i> , <i>P. mirabilis</i> , <i>B. subtilis</i>	β -Caryophyllene, germacrene A, α -humulene, germacrene D	[92]
<i>Syzygium cumini</i>	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Neisseria gonorrhoeae</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>B. subtilis</i>	α -caryophyllene, α -limonene 1,3,6-octatriene, delta-3-carene, trans- caryophyllene, α -Pinene, β -pinene	[93]
<i>Thymus vulgaris</i>	<i>S. putrefaciens</i> , <i>Clostridium botulinum</i> , <i>E. coli</i> , <i>S. typhimurium</i> , <i>S. sonnei</i> , <i>S. lutea</i> , <i>S. aureus</i> , <i>M. flavus</i> , <i>L. monocytogenes</i> , <i>B. thermosphacta</i> , <i>L. innocua</i> , <i>Clostridium perfringens</i> , <i>L. monocytogenes</i> , <i>P. putida</i>	Camphene, α -pinene, borneol, β -pinene eugenol, camphor, carvacrol, 1,8-cineole, thymol, linalool	[94]
<i>Thymus kotschyanus</i>	<i>S. aureus</i> , <i>B. cereus</i> , <i>S. epidermidis</i> , <i>E. coli</i>	1,8 cineole, borneol, Carvacrol, E-caryophyllene, thymol	[95,96]
<i>Verbena officinalis</i>	<i>E. coli</i> , <i>S. aureus</i> , <i>L. monocytogenes</i> , <i>S. typhimurium</i>	Borneol, geraniol	[97]
<i>Warionia saharae</i>	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>B. cereus</i> , <i>S. aureus</i>	β -Eudesmol, linalool, 1,8 cineole, trans-nerolidol, p-cymene, terpinen-4-ol, camphor	[97,98]

the bioactive compounds to the surface, the oxidation of EO due to environmental conditions and a considerable change in the biological activity.

3.2. Intervention of nanoemulsion based strategies to overcome resistance

Nanomaterials are being exploited as efficient carriers to deliver lipophilic drugs and bioactive molecules [99-103]. There are many advantages of going nano for drug delivery such as controlled drug release, enhanced drug solubility, improved biocompatibility and bioavailability, augmented therapeutic index, extended therapeutic effects, decreased systemic toxicity and control of increase in drug resistance. According to the recent trends, metal oxide and metal nanoparticles such as gold nanoparticles, silver nanoparticles, zinc oxide nanoparticles have found a solid ground as antimicrobial agents by specifically targeting the quorum sensing regulated pathogenesis and biofilm formation [104-107]. Emerging finds suggests a more biocompatible and enhanced stable polymeric nanoparticles which aids in encapsulation of bioactive materials which can downregulate the quorum sensing and thus effectively prevent biofilm formation [108]. NEs are novel exciting vehicles for delivering EOs for combating biofilm formation because of their many favourable properties such as thermodynamically stability and kinetic stability [109-111]. Unlike antibiotics, the antimicrobial activities of NEs are nonspecific, which makes them excellent tools for broad spectrum activity for wound treatment as well as surface decontamination and further dissipate the possibilities of development of resistance.

NEs is defined as heterogeneous system where one liquid is dispersed into another as nano droplets in the while an emulsifying agent is present [112] which mediated the amalgamation of two immiscible liquids in a micellar solution, under highly controlled conditions as the physicochemical properties of NEs are easily influenced by qualitative and quantitative compositions of both liquid and they are predominantly made in the size range of 20 to 200 nm, which makes it more suitable for the various application based on properties listed in Fig. 1.

There are two types of NEs, oil in water (O/W) and water in oil. Out of these, O/W type of NE are preferred due to its potential to solubilize and encapsulate large quantities of EOs and protect them from hydrolysis, evaporation and from drying out. The base capsules of these NEs are mostly hydrogels, as they can be fabricated using natural or synthetic polymers with three-dimensional network structure with very high-water content. It is highly biocompatible, adheres to surfaces easily which makes them ideal in the form of surface coatings to prevent biofilm formation [113-115].

Various methods of preparation of NEs have been reported, and these can be categorized into two main

divisions: high energy and low energy based on the extent of external energy provided [116,117].

The high energy method utilizes a mechanical device to generate high energy such as homogenizers, ultrasonicator, microfluidizers, and high-pressure homogenizer. These devices disrupt the dispersed phase and convert them into tiny NEs. High pressure valve homogenizer generates pressure of up to 350 MPa in the chamber and factors such as shear stress, cavitation, turbulence converts the coarse droplets to fine droplets. This is further stabilised by the addition of emulsifier. The emulsifier also reduces the re-coalescence and maintain the particle size.

Microfluidization is another technique used for the formulation of NEs in which microchannel of size 300 μm is used to reduce the particle size. The pressure involved here is 200 MPa and the flow of emulsion in the microchannel is up to 400 m/s. This high velocity through the narrow diameter generated high shear stress thereby converting the coarse emulsion into NE.

Few methods that produce stable NEs are high pressure homogenization, microfluidization, ultrasonic homogenization and phase inversion have been summarized in Table 3 [118]. NEs have the basic constituents like aqueous phase, oil/organic phase, and an emulsifying agent/surfactant [119] as depicted in Fig. 2. The surfactant usually contributes to only about 1.5 to 10%. The surfactant also helps in altering the electrostatic charge in the NEs [119,120]. In the formulation of NEs, of EOs it as always preferred to have a natural surfactant and stabilizers like protein or polysaccharides although, studies have shown that the effectiveness is compromised due to slow absorption during homogenization. Surfactant mixing techniques are of two types: mixed surfactants (emulsifier in oil and emulsifier in water) and segregated surfactants (emulsifier in corresponding phases). Formulation of O/W NEs are only successful if the process is associated with the transitional phase inversion, three phase emulsion system. In a study solely on the relationship between different formulation methods found that amphiphilic molecules like sodium dodecyl sulphate and Tweens are more successful [121,122], whereas a success story was reported in the usage of modified starch as emulsifying agent in the formulation of clove and peppermint EO based NEs [123,124]. The mechanism of antimicrobial action has been attributed to the property of intercalating the genetic material within the cells, inhibition of Adenosine triphosphate dependent transport across cell membranes, impairment of cell division, cellular death due to toxicity, increased hydroxylation leading to inhibition of metabolic activities, disruption of cell membranes and inhibition of enzymatic activity. Table 4 lists the types of NEs of EOs reported with its antibacterial effects against bacterial

strains [28,125-140]. EOs which already have antimicrobial properties can be formulated into NEs to enhance their properties and better agent efficiency against biofilms and multidrug resistant bacteria. NEs are less complex to formulate and are generally considered as safe ingredients. With the addition of emulsifier, it becomes a very stable nanomaterial and provide great versatility in application. NEs can also encapsulate various antimicrobial agents and

Table 3. Formulation techniques of nanoemulsion (NE)

Formulation techniques	Mode of action	References
Phase inversion	Phase inversion is achieved when oil is agitated in water to obtain fine dispersion of interconversion between those two phases, by varying the chemical composition or the temperature keeping either as constant.	[118]
Ultrasonication method	Vigorous agitation of regular emulsion by ultrasound renders fine nanodroplets of it. Used mostly for small batch production.	[118]
High-pressure homogenizer	High pressure with the help of a homogenizer when applied to the solution contains two separate phases in the presence of surfactants and co emulsifying agents. Though it generates too much heat thus used only for O/W with > 20% oil content.	[118]
Micro-fluidization	The coarse emulsion yielded from homogenizer is further refined to form stable NEs using an apparatus which is called a microfluidizer with pressure pump at very high pressure.	[118]
High-amplitude ultrasound	Not unlike the ultrasonication method, this is also used for small-batches formulation of NEs. Ultrasonic cavitation generates high shear forces which creates vacuum bubbles and those results in NEs.	[118]

O/W: oil in water.

Table 4. Antimicrobial effect of nanoemulsions (NEs) of essential oils (EOs)

NEs of EOs	Target organism	Antimicrobial activity	References
Monolaurin with Tween 20 and Tween 80 and Tween 40	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i>	Upto 92% inhibition in diluted NE and undiluted NE led a zero viability of <i>S. aureus</i> and <i>E. coli</i> cells in under 1 min	[28]
tri-n-butyl phosphate, soybean oil & with Triton X 100	<i>E. coli</i> O157:H7, <i>S. aureus</i> , <i>Listeria monocytogenes</i> , <i>Salmonella</i> spp., <i>Pseudomonas aeruginosa</i>	Complete reduction in planktonic bacterial viability	[125]
Thyme oil along soybean oil, with Tween 80 eugenol, cinnamon tree bark oil	<i>E. coli</i> , <i>Salmonella enterica</i> , <i>L. monocytogenes</i> , <i>E. coli</i> O157:H7	3 log or 99.9% reduction in <i>L. monocytogenes</i> and <i>E. coli</i> O157:H7	[125,126]
Ethyl oleate with Tween 80	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Antibacterial effect on planktonic bacterial cells of all tested organisms. 3 log or 99.9% reduction in viable counts of the biofilms	[127]
Eugenol with Surfynol 485W	<i>L. monocytogenes</i> , <i>E. coli</i>	Inhibition of growth of <i>L. monocytogenes</i> for up to 48 h. Viable counts of <i>E. coli</i> reduced bile duct ligation under 60 min	[128]
Clove oil with Tween 20	<i>S. aureus</i> , <i>Bacillus cereus</i> , <i>E. coli</i> O157:H7, <i>P. aeruginosa</i> , <i>Salmonella typhi</i> , <i>L. monocytogenes</i>	Exhibited larger zones of inhibition against Gram-positive strains than Gram-negative strains	[129]
Eucalyptus oil with Tween 80 and Tween 20	<i>Proteus mirabilis</i> , <i>S. aureus</i>	Showed significant cell wall disintegration	[130]
Basil oil with Tween 80	<i>E. coli</i>	99.999% reduction in viable counts in under 1 min	[131]
Tea tree oil with Tween 80	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>Propionibacterium acnes</i> , <i>E. coli</i>	Highly efficient in inhibition of tested organisms	[132-134]
Sunflower oil with Surfactin	<i>S. aureus</i> , <i>Bacillus circulans</i> , <i>Vibrio parahaemolyticus</i> , <i>E. coli</i> , <i>S. typhi</i> , <i>L. monocytogenes</i> , <i>B. cereus</i>	Increased bactericidal activity against <i>S. typhi</i> , <i>S. aureus</i> , and <i>L. monocytogenes</i>	[135]
Cinnamon leaf oil with Tween 80	<i>B. cereus</i>	Completely bactericidal (99.999%) in 2 h	[136]
Black seed oil with Tween 80	<i>S. aureus</i> , <i>B. cereus</i> , <i>Salmonella typhimurium</i>	Efficient reduction against <i>S. aureus</i> , <i>B. cereus</i> , and <i>S. typhimurium</i>	[137]
Soybean oil with cephalosporin C (CPC)	<i>Acinetobacter baumannii</i>	Inhibitive reduction in the number of CFU/mL in the duration of 15 to 60 min	[138]
Golden flaxseed oil with Tween 80	<i>S. aureus</i>	Inhibited biofilm formation	[139]
Celery oil and Tween 80	<i>S. aureus</i>	Demonstrated resistance towards microbial strain interaction	[139,140]

antivirals and can even mimic various target receptors of microorganism thereby multiplexing the mode of action. The NEs of EO can be further researched as promising candidates for therapeutic, theragnostic applications against the various nosocomial infections arising due to COVID. The future direction leads to the improvement in the precision and reproducibility of the NEs. Advanced methods of fabrication such as 3D printing has also been reported though it is relatively less explored, the concept and potential to control emulsion size and functionalization by using precise nozzles is a very promising technology.

4. Conclusion

EOs represent natural safe and effective alternatives to chemical antibiofilm agents, specifically against those associated with healthcare environments and medical-devices that are susceptible to multi-drug-resistant bacteria. Captivating results and growing interest are seen in the case of NEs formulation of EOs for the efficient combat against nosocomial infections as they offer plenteous benefits like being a natural antibacterial agent with great physicochemical equilibrium stability, and due to its complex composition, it can target various factor and sites in microbial cellular structure, they are also comparatively inexpensive, non-toxic and safe around even kids. Future studies can be carried out to study the exact model of the mechanism of the NEs of EOs and the therapeutic aspect of proper dosage and duration of treatment and safe handling issues. In conclusion, the prospects of NEs of EOs to prevent and inhibit virulence and biofilm formation in planktonic bacteria seems very promising and due to the versatilities in the formulation techniques, tailor-made NEs can be implemented for various applications, not just to fight nosocomial infections but also other areas where antimicrobial action is mandated. Amongst the plethora of nanomaterials available, stable NEs of EOs and their bioactive compound as nano bio-coatings is an interesting direction to explore.

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Ethical Statements

The authors declare no conflict of interest.

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