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Essential Oils as Skin Permeation Boosters and Their Predicted Effect Mechanisms

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Abstract

Transdermal drug delivery system is an administration route, where active molecules are administered through the skin with advantages of a lesser amount of hepatic first pass effect, constant plasma drug concentration and safety. The skin has a barrier function for the passage of medicines as well as toxic molecules, thus, permeation boosters/enhancers are used to increase the permeability of medication through the skin. In this mini review, recent studies on essential oils that can be used to increase skin penetration in transdermal applications and the possible mechanisms of their effects are reviewed. Essential oils increase skin penetration by interacting with the stratum corneum (SC). They were found to be successful in increasing skin penetration of both lipophilic and hydrophilic drugs. Moreover, essential oils do not accumulate in the body since they are volatile, and also are easily discharged from the body through feces and urine. They are preferred because essential oils are natural, mostly do not damage the skin while increasing skin penetration, less toxic, and less allergenic.

Introduction

Essential oils are fragrant secondary metabolites that are usually distilled/ extracted from plants. They are frequently used in different industrial fields such as preservatives-aroma providers in food, fragrance-antioxidant-antiaging in cosmetics, cleaning, and as aromatherapeutic- phytotherapeutic agents in health. Essential oils are applied in the treatment of various diseases predominantly due to their antimicrobial and antiviral properties[1].

Topical and transdermal drug delivery system is an administration method, where effective medication is administered through the skin that has advantages such as lower hepatic initial passage, constant plasma drug concentration and fast discharge via urine and feces. Compared to oral administration, the metabolism of drugs in the skin is very low in transdermal applications. Skin absorption depends on many factors such as source of the skin, the special structure of the skin, and the features of the applied compound/s. Stratum corneum (SC), the outermost layer of the inanimate epidermis, limits the permeation of molecules into the skin. SC has a very important function of protecting the underlying tissue from many factors such as infection, dehydration, chemicals and mechanical stress[2]. Due to the fact that skin penetration enhancers are important to support percutaneous absorption of the drugs by lipid disruption, protein modification or partitioning promotion functions reducing the barrier function of the skin, allowing molecules to pass through the layer of the skin faster[3]. The most important point for safe and effective drug delivery through the skin is the use of penetration

enhancers that cause a temporary, reversible reduction in the barrier function of the SC. Essential oils, natural alternative to former penetration enhancers, with their promising permeation enhancing activity, which are very well explained in the review of Herman and Herman, are easily penetrated by the skin[2,4]. In this mini-review, the effects of recently examined essential oils that increase skin permeability for topical and transdermal administration routes were evaluated. *In-vitro*, *in-vivo* and *ex-vivo* studies on penetration through the skin were included and possible mechanisms of permeability enhancing effects have been reviewed.

Evaluation of the Studies on Permeation Booster Effect of Essential Oils

Permeation boosters can increase drug diffusivity through the SC by affecting skin structure by means of lipids or proteins. They should be compatible with drugs, should work rapidly and effectively allowing therapeutics into the body whereas preventing loss of skin endogenous molecules (such as electrolytes, fluids), should be non-irritating, non-toxic and non-allergenic with no other pharmacological effect rather than desired ones. Alcohols including low molecular weight alkanol, glycols, glycerides, azone, urea, oxazolidinones, pyrrolidones, n-disubstituted amino acetates, sulfoxides, surface-active agents and fatty acids are some of the groups used as chemical penetration enhancers[5]. Chemical enhancers might provide poor permeability across SC, consequently, increasing their concentrations to maintain their activity that might cause side effects such as skin irritation and cytotoxicity. These efficacy, bioavailability and safety issues limit the preferences of chemical enhancers. Essential oils can easily penetrate the skin with their lipophilic characters and are easily discharged from the body through feces and urine[2]. Table 1 shows the recently studied essential oils that increase the penetration of both hydrophilic and lipophilic drugs through the skin, additionally, table also includes possible effective mechanisms of the essential oils.

Table 1: Studies evaluating the permeation boosting effects of essential oils

Essential oil(s)	Drug	Application	Results	Mechanism/Observation	References
Aloe vera, cumin, rose and tea tree oils	**Losartan potassium** (antihypertensive) (hydrophilic drug)	Wistar rats' abdominal skin (*in vitro*)	Penetration enhancing effectiveness: *A. vera*> rose > cumin> tea tree. Only enhancer to provide target flux required to deliver the therapeutic transdermal dose of losartan potassium: *A. vera* oil.	Extraction of lipid bilayers in SC (All the examined penetration enhancers) Reduction in barrier resistance of SC, intracellular transport by dekeratinization of corneocytes (*A. vera* oil)	[6]
Angelica, chuanxiong, cinnamon, clove and *Cyperus* oils (Doses: 25, 50 ve 75 µg / mL)	**Ibuprofen** (nonsteroidal anti-inflammatory) (lipophilic drug)	Dysmenorrheal model mice (*in vitro*)	Angelica and chuanxiong oils increased the penetration of ibuprofen. The pain-relieving effect of ibuprofen has higher effect with chuanxiong oil compared to ibuprofen exclusive of essential oils. Cytotoxicity of essential oils was found to be much lower than azone. Cell viability at the concentration of 75 µg/mL: Clove >Angelica oil > chuanxiong >*Cyperus*> cinnamon >azone.	Disturbing the ordered intracellular lipid structure between corneocytes in SC with an increase in intercellular diffusivity	[7]
Angelica, chuanxiong (*Rhizoma Liustici* chuanxiong), cinnamon, clove, *Cyperus* and turpentine oils (% 3 w / v)	**Ibuprofen** (nonsteroidal anti-inflammatory) (lipophilic drug)	Sprague-Dawley rats abdominal skin (*in vitro*)	Essential oils (% 3 w/v) possess lower skin cell toxicity and higher penetration effectiveness compared with azone, the common penetration enhancer. The enhancement ratio: Cinnamon (2.63) > chuanxiong (2.60) >Cyperus(2.49) > turpentine (2.23) > clove oils (1.97)>Angelica (1.83) >azone (1.77).	Disintegration of the highly ordered intercellular lipid structure in SC	[8]
Cinnamon oil	**Ibuprofen** (nonsteroidal anti-inflammatory) (lipophilic drug)	Rat abdominal skin (*in vitro*)	The enhancing rate: Cinnamon oil (3.56) >azone (2.47) >cinnamaldehyde (1.13)	-	[9]

Copaiba oil (% 1-50 and W/w)	**Celecoxib**(% 2 w/w) (nonsteroidal anti-inflammatory) (lipophilic drug)	Porcine ear skin, Swiss mice-44 (*in vitro* / *in vivo*)	25% copaiba oil increased penetration and anti-inflammatory activity of celecoxib.	Disorganization of SC Increased cell infiltration Induced angiogenesis (without irritation) Inhibited protein extravasation and ear oedema	[10]
Eucalyptus oil (10 % v/v)	**Chlorhexidine digluconate**(2% w/v) (antiseptic)	Full-thickness donor human skin (*in vitro*)	The combination increased the amount of chlorhexidine digluconate, which penetrated into the skin within 2 min (10%(v/v) eucalyptus oil + 2% (w/v) chlorhexidine digluconate + 70% (v/v) isopropyl alcohol). Eucalyptus oil significantly increased the penetration of chlorhexidine digluconate into the layers of the skin. Combination of eucalyptus oil with chlorhexidine has produced a synergistic antimicrobial effect.	Increasing skin penetration by disrupting intracellular lipids and changing SC membrane fluidity	[11]
Eucalyptus sp. oil (5%)	**2,3,5,6-tetramethylpyrazine** (cardiovascular and cerebrovascular disorders treatment)	Sprague-Dawley rat (*in vitro* / *in vivo*)	Eucalyptus oil was found to enhance the penetration to the greatest extent with the optimal concentration being 5%. The flux was 4.5-fold greater than the no enhancer control.	Changing of SC	[12]
Eucalyptus sp., peppermint and turpentine oils (15%)	**Ketoconazole**(100 mg) (antifungal) (lipophilic drug)	*in vitro*: cellulose membrane *ex vivo*: pig skin	Eucalyptus oil formulation revealed *in vitro* release and greater permeation compared with other essential oil containing formulations. (eucalyptus oil> turpentine oil > peppermint oil > control)	Changing and increasing permeability of the skin barrier	[13]
Eucalyptus, clove and lemon oils	**Felodipine**(0.04 g) (antihypertensive) (lipophilic drug)	Rabbit ear model (*in vitro*)	Penetration study showed the superiority of oil containing niosomes. Clove oil or eucalyptus oil showing a trend of increased drug release compared with plain niosomes. In contrast, lemon oil reduced drug release rate.	Membrane fluidization and modulating	[14]
Frankincense and myrrh essential oils	**Chuanxiong** (pain relief and promoting blood circulation, plant extract)	Mice skin (*in vitro*)	Frankincense and myrrh essential oils increased skin blood flow and transdermal permeability more than azone.	Promote the elimination of drugs from epidermis to dermal capillaries through increase of skin blood flow	[15]
Mentha haplocalyx essential oil	**Ferulic acid** (antioxidant and anti-inflammatory), **geniposide** (hepatoprotective, neuroprotective, anti-diabetic, antiproliferative, antioxidant), **osthole** (plant derived coumarin), **puerarin** (cardioprotection, neuroprotection, antioxidant, anticancer, antiinflammation), **tetramethylpyrazine** (treatment of coronary heart disease, diabetes, cancers, liver injury)	(*in vitro*)	Essential oil increased the penetration of drugs.	Affecting SC lipids	[16]

Patchouli oil (0-1%w/v, 7 formulation)	**Indomethacin**(30 mg) (nonsteroidal anti-inflammatory), (lipophilic drug)	Wistar albino rats (*in vitro*)	Patchouli oil enhanced the permeation of indomethacin across rat epidermis with increasing concentration of patchouli oil. (1% w/v of patchouli oil-maximum transdermal flux)	Increasing transdermal penetration by partial extraction of lipids and change protein conformation in the SC	[17]
Rosemary essential oil (0.1,0.5,1.0%w/w)	**Diclofenac sodium** (% 1) (nonsteroidalanti-inflammatory) (lipophilic drug)	Swiss–Webster mice (*in vivo*)	Rosemary essential oil at 0.5% and 1% concentration increased the percutaneous absorption of diclofenac. The most enhancing effect was observed in 1% concentration.	Increased lipid disruption in the SC	[18]
Sinapis alba L. seed essential oil (0.5,2.0,5.0% v/v)	**Paeonol** (anti-inflammatory, anti-tumor activity, treatment of neurodegenerative and cardiovasculardiseases), **osthole** (plant derived coumarin), **5-Fluorouracil** (antineoplastic)	Sprague Dawley rats, human skin epidermal keratinocytes cells (*in vitro*)	Compared to azone, *S. alba* oil showed greater penetration enhancing effects in all drugs. Penetration effect of essential oil differed according to the polarity of drugs: Medium polarity > hydrophilic > lipophilic. [($log_{Ko/w}$) n-octanol/water partition coefficient:5-Fluorouracil −0.95; paeonol 2.054; osthol 3.85] The study showed that *S. alba* oil induced less irritation than azone and furthermore it didn't induce skin irritation when the concentration was lower than 2% (v/v).	Induced skin lipid structural disorder Increased the distance between the SC, increased cell membrane fluidity Cellular experiments: It increased intracellular Ca^{2+} concentration, inhibited Ca^{2+}-ATPase activity, changed the membrane potential in human skin epidermal keratinocytes cells, which promoted drug transfer into the skin	[19]
Turpentine oil (0-3%)	**Ibuprofen** (1% w/v) (nonsteroidal anti-inflammatory) (lipophilic drug)	*in vitro*: cellulose membrane *ex vivo*: rabbit skin	Formulation with 3% turpentine oil showed a maximum flux of 17.26 mg/cm^2/h across the rabbit abdominal skin and 10.87 mg/cm^2/h across artificial skin.	Disruption of the SC	[20]
Turpentine oil (0-2.5%,6 formulation)	**Diclofenac diethylamine** (20% w/w) (nonsteroidal anti-inflammatory) (lipophilic drug)	*in vitro*: artificial skin *ex vivo*: rabbit abdominal skin	The increasing concentration of turpentine oil showed an increase in total drug permeation, but the effect was not so pronounced after adding 2% concentration of turpentine oil.	Increasing disruption of the SC layer	[21]
Wintergreen oil	**Osthole** (plant derived coumarin) (lipophilic drug), **geniposide** (hepatoprotective, neuroprotective, anti-diabetic, antiproliferative, antioxidant) (hydrophilic drug)	Rat skin (*in vitro*)	The wintergreen oil in appropriate concentration could effectively increase penetration of osthole and geniposide. It provided greater penetration for the lipophilic osthole.	Affecting SC lipids reduced dense SC and the skin barrier function	[22]
Zanthoxylum bungeanum essential oil (1-10%)	**Indomethacin**(nonsteroidal anti-inflammatory) (lipophilic drug), **5-fluorouracil** (antineoplastic) (hydrophilic drug)	Sprague-Dawley rats, HaCaT cells (*in vitro*)	*Z. bungeanum* oil facilitated the penetration of both hydrophilic and lipophilic drugs in a concentration-dependent. It had a higher efficiency for the penetration of the hydrophilic drugs than for that of the lipophilic drugs	SC / vehicle partition coefficient saturated solubility changes of SC structures	[23]

Discussion and Conclusion

Permeation boosters/penetration enhancers, which can facilitate the passage of the drug through the skin layers, are used as excipients in topical or transdermal formulations. The penetration enhancing effects of essential oils with important biological activities are promising. In this study, it was determined that essential oils increase the penetration of plant extracts (i.e. Chuanxiong)[15], hydrophilic drugs as well as lipophilic drugs (such as indomethacin and 5-fluorouracil)[23](Table 1). Penetration effects of essential oils differ according to the polarity of the drugs[19,23]. In addition, the chemical nature of the essential oil also affects the penetration of drugs. For instance, *Sinapis alba* L. seed and *Z. bungeanum* essential oils increased the absorption of 5-Fluorouracil, a hydrophilic drug, more than osthole and indomethacin, lipophilic drugs [19,23]. On the other hand, wintergreen oil increased the absorption of the lipophilic drug osthole more than the hydrophilic drug geniposide[22]. While hydrophilic drugs are absorbed more in the presence of essential oils with polar functional groups, lipophilic drugs are absorbed more in the presence of essential oils with nonpolar functional groups. This condition also highlights the importance of choosing the appropriate penetration enhancer.

Model drugs listed in Table 1 are generally drugs with high hepatic first pass metabolism, low half-life, and therefore low bioavailability. By administering these drugs transdermally and together with essential oils, the hepatic first pass effect is lessened or maybe eliminated and the dose can be reduced. Essential oils facilitate the passage of drugs through the skin, whereas, the effect of essential oils on the solubility of the model drug is not clear. Lan et al., found that *Z. bungeum* oil slightly reduced the saturated solubility of 5-fluorouracil with increasing oil concentration, while indomethacin gradually improved the saturation solubility, the most probably *Z. bungeum* oil significantly altered the thermodynamic activity of indomethacin[23]. Jiang et al., observed that the solubility of ibuprofen did not significantly differ with the effect of in between essential oils and azone, that the drug's thermodynamic activities did not differ significantly. However, the solubility of ibuprofen in chuanxiong oil was slightly higher than that of other essential oils[8].

Essential oils are a blend of phytochemicals including active ingredients with biological activities. When choosing essential oils as penetration enhancers in formulations, the biological properties of essential oils should be taken into consideration. Synergistic effects will be observed in formulations chosen according to the biological activities of essential oils. Karpanen et al., presented that the use of eucalyptus essential oil, which has antimicrobial activity, in a formulation increases the penetration of chlorhexidine as well as its antimicrobial activity[11]. Similarly, in another study, adding 25% copaiba oil to the formulation increased both the penetration and anti-inflammatory activity of celecoxib[10].

Evaluation revealed that the main mechanism for increasing the penetration of the drugs by essential oils is the disruption of the highly ordered intracellular lipid structure in SC. Additional mechanism includes changing the SC membrane fluidity by means of essential oils that cause to broken of hydrogen bonds, changes in the condition, conformation, structure, of SC lipids and keratin. The ion pump in the structure of the cell membrane provides an ion concentration gradient in and outside of the cell. Disruption of balance intracellular and extracellular Ca^{2+} impairs membrane potential and membrane fluidity of keratinocytes. In order to give an example, studies on *Sinapis alba* L. seed essential oil demonstrated that the oil inhibited Ca^{2+}- ATPase activity thus enhanced intracellular Ca^{2+} concentration. Increasing Ca^{2+}concentration changed the membrane fluidity and intercellular junctions as a result, improved intercellular space. Subsequently, enhancing the penetration occurred by changing SC structure[19]. All these conditions temporarily disrupt the barrier of the skin structure, consequently, escalation of drug permeability is observed. In order to reveal the mechanisms of increase in skin permeability, Fourier transform infrared spectroscopy (FTIR) was exploited. The study revealed that changes in the barrier function of the skin caused by essential oils were reversible, in other words, essential oils increased permeability without causing permanent damage. For instance, eucalyptus, peppermint and turpentine oils increased the penetration of ketoconazole without any permanent change in the structure of skin barriers[13].

Some studies in comparing the penetration enhancing effect of essential oils with other chemical enhancers such as azone have shown the moderate elevated activity over essential oils[7-9,15,19]. Ruan et al., demonstrated that increased penetration enhancer concentrations (both azone and essential oil) cause to increase in interlayer distance of SC, significantly reducing the number of SC layers. At 5% concentration, the SC structure peeled off after severe damage[19]. Essential oils are considered less toxic than chemical boosters, as they used in very less concentrations, easily penetrate the skin and are easily excreted from the body through feces and urine. However, more controlled studies using different *in vitro*, *in vivo* experiments with various skin origin and penetration enhancers are needed to prove the superiority of the individual ones among the all tested enhancers. Furthermore, the evaluation and comparison of the penetration boosting effects of essential oil and its active components proved that the multi-component structure of the essential oil creates a synergic effect. Li et al., showed that the penetration enhancing effect of cinnamon oil on ibuprofen is greater than only cinnamaldehyde, which is the main component of cinnamon oil[9].

Since the availability of human skin, which is the safest model for penetration tests, is limited, various *in vitro* and *in vivo* animal models with pig, porcine, rabbit, rat skins were used in above mentioned studies reviewed in this report. The researchers should keep in mind that to predict percutaneous absorption and correct correlation between animal and human skin models might differ sometimes since absorption can be higher in animal skin due the different skin structure[2]. In order to eliminate finding a skin model and origin of a skin, Gupta et al., compared the experimentally reported effects of chemical permeability enhancers on skin from with the simulation results showing that simulation results were in good agreement with the experimental measurements[24]. They concluded that the studies presented validate the utility of *in-silico* models for designing, screening and testing of novel and effective chemical permeability enhancers, which can be applied to the essential oils in further.

In the studies examined in table 1, concentrations of essential oils were associated with a higher penetration enhancing effect[7,17,18,20]. It has been shown that increased penetration by temporarily weakening the SC barrier without damaging viable cell, therefore, essential oils mostly do not cause irritation and are safe[12,17]. However, undesirable cases can be observed depend on origin of the oil, the sensitivity of an individual or misusage during the application of the essential oils. There has been a case of laryngeal edema as a result of accidental ingestion of wintergreen oil (5 ml) by a child[25]. There are contact dermatitis and contact allergy cases due to topical use of lavender, lemongrass and peppermint oils[26]. In the light of this information, the formulation should be prepared selecting origin of oils and consuming essential oils at appropriate concentrations.

Another point to be should be considered about the usage of essential oils with carrier oils. Essential oils are diluted with carrier oils in aromatherapy. While diluting the essential oil, the effect of carrier oils on transdermal applications should be taken into account. Matsumoto et al., indicated that jojoba oil, which is frequently used as a carrier oil, elevates serum non-esterified fatty acid (NEFA) levels after 30 minutes transdermal administration onto mice. That bring attention to possible effect of carrier oils[27]. Solanki et al., investigated the effect of topical application of safflower oil and coconut oil on infants. They showed that topically applied oil can be absorbed in newborns and the fatty acid components of the oil can affect changes in fatty acid profiles of massaged infants[28].

According to recent studies, essential oils can be easily found, reliable penetration enhancer option in topical and transdermal preparations due to their natural, less toxic and less allergenic features. However, further studies are needed with individual essential oils with different drugs before they can replace former penetration enhancers.

Conflicts of Interest Statement

The authors, Ufuk Koca-Caliskan and Methiye Mancak-Karakus certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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