ELSEVIER

Status of terpenes as skin penetration enhancers

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Since its introduction, transdermal drug delivery has promised much but, in some respects has still to deliver on that initial promise, due to inherent limitations imposed by the percutaneous route. The greatest obstacle for transdermal delivery is the barrier property of the stratum corneum. Many approaches have been employed to breach the skin barrier, of which, the most widely used one is that of chemical penetration enhancers. Of the penetration enhancers, terpenes are arguably the most highly advanced and proven category and are classified as generally regarded as safe (GRAS) by the Food and Drug Administration. This paper presents an overview of the investigations on the feasibility and application of terpenes as sorption promoters for improved delivery of drugs through skin.

Introduction

Drug delivery via the percutaneous route potentially has many advantages over intravenous and oral administration [1] but human skin is designed to be a barrier to the passage of molecules either from inside to out or vice versa [2]. The principal barrier to topical drug delivery is the stratum corneum, which poses a formidable barrier to drug penetration, thereby limiting topical and transdermal bioavailability [3]. Many approaches have been employed to mitigate stratum corneum permeability, and the most commonly used approach is that of sorption promoters, also known as penetration enhancers [1,4]. These have been used in transdermal research since the 1960s [5]. Terpenes are a very safe and effective class of penetration enhancers, obtained from natural sources, the FDA classifies them as generally regarded as safe (GRAS) [6]. They cause no skin toxicity or if any, only mild irritation [7,8]. Even terpenes, which are considered to be skin irritants, did not cause lasting erythema [9]. Terpenes consist of repeated isoprene (C_5H_8) units [10] joined together from head to tail [11]. Apart from carbon and hydrogen, terpenes may also contain oxygen [2] such as in carvone, thujone, menthol, and so on. Terpenes can be classified depending upon the presence of the number of isoprene units [11] (Table 1) and the chemical groups (i.e. alcohols, esters, ketones, and so on) [13] (Table 2).

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As the name suggests, volatile oils or essential oils are volatile in nature. They are widely used therapeutically, as inhalations (e.g. eucalyptus oil), orally (e.g. peppermint oil), as mouthwashes and gargles (e.g. thymol). Also, many essential oils are used in aromatherapy nowadays. Clove oil and thyme oil are used as antiseptics, owing to their high phenol content [12]. They are also used as flavoring agents (e.g. lemon oil), in perfumery (e.g. rose oil), or as starting materials for the synthesis of other important products (e.g. turpentine oil). Besides these uses, terpenes (constituents of volatile oils) exhibit excellent permeation-enhancing effects to facilitate transdermal drug delivery [6]. Terpenes can enhance the permeation of both lipophilic drugs (such as testosterone) and hydrophilic drugs (such as propranolol) [6]. In this paper we present a brief introduction to terpenes followed by a review of various reports on the utility of terpenes as penetration enhancers.

Factors governing the activity of terpenes as penetration enhancers

The activity of terpenes as penetration enhancers is primarily related to their chemical structure as well as the physico-chemical properties of the drug, as mentioned below.

Lipophilicity

High lipophilicity is an important structural feature for terpenes as sorption promoters for lipophilic drugs [14]; accordingly, hydrocarbon, nonpolar terpenes (e.g. limonene) are more potent enhan-

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TABLE 1

Classification of terpenes depending upon the number of isoprene units

C_{10}	Monoterpenes
C_{15}	Sesquiterpenes
C_{20}	Diterpenes
C_{25}	Sesterterpenes
C_{30}	Triterpenes
C_{40}	Tetraterpenes

cers for lipophilic drugs (indomethacin) than oxygen-containing polar terpenes [15,16] (1,8-cineole, carvone) and vice versa [17].

Size and chirality

The size of a terpene is an important criterion in determining its enhancing capacity. Smaller terpenes tend to be more active sorption enhancers than larger terpenes [2].

Terpene stereoisomers also affect the enhancement potential of particular molecules. It has been commonly observed that the (−) enantiomer of a terpene is a more effective penetration enhancer than the corresponding (±) racemate or the (+) isomer [18].

Boiling point and energy of vaporization

The boiling point of a terpene is inversely related to its skin permeation-enhancing capacity, for example, cineole, with a boiling point of 173 °C, is the most effective enhancer for the skin permeation of zidovudine compared to other terpenes with higher boiling points (carvone: 230 °C; pulegone: 224 °C; menthone: 210 °C; α-terpineol: 217 °C; and menthol: 215 °C) [17].

A similar inverse relationship exists with respect to energy of vaporization. Terpenes with lower energies of vaporization show greater permeation-enhancing properties than those with high energies of vaporization towards hydrophilic drugs, for example, cyclic ether terpenes, such as anethole and cineole are good enhancer candidates for the hydrophilic drug, 5-fluorouracil [14].

Degree of unsaturation

Smaller alcoholic terpenes with a higher degree of unsaturation are good candidates to enhance the permeation of hydrophilic drugs [14]. On the contrary, it has also been reported that terpenes with a minimal degree of unsaturation, like menthol and cineole, are good sorption promoters for polar and water-soluble drugs [19].

The applications of various individual terpenes in the area of transdermal drug delivery are discussed herein and a summary is presented in Table 3.

TABLE 2

Classification of terpenes depending upon their chemical composition

Alcohols	Linalool, geraniol
Esters and alcohols	Linalool, linalyl acetate, menthol, menthyl acetate
Aldehydes	Cinnamaic aldehyde, cinnamic aldehyde
Ketones	Carvone, thujone
Phenols	Eugenol, thymol
Ethers	Anethole, cineole
Peroxides	Ascaridole

Menthol

Menthol is obtained from flowering tops of *Mentha piperita*. The main form of menthol occurring in nature is (−)-menthol. Its melting point is 42–45 °C (see http://www.en.wikipedia.org/wiki/Menthol) and it is frequently used in antipruritic creams and as an upper respiratory tract decongestant [20]. Menthol has been a traditional and, arguably, the most effective penetration enhancer that, along with limonene, can be considered as the prototype for the use of terpenes as penetration enhancers. It has been used as an enhancer for transdermal delivery of variety of drugs including imipramine hydrochloride [19], caffeine, hydrocortisone, triamcinolone [21], propranolol hydrochloride [22], and zidovudine [17,23]. Synergistic application of terpenes with iontophoresis has also been described in the literature; terpenes, such as menthol, cineole, and terpineol, when used along with iontophoresis have been shown to increase the flux of buspirone hydrochloride by more than 200-fold compared to a 15-fold increase using iontophoresis alone. Of the above-mentioned terpenes, menthol yielded a higher flux compared to cineole and terpineol [24].

Menthol has been reported to be a better penetration enhancer than other terpenes, viz., terpineol, menthone, pulgeone, carvone, and so on, and is comparable to cineole for skin permeation enhancement of imipramine hydrochloride [19]. Menthol also seems to be a better penetration enhancer for the transdermal delivery of propranolol hydrochloride. In one study [25], four terpenes (L-menthol, (+)-limonene, (±)-linalool and carvacrol) at three different concentrations (1, 5, and 10% (w/w)) were investigated for their ability to enhance permeation of propranolol hydrochloride in a mouse skin model. The permeation of propranolol was not affected by increasing the terpene concentration from 5 to 10% (w/w), with the exception of linalool which shows an exaggerated concentration effect. Among the above terpenes, menthol (1%, w/w) was claimed to be the best penetration enhancer, as it presented relatively higher skin permeation with a shorter lag time than the other compounds. In other work, Fujii *et al*. compared the permeation-enhancing effect of L-menthol with *p*-menthane-3,8-diol (MDO), a metabolite of L-menthol, through Yucatan micropig skin using antipyrine (a hydrophilic drug) and indomethacin (a lipophilic drug) as model drugs. They concluded that both L-menthol and MDO have a similar enhancing effect on the skin permeation of indomethacin, while MDO exhibits a lesser effect on percutaneous transport of antipyrine [26].

The major purported mechanism of action for permeation enhancement is a disruption of the hydrogen bond network at the head of ceramides in the lipid bilayer. This has been proposed by many workers, based on differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) studies [19,27,28]. DSC and FT-IR techniques are commonly employed for the determination of mode of action of terpenes on permeation of actives through skin. DSC provides information about changes in the thermotropic behavior of stratum corneum proteins and lipids on interaction with terpenes, while FT-IR provides information about molecular and conformational changes [29]. Usually, terpenes enhance drug permeation by any of the following three mechanisms: disruption of the highly ordered lipid structure of stratum corneum [6,21,27,30]; increased drug diffusivity in stra-

TABLE 3

Applications of various terpenes in transdermal drug delivery

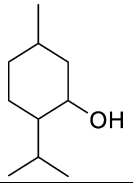
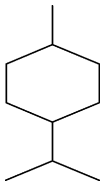
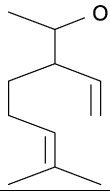
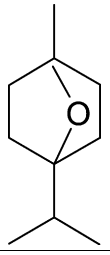
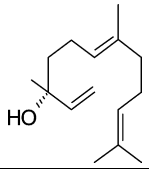
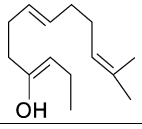
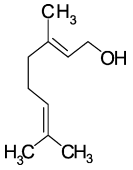
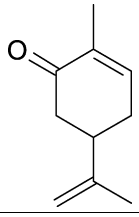
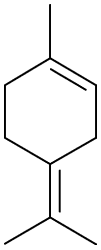
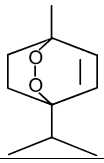
Terpene	Type	Chemical formula	Chemical structure	Permeant	Description	Refs
Menthol	Monoterpene alcohol	$C_{10}H_{20}O$		Buspirone hydrochloride	Menthol yielded a highest flux in comparison to cineole and terpineol	[14]
				Imipramine hydrochloride	Menthol found better penetration enhancer than terpineol, menthone, pulgeon, carvone, etc.	[19]
Limonene	Monoterpene	$C_{10}H_{16}$		Butyl paraben, mannitol	Limonene enhances permeation of lipophilic drug but ineffective for hydrophilic drug	[34]
				Sumatriptan succinate	Limonene found best enhancer than α-bisabolol and 1,8-cineole for sumatriptan succinate	[35]
				Nicardipine hydrochloride	Increased bioavailability and prolonged steady state concentration could be achieved using 4% (w/w) limonene in nicardipine transdermal therapeutic system	[36]
Linalool	Monoterpene alcohol	$C_{10}H_{18}O$		Haloperidol	Linalool reported as the best possible enhancer for transdermal delivery of HP followed by carvacrol and terpineol	[6]
Cineole	Ether	$C_{10}H_{18}O$		Propranolol hydrochloride	Cineole reported as optimized penetration enhancer than menthol and propylene glycol for the permeation of propranolol hydrochloride across rat skin	[22]
Nerolidol	Sesquiterpene alcohol	$C_{15}H_{26}O$		Nicardipine hydrochloride, hydrocortisone, carbamazepine, tamoxifen	Nerolidol is found to be good candidate for the enhancement of hydrophilic drugs rather than lipophilic drugs	[43]
Farnesol	Sesquiterpene alcohol	$C_{15}H_{26}O$		Diclofenac sodium	Farnesol (0.25%, v/v) provide 78-fold increase in permeation of DS followed by carvone, nerolidol, menthone, limonenoxide	[45]
Geraniol	Monoterpene alcohol	$C_{10}H_{18}O$		Caffeine	Geraniol provided a 16-fold increase in permeation of caffeine	[21]
Carvone	Ketone	$C_{10}H_{14}O$		Nicardipine hydrochloride	Carvone provides three-fold increase in the bioavailability of NHCL across rat skin	[47]
				Tamoxifen	Carvone significantly enhances the permeation of TAM followed by cineole, thymol, and menthol	[48]

TABLE 3 (*Continued*)

Terpene	Type	Chemical formula	Chemical structure	Permeant	Description	Refs
Terpinolene	Monoterpene	$C_{10}H_{16}$		Dapiprazole	Terpinolene is found to be effective enhancer for the transdermal delivery of DAP-B through mouse skin	[18]
Ascaridole	Monoterpene peroxide	$C_{10}H_{16}O_2$		5-Fluorouracil	Ascaridole reported as comparable to 1,8-cineole and more effective than ylang ylang oil and anethole	[1]

tum corneum or increased drug partitioning into stratum corneum [31,32]. Another mode of action that has been postulated is that the terpenoids increase electrical conductivity of tissues thereby opening polar pathways within the stratum corneum [33]. The mechanism of permeation of terpenes, such as menthone and limonene in combination with ethanol using propranolol HCL as the permeant across porcine epidermis by FT-IR, revealed that the above enhancers showed a decrease in peak area and height for both symmetric and asymmetric C–H stretching absorbance in comparison with untreated skin which, indicated above enhancers act by stratum corneum lipid extraction [28]. The said mechanism was later corroborated by these workers using tamoxifen as a model drug [27].

Limonene

Limonene is a hydrocarbon lipophilic terpene, obtained from the lemon peel of *Citrus limon*. It is a chiral molecule and, as is common with such molecules, biological sources produce one specific enantiomer: D-limonene, ((+)-limonene). Racemic limonene is known as dipentene (see http://www.en.wikipedia.org/wiki/Limonene).

Limonene enhances the permeation of lipophilic (butyl paraben) and amphiphilic (6-mercaptopurine) compounds, but is ineffective for hydrophilic compounds, such as mannitol [34]. In another study, limonene was found to be the best penetration enhancer viz-à-viz α-bisabolol, 1,8-cineole, ethanol, polyethylene glycol 600, span 20, oleic acid, and so on, using sumatriptan succinate as the model drug [35]. Increased bioavailability and prolonged steady-state concentration could be achieved using 4% (w/w) limonene in a 2% (w/w) hydroxy propyl cellulose gel, incorporating nicardipine hydrochloride, as transdermal therapeutic system [36]. Another gel formulation has been developed very recently [37] containing terpenes, including limonene, linalool, and cineole, in propylene glycol. The above formulation improved permeability 26.5-fold and reduced the lag time by a considerable extent. Ethanol (30%) and propylene glycol (20%) were used as co-enhancers with terpenes.

The combination of D-limonene with ethanol and propylene glycol is reported as the most effective enhancer system for permeation of midazolam compared with control (ethanol and propylene glycol only) [38]. Elsewhere, limonene is claimed to be a better skin penetration enhancer than oleic acid for the percutaneous delivery of dihydrotestosterone through hairless mouse skin [39]. The effect of three terpenes (eugenol, limonene, and menthone) at 5% concentration in combination with 50% propylene glycol (PG) in enhancing permeation through porcine epidermis was studied by Kaidi and Singh, using tamoxifen as the model drug. Of the above terpenes, limonene showed the greatest improvement in the permeation of tamoxifen. Lipid extraction of stratum corneum was the suggested mechanism of action [40].

Linalool

Linalool is obtained from the fruits of *Coriandrum sativum*. It is a naturally occurring alcohol terpene with many commercial applications, the majority of which are based on its pleasant scent. It is found in many flowers and spice plants, such as coriander seeds (see http://www.en.wikipedia.org/wiki/Linalool). Vaddi *et al.* compared the penetration enhancement capacity of linalool with carvacrol and terpineol using haloperidol (HP) as model drug in neat propylene glycol, a widely used vehicle for dermatological preparations. The solubility and flux of HP were increased by all the terpenes over control. The above workers claimed linalool as the best possible enhancer for transdermal delivery of HP followed by carvacrol and terpineol. Using FT-IR and DSC techniques, they proposed that the terpenes interact with stratum corneum lipids [6].

Cineole

Cineole is the primary chemical constituent of *Eucalyptus globulus*, and other species of Eucalyptus. It is a cyclic ether and a monoterpene, also known by a variety of synonyms: 1,8-cineole, limonene oxide, cajeputol, 1,8-epoxy-*p*-menthane, 1,8-oxido-*p*-menthane, and eucalyptol *inter alia* (see http://www.en.wikipedia.org/wiki/Eucalyptol). Cineole is reported to be the most efficient penetration enhancer for propranolol hydrochloride across rat skin, compared with menthol and propylene glycol [22]. In another study [17], the mechanism of cineole and other oxygen-containing monoterpenes namely menthol, menthone, pulgeone,

α-terpineol and carvone, on percutaneous absorption of zidovudine across rat skin was investigated. Neither partition coefficient, nor thermodynamic activity was altered by terpenes; it was suggested that the possible mechanism of permeation enhancement of zidovudine by terpenes was modification of skin barrier properties. The effect of 1,8-cineole and menthol on stratum corneum lipids and permeation of zidovudine across human cadaver skin was studied by Narishetty and Panchagnula [23]. DSC and attenuated total reflectance Fourier transform infrared spectroscopy (ATR–FT-IR) were used to determine the effect of terpenes on stratum corneum lipids. Both enhancers, applied at 5% (w/v) in 66.6% ethanol as a vehicle, improved the flux of zidovudine across human cadaver skin. DSC and ATR–FT-IR analysis revealed that the 1,8-cineole and menthol enhanced permeation of zidovudine by transforming stratum corneum lipids from a highly ordered orthorhombic perpendicular subcellular packing to a less ordered, hexagonal subcellular packing. Both terpenes show effects on both lipid alkyl tails and polar head groups, as indicated by reduction in transition temperature (T_m) and blue shift in nonhydrogen bonded amide I stretching frequency, respectively, these findings suggested that the above terpenes mainly act at polar head groups and break interlamellar and intralamellar hydrogen bonding networks [23].

Recently, Raman spectroscopy has been used to investigate the interaction of terpene and human skin [41]. Raman spectroscopy is a versatile and nondestructive method for skin study and provides advantages over infrared spectroscopy for examining this type of naturally hydrated tissue. The Raman spectrum of 1,8-cineole-treated, excised, full thickness human skin showed marked changes in the (CH)-stretching region compared with untreated skin. The application of 1,8-cineole on excised, full-thickness human skin altered the order–disorder equilibrium of the stratum corneum lipid domain, producing interfacial defects between ordered and disordered domains, allowing increased drug delivery through the tissue after application of the penetration enhancer [41].

Nerolidol

Nerolidol, also known as peruviol, is a naturally occurring sesquiterpene found in the essential oils of many types of plants and flowers. Nerolidol is present in neroli, ginger, jasmine, lavender, tea tree, and lemon grass. It is used as a flavoring agent and in perfumery. It is also currently being investigated as a skin penetration enhancer for transdermal delivery of therapeutic drugs (see http://www.en.wikipedia.org/wiki/Nerolidol). It would appear to act by increasing the diffusion coefficient of drugs such as 5-fluorouracil [42]. In another study [43], nerolidol was found to be the most efficient penetration enhancer of four different terpenes (fenchone, thymol, D-limonene, and nerolidol) with respect to four model drugs: nicardipine hydrochloride, hydrocortisone, carbamazepine, and tamoxifen with differing lipophilicities. All the above terpenes were more effective at enhancing the penetration of hydrophilic, rather than lipophilic, drugs. Selegiline hydrochloride is another active that has been used to investigate the effect of terpenes (nerolidol, carvone, and anethole), with nerolidol providing a 3.2-fold increase in permeation across rat skin in comparison to control [44]. The permeation-enhancement activity of nerolidol is attributed to its amphiphilic structure that is suitable for alignment within the lipid lamellae of the stratum corneum, thus disrupting its highly organized packing [42].

Farnesol

Farnesol is a sesquiterpene alcohol, present in many essential oils, such as citronella, neroli, cyclamen, lemon grass, tuberose, rose, musk, balsam, and tolu. It is used in perfumery to emphasize the odors of sweet floral perfumes (see http://www.en.wikipedia.org/wiki/Farnesol). It has been reported [45] that farnesol (0.25%, v/v) enhances the permeation of diclofenac sodium, with respect to other terpenes, in the following order: farnesol > carvone > nerolidol > menthone > limonenoxide. However, at 2.5% (v/v) concentration nerolidol was found to be the best candidate with a 198-fold increase in the permeability coefficient of diclofenac sodium followed by farnesol with a 78-fold increase in permeation.

Geraniol

Geraniol, also called rhodinol, is a monoterpenoid and an alcohol. It is one of the primary components of oil-of-rose and palmarosa oil. It also occurs in small quantities in geranium, lemon, citronella, and many other essential oils. It has a rose-like odor, for which it is commonly used in perfumes (see http://www.en.wikipedia.org/wiki/Geraniol). The effect of 11 monoterpenes including geraniol (1: limonene; 2: menthone; 3: terpinen-4-ol; 4: α-terpineol; 5: 1,8-cineole; 6: carvone; 7: verberone; 8: fenchone; 9: *p*-cymene; 10: neomenthol; 11: geraniol), on percutaneous absorption of three different model drugs with varying lipophilicities (caffeine, hydrocortisone, and triamcinalone acetonide) was investigated [21] by Godwin and Michniak. Terpenes were applied in propylene glycol to mouse skin. Geraniol provided a 16-fold increase in the permeation of caffeine, though the above terpenes were not as effective for the delivery of hydrocortisone. In another investigation [46], in a gel containing 5-fluorouracil, the addition of tetrahydrogeraniol (THG), which is a chief chemical constituent of oils-of-rose, markedly enhanced the 5-fluorouracil permeability. The maximum flux was obtained at a concentration of 8% THG.

Carvone

Carvone is found naturally in many essential oils, but is abundant in caraway seed (Carum Carvi) oil. It is used in aromatherapy and alternative medicine (see http://www.answers.com/topic/carvone). Krishnaiah *et al.* reported that carvone (8%, w/w) incorporated in a hydroxy propyl cellulose (HPC) gel enhanced the permeability of nicardipine hydrochloride across rat skin, resulting in a threefold increase in bioavailability [47]. In another study, Gao and Singh, compared the effect of four cyclic terpenes (carvone, 1,8-cineole, menthol, and thymol), in combination with 50% ethanol, on the transdermal delivery of tamoxifen across porcine epidermis. Carvone enhanced the permeation of tamoxifen more than cineole, thymol or menthol. The possible mechanism of carvone suggested by these workers was the disruption of the highly ordered intercellular lipid structure of the stratum corneum [48].

Terpinolene

Terpinolene is most commonly used in the fragrance and textile industries. The permeability of the dapiprazole base (DAP-B) using

different penetration enhancers including terpenes ((−) α-bisabolol, (±) α-bisabolol, L-carvone, D-limonene, L-limonene, mircene, α-pinene, terpinolene, and eucalyptol) in a series of liquid and semisolid vehicles through hairless mouse skin was investigated by Monti *et al.* [18]. Terpinolene caused maximum skin permeation of DAP-B through liquid vehicle whereas in the semisolid vehicles D-limonene is the most active enhancer followed by (−) α-bisabolol, L-limonene, terpinolene, and α-pinene in that order.

Ascaridole

Ascaridole is a bicyclic monoterpene that has an unusual bridging peroxide functional group. It is the primary constituent of the oil of chenopodium or Mexican Tea (*Chenopodium ambrosioides*) (see http://www.en.wikipedia.org/wiki/Ascaridole). It has been investigated for its penetration enhancing activity using 5-fluorouracil as the model drug and has been shown to be comparable to 1,8-cineole and more effective than ylang ylang oil and anethole [1].

Other terpenes and essential oils

Carvacrol, or cymophenol, is a constituent of the oil of thyme, oil obtained from pepperwort and wild bergamot (see http://www.en.wikipedia.org/wiki/Carvacrol). Thymol is a monoterpene phenol, found in oil of thyme, with strong antiseptic properties. It is also called 'hydroxy cymene' (see http://www.en.wikipedia.org/wiki/Thymol). Anethole or *trans*-anethole is an aromatic compound that accounts for the distinctive 'licorice' flavor of anise, fennel, and star anise (see http://www.en.wikipedia.org/wiki/Anethole). Carvacrol, thymol, and *t*-anethole are reported to be as effective as reference terpene (L-menthol) in enhancing the transport of both zidovudine and pentamidine [13,49].

Niaouli oil is extracted from *Melaleuca viridiflora* (also known as *Melaleuca quinquenervia*) of the *Myrtaceae* family. The main chemical components of niaouli oil are 1,8-cineole, terpineol, limonene, α-phellandrene, α and β pinene, linalool and piperitone. Niaouli oil is considered a safe oil, since it is non-toxic, non-irritant and non-sensitizing (see http://www.essentialoils.co.za/essential-oils/niaouli.htm). Monti *et al.* evaluated the six essentials oils (cajuput, cardamom, melissa, myrtle, niaouli, and orange oil), all essential oils were used at 10% (w/w) concentration in propylene glycol (PG), using estradiol as drug model. Among the oils, niaouli was found to be the best penetration enhancer for estradiol [50]. Basil oil is the latest of the essential oils to have found use as penetration enhancer [51]. It is extracted through steam distillation of the leaves of *Ocimum basilicum* (Lamiaceae formerly Labiatae family) and is an economical source of terpenes including methyl chavicol, eugenol, linalool, camphor, and methyl cinnamate.

Conclusion

Terpenes have been used for therapeutic purposes since ancient times. However, in recent years they have found applications as adjuvant in the form of penetration enhancers for improved transdermal and transmucosal drug delivery. They are very safe, non-irritant and non-toxic to skin and are, arguably, the most effective class of sorption promoters for a wide variety of medicaments. Terpenes like menthol, cineole, and limonene have been used for permeation enhancement of both hydrophilic and lipophilic drugs. Further research is in progress across the globe to harness the enhancement potential of some new terpenes. The authors imagine new transdermal formulations bearing terpenes as penetration enhancers being commercialized in the coming years.

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