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ROLE OF ESSENTIAL OILS IN THE PREPARATION OF TOPICAL ANTIMICROBIAL MICRO EMULSION: A REVIEW

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ABSTRACT

Essential oils are considered as a 'natural' remedy for problems. As they are extremely complex mixtures, they show the effects either alone or in synergy. Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water, surfactant and cosurfactant. As some essential oils are showing very good antimicrobial property they are used as oil phase in the preparation of microemulsion. In this section we are going to review how the bioactive compounds present in natural oils are advantageous in natural oil loaded antimicrobial micro emulsion drug delivery system.

KEYWORDS: essential oils, antimicrobial property, Microemulsion.

INTRODUCTION

Plant essential oils and their major chemical constituents are potential candidates as antibacterial agents. Several types of essential oils and their major chemical constituents from various medicinal aromatic plants s have been reported to possess a wide range of bacterial inhibitory potentials.[1]

Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. These systems are generally used for local skin infection like fungal or bacterial infection or in place where other routes of the drug administration fail. These preparations are applied onto the skin surface for providing local or systemic effects. Topical route favours safe and effective delivery of drug molecules with lower doses as compared to the conventional system.[2]

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. To date microemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration.[3]

Essential oils

Essential oils are aromatic, concentrated oily liquids obtained from plant organs, i.e. seeds, fruits, fruits peel, flowers, roots, rhizome, buds, twigs, leaves, wood or bark.

Extraction of essential oils

Several techniques can be used to extract essential oils from different parts of the aromatic plant, including solvent extraction, expression under pressure, effleurage, and distillation extractions. However, hydro, or steam, distillation is the most commonly used method. The steam distillation is a separation process based on the difference in composition between a liquid mixture and the vapour formed from it. The mechanical process is used exclusively for citrus fruit because their essential oils are contained in micro vesicles located in the peel and may be extracted by pressure or friction. Dry distillation, without addition of water vapor, is used for wood, bark, and roots. For perfume uses, extractions with lipophilic solvents and sometimes with supercritical carbon dioxide are desired. The chemical profile of the essential oil products differs not only in the number of molecules, but also in the stereochemical types of extracted molecules, according to the type of extraction. Therefore, the type of extraction is chosen according to the purpose of the use. The essential oil composition can also be changed after extraction. Depending on the storage conditions, they can quickly become oxidized, and this oxidation is responsible in some cases for variation on the pharmacological activities. To monitor these phenomena, most of the commercialized plant extracts are Chemo typed by gas chromatography and mass spectrometry analysis.[4]

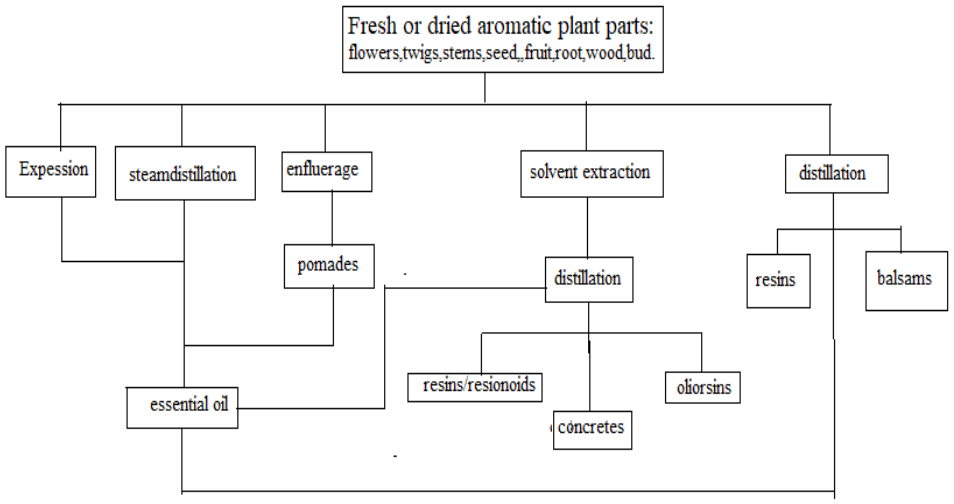

Figure 1: different extraction techniques of essential oil.

Table No.1: Some Essential Oils and Their Antimicrobial Effect.

Sl no	Essential oil	Active constituents	Potency of essential oils (Zone of inhibition) (mm)
1	Eucalyptus [5] *(Eucalyptus globulus)* *(Eucalyptus camaldulensis)*	1,8-cineol and α-pinene	**E globulus (20 µl) E camaldulensis (20 µl)** S. aureus 40 30 E. coli 24 18
2	Mustard Oil[6] (*Brassica nigra)*	oleic acid, linoleic, linolenic acid, erucic acid.	**Mustard Oil (100 µl)** B. cereus 20.0 L. monocytogenes 14.2 M. luteus 15.9 S. aureus 18.9 E. coli 11.9 S. typhimurium 11.67 B. cereus (MTCC 1272) 23.3 S. typhimurium (MTCC 3224) 11.3
3	Lavender[7] (*Lavandula bipinnata)*	linalool, linalyl acetate, cineole B-ocimene, terpinen-4-ol, camphor.	**Lavender (30 µl)** E. coli 100 P. aeruginosa 70 Sh. Dysentery 110 E. faecalis 100 S. aureus 130 B. subtilis 130 Micrococcus 120
4	Lemongrass[8] (*Cymbopogon Citratus*)	Myrcene, Citral, Citronellal, Geranyl Acetate, Nerol, Geraniol, Limonene.	**Lemongrass (20 µl)** Edwardsiella tarda 44 Citrobacter freundii 12 Proteus mirabilis 24 Salmonella enterica 13 A. hydrophila 32
5	Lemon Peel[9] *(Citrus × limon)*	β-Pinene, Limonene, Linalool, α-Terpineol, linalyl acetate, Acetate geranyl, Nerolidol, Acetate neryl and Farnesol.	**Lemon Peel (100 µl)** S. aureus 26 E. coli 19 C. albicans 22 Trichophyton rubrum 17

6	Neem[10] *(Azadirachta indica)*	azadirachtin and the others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin	**Neem Oil (15 µl)** S. typhi 10 E. coli 11 Vibrio cholerae 17 Bacillus subtilis 17
7	Tulsi[11] (*Ocimum tenuiflorum)*	Oleanolic acid, Ursolic acid, Rosmarinic acid, Eugenol, Carvacrol, Linalool, and β-caryophyllene.	**Tulsi oil (20 µl)** E. coli 15 P. aeruginosa 17 S. aureus 41
8	Sandalwood[12] *(Santalum album*.)	Santalol and Santyl Acetate.	**Sandalwood (23 µl)** E. coli 22 S. aureus 17 P. valgaris 14 P. syringae 12 X. malvacearum 24 S. typhi 16 B. cereus 15 E. fecalis 14
9	Cinnamon.[13] (*Cinnamomum zeylanicum)*	Cinnamyl acetate trans-α-bergamotene caryophyllene oxide	**Cinnamon Oil (50 µl)** Bacillus cereus 29 Bacillus subtilis 16 Bacillius sp. 15 S. aureus 20 S. epidermidis 15 Listeria monocytogenes 18 Micrococcus luteus 18 E. coli 16 Klebsiella sp. 14 Pseudomonas aeruginosa 16
10	Bael[14] *(Aegle Marmelos)*	marmelosin, luvangetin, psoralen, tannins, marmin.	**Bael** E. coli 7 (50 µl) S. aureus 5 (50 µl) Bacillus subtilis 7 (50 µl) Klebsiella pneumonia 7 (100 µl) Pseudomonas aeuroginosa 4 (25 µl) Salmonella typhimurium 6 (100 µl)
11	Aniseed[15] *(Pimpinella anisum L)*	trans-anethole, estragole. cis-anethole, carvone, β-caryophyllene, dihydrocarvyl acetate, estragole and limonene	**Aniseed (50 µl)** S. pyogenes 10 S. pneumoniae 26 S. songuins 16 S. epidermidis 11 S. aureus 14 Acinetobacter baumannii 30 Salmonella aerizonae 12 Hafnia alveie 09 Yersinia enterocolitica 10 E. coli 21 Klebsiella pneumoniae 09
12	Basil oil[16] *(Ocimum basilicum)*	Linalool, eugenol, tau-cadinol, α-bergamotene, 1,8-cineole, germacrene D, β-ocimene, α-caryophyllene, camphor, and α-guaiene	**(20 µl) S. aureus E. coli** O. basilicum var. Genovese 15 12 O. tenuiflorum 10 10 O. gratisimum 11 11

13	Thyme oil[17] *(Thymi aetheroleum,)*	thymol, p-cymene, carvacrol, linalool, β-caryphyllene, and terpinen-4-ol	**Thyme Oil (20 µl)**	
			S. aureus	20
			B. subtilis	19
			E. coli	12
			P. aeruginosa	11
14	Sage oil[18] *(Salvia officinalis L)*	1,8-cineole, camphor, α-thujone, β-thujone, borneol, and viridiflorol.	**Sage Oil (20 µl)**	
			S. aureus	13
			B. subtilis	14
			E. coli	7
15	Oregano[19] *(Origanum onites)*	Myrcene, a-terpinene, c-terpinene p-cymene Bornylacetate, Borneol Thymol, Cavracrol	**Oregano Oil (50 µl)**	
			B. amyloliquefaciens	55
			B. brevis	55
			B. subtilis	46
			E. faecalis	49
			E. coli	32
			P. vulgaris	53
			S. aureus	36
			Y. enterocolitica	45
16	Orange[20] *(Citrus sinensis) (Citrus aurantium)*	α-Pinene, limonene, citral, decanal, and linalool, Nonanal and terpineo		**C. aurantium C. sinensis (100 µl)**
			B. cereus	08 12
			S. flexneri	12 13
			K. pneumoniae	13 14
17	Rosemary[21] *(Rosmarinus officinalis L.)*	1,8-cineol, camphor, α-pinene, limonene, camphene linalool.	**Rosemary (50 µl)**	
			S aureus	24
			E. coli	17
18	Black cumin[22] *(Nigella sativa)*	Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α and β-pinene, d-limonene, d-citronellol, p-cymene	**Black cumin (60 µl)**	
			E. coli	23
			S. typhi	21
			S aureus	21
			Enterococcus faecalis	20
			Pseudomonas aeruginosa	18
19	Black pepper[22] *(Piper nigrum)*	caryophyllene, 3-carene, and D-limonene caryophyllene, humulene, caryophyllene oxide spathulenol.	**Black Pepper (60 µl)**	
			E. coli	22
			S. typhi	22
			S aureus	21
			Enterococcus faecalis	19
			Pseudomonas aeruginosa	18
20	Turpentine oil[23] *(Pistacia atlantics Desf.)*	α-pinene, β-pinene, camphene, limonene, dipentene, 3-carene, and terpinolene.	**Turpentine Oil (15 µl)**	
			S. aureus	23
			E. coli	11
			Streptococcus pyogenes	16
21	Nutmeg[24] *(Myristica fragrans)*	alpha. -Thujene, 1R-. alpha. -Pinene, Beta-Fenchene, Camphene, Sabinene, Beta -Pinene, Phellandrene, Carene.	**Nut meg (100 µl)**	
			S. aureus	18
			S. epidermis	16
			Shigella dysenteriae	17
			S. typhi	12
22	Dill[25] *(Anethum graveolens)*	carvone L. limonene, α-phellandrene, apiol, carvon.	**Dill (5 µl)**	
			E. herbicola	8
			P. putida	14

Pharmacological aspects of bioactive natural oils

Essential oils are complex mixtures of numerous molecules that have different mechanisms of action. several oils produce Destruction of outer and inner membrane, good cell penetration role .Phenolic groups present in the essential oils they affect the mitochondrial membranes and depolarize them by decreasing the membrane potential, affecting ionic Ca++ cycling and other ionic channels, reducing the pH gradient, collapsing the proton pump, and depleting the ATP pool

Thus the membrane permeability alters results in the leakage resulting in leakage of radicals, cytochrome C, calcium ions, and proteins, as in the case of oxidative stress and bioenergetics failure, which may explain their pharmacological and possible toxic effects .It also shows some anti mutagenic properties of plant extracts by inhibition of penetration of the mutagens into the cells, inactivation of the mutagens by direct scavenging, inhibition of metabolic conversion by P450 of pro mutagens into mutagens, or activation of enzymatic detoxification.[4]

Microemulsion

Theories of microemulsion

- **Interfacial theory**

It is also called as mixed film or dual film theory. Surfactant and co-surfactant together forms complex film at the oil water interface and thus creates generation of micro emulsion droplets

- **Solubilization theory**

This theory assumes that swollen micellar system forms in the form of micro emulsion. Oil solubilised due to normal micelle formation and water solubilised by reverse micelle formation. Phase diagram is generally useful to understand this theory assumption

- **Thermodynamic theory**

When interfacial tension between two immiscible phases reduces to zero, causes spontaneous formation of micro emulsions and formed negative free energy helps to make emulsion thermodynamically stable.[26]

Methods of preparation

- Phase titration method: Micro-emulsion was prepared by dispersing required quantity of drug in appropriate quantity of oil which is required for the solubilisation of drug. The mixture was homogenized and accurately weighed quantity of surfactant: co surfactant blends was added in small portion with stirring to it. The blends were mixed thoroughly using magnetic stirrer and drop wise double distilled water added to it with continuous stirring around 10minute and rate of stirring was optimized as per requirement of particle size.[27]

- **Phase inversion temperature method**

Phase inversion of microemulsions means conversion of O/W to W/O system by adding excess of the dispersed phase or by rising temperature when non-ionic surfactant is used to change spontaneous curvature of the surfactant which brings system near to minimal surface tension and to form fine dispersed oil droplets. This method shows extreme changes in particle size which further leads to changes in in-vivo and in-vitro drug release pattern.[27]

Components used in topical microemulsion

The following examples are commonly used formulations components of Topical microemulsions.[28]

Table No. 2: Components used preparation of topical microemulsion.

Components	Examples
Oil	Ethyl oleate, Mineral oil, Isopropyl myristate, Decanal, Oleic acid, Vegetable oils (TABLE 1), Medium chain length triglyceride.
Surfactant	Polysorbate (Tween 80 and Tween 20), Lauro macrogol 300, Lecithins, Decyl poly glucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG-8 caprylic/capril glyceride (Labrasol).
Co-surfactant	Sorbitan monooleate, Sorbitan monostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy) ethanol (Transcutol P) and Ethanol.

Applications of topical microemulsion

- **Antifungal**

Superficial mycoses usually respond to topical therapy. In the Settling of eczema, t opical antifungal agents such as ketoconazole are used to reduce the fungal infection caused by Pityrosporum ovale or Malassezia furfur. Antifungal agents e.g. miconazole, ketoconazole, and itraconazole being lipophilic in nature have been formulated as microemulsions to impart to them the advantages like ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared between conventional dosage forms.[2]

- **Antiviral**

A study was done to investigate and evaluate microemulsion and microemulsion-based hydrogel as a topical delivery system for penciclovir in comparison with a commercial cream. Acyclovir containing microemulsion-based formulations for topical delivery were developed using isopropyl myristate/Captex 355/Labrafac as an oil phase, Tween 20 as surfactant, Span 20 as cosurfactant, and water dimethyl sulfoxide as an aqueous phase.[2]

Table No. 3: Recent works on essential oil based antimicrobial microemulsion.

Sl.No	Author	Natural Oil	Components	Affected Bacterial Strains	Report
1	Amrish Chandra[29] (2009)	Nutmeg, olive oil. (*Myristica fragrans)* (*Oleaeuropaea)*	Surfactant: Egg lecithin, Co-Surfactant: isopropyl alcohol, distilled water aqueous phase. Drug: Dexamethasone	Escherichia coli, Aeromonas hydrophilia, Salmonella choleraesuis, Pseudomonas aeruginosa, Staphylococcus aureus.	Their Microemulsions formulations showed increased permeation rate of dexamethasone. Non irritating to the skin. microemulsion based on nutmeg oil demonstrated a significantly higher anti-inflammatory potential.
2	Sitthiphong Soradech[30] (2018)	Diels (*Tiliacora triandra*)	Surfactant: tween 80, Co-Surfactant :95%ethanol, deionized water.	Escherichia coli Shigella sonnei Shigella dysenteriae Agroba cterium spp.	They reported microemulsions are no cytotoxic to human dermal skin fibroblast and melanoma cells.
3	Shweta Bharade,[31] (2019**)**	Neem Oil (*Azadirachta indica)*	Surfactant: Labrasol, Co-Surfactant: plurol oleique Water, salicylicacid.	Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa, and Escherichia coli.	They concluded the microemulsion formulation can be used as a one of the formulation techniques to enhance the bioavailability of the poorly soluble and permeable drugs. And they developed a successful new topical formulation for the delivery of salicylicacid was able to increase the efficacy of the currently available commercial products for the topical treatment of psoriasis.
4	Azka Gulla,[32] (2020)	Clove oil cinnamaldehyde and berberine (*Syzygium aromaticum)*	Surfactant: Tween 80, Co-Surfactant: PEG 400 Water.	Gram-negative bacteria as E. coli, Salmonella, and P. aeruginosa, and Gram-positive bacteria as Staphylococcus, Streptococcus, and L. monocytogenes, and Aspergillus.	They developed formulation was confirmed the combination of herbal drugs, are incorporated in a microemulsion, is sufficient to produce antibacterial activity against S. epidermidis.
5	Qixin Zhong[33] (2016)	Cinnamon bark oil, soybean oil. (*Cinnamomum verum)*	Surfactant: Tween 80, Co-Surfactant: propylene glycol, Water.	Listeria monocytogenes, Salmonella enterica.	They reported antimicrobial activity of essential oils.
6	Khokhra Sonia[34] (2011)	tea tree oil (*Melaleuca alternifolia)*	Surfactant: tween 80, Co-Surfactant: isopropanol, Isopropyl myristate ethanol, and propylene glycol as water.	Mycobacterium avium ATCC 4676 (105), Escherichia coli, Haemophilus influenzae, Streptococcus pyogenes, and Streptococcus pneumoniae.	They concluded the Tea tree oil has anti-inflammatory effects that could help to treat patients suffering from psoriasis.
7	Rahmah Elfiyani,[35] (2011)	Eucalyptus Oil (*Eucalyptus globulus)*	Surfactant: Tween 80, Co-Surfactant: ethanol, Water.	Escherichia coli and Staphylococcus aureus.	They reported Eucalyptus oil microemulsion stability get increased by increasing in the concentration of Tween80and ethanol.

8	Fabio Valoppi[36] (2017)	Lemon oil (*Citrus × limon)*	Surfactant: Tween 80, Co-Surfactant: ethanol	Pseudomonas aeruginosa, Escherichia coli and Enterobacter aerogenes.	They studied Terpenes present in lemon oil opposes the formation of stable micelles during phase inversion. Loading capacity of lemon oil increased by using peanut oil.
9	Pensak Jantrawut[37] (2018)	orange oil (*Citrus sinensis)*	Surfactant: Tween 80, Co-Surfactant: propylene glycol.	Staphyloccocus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa.	They reported Orange oil film (control) showed a loose structure with micropores inside film's matrix because orange oil evaporated during the drying process film showed higher antimicrobial activity against S. aureus and P. acnes than the control film.
10	Vijayalakshmi Ghosh[38] (2012)	Mustard oil (*Brassica nigra).*	Surfactant: Tween 20, water.	Escherichia coli, Staphylococcus aureus, Vibrio cholerae, Klebsiella spp. and Salmonella spp.	Their study showed very good antimicrobial effect against E. coli mustard oil microemulsion demonstrated bactericidal activity by altering the functional groups present on bacterial surface.

Review of litreture

Burt Sara et al (2004)., investigated antibacterial activity of essential oils against Listeria monocytogenes, Salmonella typhimurium, Escherichia coli, Shigella dysentery, Bacillus cereus and Staphylococcus aureus at levels between 0.2 and 10 µl/ml. They identified number of Essential oil components, as effective antibacterial, e.g. carvacrol, thymol, eugenol, perillaldehyde, cinnamaldehyde, and cinnamic acid, having minimum inhibitory concentrations of 0.05–5 µl ml *in vitro*. They reported that hydrophobicity of essential oils enables them to partition in the lipids of the cell membrane and mitochondria, rendering them permeable and leading to leakage of cell contents.[39]

Gull A et al (2020) They investigated a combination therapy of clove oil, cinnamaldehyde and berberine in a microemulsion against Staphylococcus epidermidis. The microemulsion was prepared using an oil mixture (clove oil and cinnamaldehyde), surfactant mixture Tween 80 and PEG 400 and water. It Shows the 67.81 nm average droplet size and 36.5 cps viscosity. The optimized formulation shows antibacterial effect on planktonic as well as biofilm-forming bacterial cells.[32]

M Dávila et al (2020) They studied antimicrobial effect of essential oil based micro emulsion against Escherichia coli and Listeria monocytogenes. They consider cinnamon essential oil, oregano essential oil, and rosemary essential as oil phase tween80 as emulsifier. The microemulsions (oil-in-water, O/W) of essential oils were prepared using high-frequency ultrasound, applying a wave amplitude of 84 lm for 15 min. The antimicrobial activity was determined by inoculating 108 CFU/mL of bacteria. The minimum inhibitory concentration and the minimum bactericidal concentration less than values obtained for the non-encapsulated essential oil. This study demonstrates that high-frequency ultrasound is a suitable technique for obtaining stable microemulsions to deliver natural antimicrobials.[40]

Aggarwal et al (2013)., investigated microemulsion formulation of Griseofulvin for the treatment of dermatophytosis. The developed formulation was evaluated for drug content, pH, stability, dermato pharmacokinetics and antifungal activity against MicroPorum canis using guinea pig model for dermatophytosis. They reported that formulation was non-sensitizing, histo pathologically safe, and stable at 5±3°C, 25±2°C and 40±2°C for a period of six months. [41]

CONCLUSION

Essential oils are extremely complex mixtures which consists of multiple chemical constituents, they act against the certain bacterial strains very effectively either in alone or synergy with the drug. Improper and extensive usage of antibiotics results in rise of antibiotic-resistant microbes. Increase in the doses may cause toxicity, to overcome this problem essential oils with good antimicrobial effect are used. They show synergism with the drug and shows bacteriostatic or bacteriocidic effect without or less side-effects. essential oils show good therapeutic effect in the encapsulated system then in the free form. Bioactive components of essential oils are advantageous in the preparation of essential oil loaded microemulsions.

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