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Review Article

A Comprehensive Review on Natural Products as Chemical Penetration Enhancer

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Abstract

The drug delivery within the stratum corneum of the skin prevails a challenging area for the pharmaceutical field, especially to the formulation scientists. Several investigations revealed that the lipid domain, which is the integral component of the transport barrier, must be breached if it is to be delivered transdermally at an appropriate rate. In particular, transdermal drug delivery has intrigued researchers with multiple suggestions because multiple dosing or insufficient drug delivery or characteristics of various drugs often results in low therapeutic effects. The application of permeation or penetration enhancers may prolong the number of drugs that can be offered topically. The application of any natural permeation enhancer is innoxious over the artificial permeation enhancers. The natural permeation enhancers are investigated, so notably include essential oils, terpenes, terpenoids, fatty acid esters, etc., have a certain effect in the transdermal drug delivery system. Despite decades of investigation on the natural chemical penetration enhancer, the researchers could not establish the effectiveness of natural penetration enhancers clinically due to the lack of in vivo models. Several factors, like solubility, solvent selection, experimental models, etc., has restricted the application and development of natural penetration enhancers in topical drug delivery systems, especially in the patches. Therefore, further investigation needs to do on skin irritation to decide natural penetration enhancers controlling optimum enhancement effects with minimal skin irritation. This review gives a comprehensive literature survey on naturally obtained chemical penetration enhancers and their future possibilities.

Keywords: Topical Drug delivery system, Natural products, Penetration enhancer, Stratum corneum, *In vivo* models.

1. INTRODUCTION

The expansion of controlled release drug delivery systems has generated exceptional interest in pharmaceutical science from the last few years [1, 2, 3]. In particular, transdermal drug delivery has intrigued researchers with multiple suggestions because multiple dosing or insufficient drug delivery or characteristics of various drugs often results in low therapeutic effects [4, 5, 6]. Amid these techniques, films or patches, and gels have been extensively designed for skin diseases or topical care in the last few decades. These dosage forms can also incorporate drugs for therapeutic applications [7, 8, 9]. Films or patches have the advantages of being a drug reservoir, adhesive properties, and precise performance at a targeted site on the skin surface, thereby prolonging the drug release and improving therapeutic effects. However, the fixed size and shape of these dosage forms are constraints, especially for patients in some restrictive conditions.

In contrast to films, the hydrogel structure is flexible and easy to practice [10, 11]. The drug delivery within the stratum corneum of the skin prevails a challenging area for the pharmaceutical field, especially to the formulation scientists. The stratum corneum of the skin restricts the drug permeation through the skin. Several investigations revealed that the lipid domain, which is the integral component of the transport barrier, must be breached if it is to be delivered transdermally at an appropriate rate. Therefore, skin permeation enhancement in the transdermal drug delivery system is presently an important sphere of pharmaceutical and toxicological investigation [12].

The application of permeation or penetration enhancers may prolong the number of drugs that can be offered topically. Several techniques have also been proposed, e.g., physical (phonophoresis, electroporation, iontophoresis, magnetophoresis, microfabricated needle, and laser technologies, etc.), chemical (synthesis of lipophilic analog, delipidization of stratum corneum, co-administration of penetration enhancers, colloidal formulations such as liposomes, niosomes, and microemulsions), biochemical, supersaturation, etc. to enhance the permeation of the drug molecule across the skin barrier [12]. Chemical techniques are also introduced in utilizing chemical excipients, which can reversibly alter the structure of the stratum corneum. The chemical enhancer may improve the solubility within the stratum corneum or increase the lipid fluidity with the

intracellular bilayers [12]. The role of penetration enhancer embodiment in topical formulations would allow the delivery of high molecular weight of drugs through the stratum corneum will be well documented and validated shortly [12].

1.1. Strategies involved in permeation process across stratum corneum (SC)

Stratum corneum is a thin heterogeneous layer consisting of keratinized epidermal cells, and separated by an intracellular lipid domain [13]. This composition of the corneocytes within the lipid-protein matrix resembled a brick wall, with the corneocytes being the bricks, and the lipid-protein matrix is the mortar [14]. The dead cells overlap with each other by some enzymes and are typically embedded in an intracellular matrix of a complex mixture of lipids [14]. There are several mechanisms by which a drug molecule can penetrate across the stratum corneum (SC). The most common pathways for penetrating SC involved intercellular, transcellular, appendageal routes, etc., which can be studied in the pharmacodynamic domain. The appendageal route is not considered a significant pathway for drug permeation because sweat glands and hair follicles only occupied 0.1% of the total surface of the human skin [15]. However, drug delivery via this route may be relevant for the permeation of slowly diffusing compounds and very high molecular weight substances, such as nanoparticles [15].

The intercellular spaces or route is another most encouraging route of drug molecule permeation over the transcellular space in the most empirical studies. The thickness of the SC is much more inferior than the diffusional pathlength. The diffusional pathlength involves persistent diffusion of the drug molecule and can restrict between polar head groups and alkyl chains of the intercellular lipids [16]. The diffusion mechanism includes the penetration of drug molecules from a higher concentration to one of the lower concentrations. Fick's first law of diffusion can describe steady-state diffusion where the rate of transfer or flux (J) of the diffusive substance is proportional to the velocity of the molecular movement within the diffusion layer (diffusion co-efficient, D), and the concentration gradient is estimated over the membrane [16]. Various drug molecules may interact with the different skin layers in the route of percutaneous penetration, appearing in limited absorption [14, 17]. These interplays may be in the form of reversible/irreversible binding to individual structures in the biological tissue, such as the SC keratin and specific sites in the skin to produce a physiological response (e.g., therapeutic activity or an allergic reaction) [17]. Drug binding is distinguished from drug accumulation or retention in the different compartments; thus, high molecular weight drug partition limits the drug diffusivity across the SC. A further possibility is that both processes may provide to the skin's reservoir capacity for certain compounds, e.g., steroids [14, 17].

1.2. Ideal characteristics of permeation enhancer

The penetration or permeation enhancer is also known as accelerants or sorption promoters, which regulate the drug molecule penetration without affecting the viable cells. The most well-known mechanism of penetration enhancers associated with the reversibly altering of the physiochemical nature of the SC to defeat its diffusion resistance. Various literature pieces were reviewed and noticed that the ideal characteristics of a permeation enhancer include non-toxicity, non-sensitizing, non-irritating, rapid activity with predictable and reproducible, pharmacologically inert, chemical compatible, etc. [18].

The permeation enhancer should not extricate the endogenous material of the skin but should have specific spreadable properties on the skin surface. The enhancer should have the same solubility profile as that of the skin. It should be removed completely after the removal of the transdermal systems. If the substance is a liquid and used at high-volume fractions, it should be a suitable solvent for drugs [18]. The mechanism of permeation enhancer involved solubilizing the skin-tissue components, interaction with intracellular lipids leads to disruption of lamellar structure, interaction with intracellular proteins leads to trouble in the corneocyte layer, enhanced partition co-efficient of the drug molecule, using co-enhancer or cosolvents in the SC [19-21]. However, there is no before-mentioned penetration enhancer to possess all the above parameters. The principal task of drug delivery scientists is to decrease the toxicity and sensitizing effect of the permeation enhancer while selecting the transdermal drug delivery system.

2. CHEMICAL PENETRATION/PERMEATION ENHANCER

In the last few decades, a considerable number of compounds have been reported as a penetration enhancer. Hence the studies of various chemical penetration enhancers are very imperative to develop any transdermal or topically utilized drug delivery system. On the other hand, the classification of different chemical enhancers is also notable for experimentation.

2.1. Natural products as skin permeation enhancer

The absorption of drugs within the percutaneous route is quite challenging, and hence adequate natural and synthetic permeation enhancer widely used in transdermal drug delivery systems. The application of any natural permeation enhancer is innoxious over the artificial permeation enhancers, considering the most common synthetic permeation enhancers such as DMSO, DMF, ionic surfactants, etc., are connected with unpleasant and toxic side effects [22, 23]. The natural permeation enhancers are investigated, so notably include essential oils, terpenes, terpenoids, fatty acid esters, etc., have a certain effect in the transdermal drug delivery system. It has been demonstrated after several studies that iontophoresis in combination with enhancers (e.g., linolenic acid) modified the highly compact cells of the stratum corneum into a looser network of filaments, disrupted the keratin pattern, and resulted in swelling of stratum corneum cell layers of human epidermis, thus enhancing the flux of medication through human epidermis [24].

2.1.1. Essential oils, terpenes, and terpenoids

Naturally occurring terpenes are the most convenient volatile oils constituted of hydrocarbons and oxygenated derivatives such as alcohols and their glycosides, ethers, aldehydes, and phenols, ketones, oxides, carboxylic acids, and esters [25]. Terpenes are the most popular clinically efficient permeation enhancer used in transdermal drug delivery systems due to their following advantages such as reversible alteration in the SC, percutaneous absorption enhancement, low toxicity, low irritational effect, etc. [26]. The physicochemical properties and chemical structure of the terpenes intensify the permeation activity of the terpenes. The permeability co-efficient of the various terpenes has been studied tentatively using human and animals' skin and found the larger value of Log P is more efficient than the smaller Log P value of terpenes [27]. It has also been found that liquid terpenes can obtain more hydrogen bonds with SC and produce a more beneficial

permeation effect than the solid terpenes. Triterpenes and tetra-terpenes generally have a poor penetration effect than other terpenes, while aldehyde or ester functional group improves their performance [28].

Polar terpenes comprising oxygen molecules were found to be more potent for hydrophilic drugs than the lipophilic terpenes. Smaller terpenes tended to be more intense than the larger terpenes. Hydrocarbons terpenes with lipophilic drug combinations are more effective in the transdermal drug delivery system [29, 30]. However, smaller alcoholic unsaturated terpenes are a desirable candidate for the permeation of hydrophilic drugs. Besides, polar bi-cyclic terpenes with oxygen molecules exhibited a lesser permeation effect than other cyclic terpenes. Various terpenes such as 1,8-cineole, menthol, limonene, etc., were effective in multiple in vivo skin permeation models [31-33]. Other prototypes of terpenes such as monoterpenes, sesquiterpenes, etc., are also investigated in topical drug delivery systems and affirmed not effective than polar terpenes. The various studies examined the possible reasons, e.g., diffusional area, the concentration of the terpenes used, etc. have not emerged as conventional penetration enhancers. Even for menthol, the available literature does not provide substantial evidence that it can enhance topical or transdermal drug delivery in humans [34-36].

Cornwell et al., reviewed the effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin. The absorption of 5-flurouracil was increased by using sesquiterpenes saturated in dimethyl isosorbide [37]. Several transdermal systems containing L-menthol, generally obtained from peppermint oil, are also effective for regulating hormones and drugs. Some investigators also mixed L-menthol with the drug moiety to make a eutectic mixture. The initial melting point drops, leading to more absorption of the drug molecule by enhancing the formulation's solubility. By increasing the drug solubility, L-menthol alters the SC barrier [38, 39].

2.1.2. Saponins

Saponins are also termed natural surfactants utilized extensively in the transdermal drug delivery system. Saponins are generally derived from glycosides occurring in plants containing steroidal or triterpenoid aglycone to which one or more sugar chains are connected [40, 41]. Generally, saponins molecules are arranged with hydrophobic molecules or moieties encompassing the outer parameter resulting in lesions in the membrane plane due to micelle-like aggregations [42]. A comprehensive investigation was done on the mechanism of saponins and found that it can develop pores in the membranes, leading to long-lasting effects and permeating large-sized molecules, e.g., ferritin [41, 42]. Saponins may combine with the polar heads of membrane phospholipids and hydroxyl groups of cholesterol, leading to micelle-like aggregates. Furthermore, their hydrophobic interior of the bilayers may also conjugate with a hydrophobic aglycone backbone. Both of these outcomes may contribute to the alteration of the lipid environment and hence improve absorption [43, 44].

Saponins comprise of hemolytic movement, which is correlated with the association of saponins with steroids, particularly cholesterol. The hemolytic capability of saponins displaces significantly with the structure of glycoside, and it includes bringing down of interfacial strain between the fluid and lipid periods of the erythrocyte film about the emulsification of the lipids and their subsequent discharge from the layer [45]. Saponins are holding of one side chain group, additionally upgrading potential in examination with saponins containing two sugars [12]. Then again, expanding the measure of sugar side chains grew the film porousness for calcium particles [46-48]. In this manner, the upshots from past examinations reveal that the hemolytic movement and upgrading potential saturation might be because of the blend of target layer synthesis, the saponin side chain(s), and the design of the aglycone [49]. The consequences of the past examinations done by the specialists on skin penetration improvement uncover that saponins have the potential to promote the porousness of different cured medications (model pervades, for example, aceclofenac, gentamicin sulfate, and carvedilol, diclofenac sodium.

2.1.3. Fatty acids

Fatty acids have been adopted as permeation enhancers and have been effective and safe in transdermal drug delivery systems. Fatty acids generally consist of an aliphatic hydrocarbon chain along with a terminal carboxylic acid group. The saturated or unsaturated aliphatic chain length, in the number, position, and configuration of double bonds, may differ from one another. They have a more exalted capacity increasing for the absorption of lipophilic drugs [50, 51]. Fatty acids appear to be clinically satisfactory penetration enhancers as designated by the following benefits, i.e., the non-irritational effect on the skin, no-toxicity, wide range of compatibility, very high skin flux, etc. The fatty acids in transdermal formulations appear to reduce skin irritation and sensitization, which is a further prevalent problem associated with some medications [50, 51].

A numeral number of investigations has clearly illustrated that the length of the alkyl chain of the fatty acids affects percutaneous drug absorption [52]. Pieces of evidence from several studies have revealed that the enhancing effects of saturated fatty acids were greatest for C10 and C12 fatty acids. Besides, the activator activity was influenced by the saturation of binding and affirmed that long-chain unsaturated fatty acids showed an improvement over the analogous saturated fatty acids [50]. In addition, branching fatty acids appear to affect their permeation enhancement activity. It was determined that PUFA linoleic, alpha-linolenic acids and arachidonic acids are polyunsaturated fatty acids in nature to improve skin penetration stronger than the mono-unsaturated fatty acids. A general trend was observed that the unsaturated fatty acids effectively enhance the percutaneous absorption of drugs, their saturated counterparts [53]. The improvement effects of fatty acid on penetration through the stratum corneum are dependent on the structure. They have associated a balance between the permeability of pure fatty acids through the stratum corneum and the interaction of acid skin lipids. The fatty acid concentrations also resemble to influence their improvement activities. The permeability of the skin meloxicam through the human cadaver skin increased as the concentration of oleic acid increased 0.4 to 1% [53]. Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of oleic acid. It is fascinating to record that many of the penetration enhancers such as azones containing saturated or unsaturated hydrocarbon chains and some structure-activity relationship (SAR) were interpreted by some researchers and affirmed that using a wide range of fatty acids, acids, alcohols, sulfoxides, surfactants and amides as enhancers is also effective [53, 54].

2.1.4. Herbal extracts

Herbal extracts are the most expensive materials in today's society. The nature of the herbal extracts is non-toxic,

biocompatible, biodegradable in the body, and hence the use of these materials has lots of advantages. Some of the herbal extracts have the ability to penetrate the SC without any penetration enhancer. In vivo investigations on the penetration, the study showed flavonoids such as flavones, apigenin, chamomile, luteolin, apigenin, and 7-O-beta-glucoside, etc., could not only absorbed the skin surface but also penetrate without the proximity of any penetration enhancer. Hence, these materials are important for the topical drug delivery system [55]. According to the various skin permeation study with Franz diffusion cell apparatus, alkaloids showed an effective skin permeation model that permeates 5-fluorouracil and benzoic acid. In the in vivo studies of skin permeation, the methanolic extract of Coptis japonica results in three alkaloids, e.g., berberine, effectively coptisine, and palmatine, which showed improved skin permeation of hydrophilic permeant 5-fluorouracil [56].

Papain is the most common cysteine protease enzyme isolated from Carica papaya, was investigated in vitro and in vivo skin permeation study of low molecular weight heparin. The investigators suggested that the combined administration of heparin's low molecular weight with papain can be a new approach to improved heparin administration and bioavailability [57]. Another study was investigated to check the permeability of the compounds based on a different range of lipophilicity, such as ether extract of Senkyu. The investigation revealed that the ether extract of Senkyu had improved the permeability in vitro and in vivo with the same patency rate. It was concluded that natural compounds having high lipophilicity could permeate the mouse skin in vivo due to the accumulation property. Thus, the ether extract of Senkyu can be used to improve the lipophilicity of moderate lipophilic compounds [58]. The permeation of the aceclofenac drug through human cadaver skin is also challenging, and thus, the study of the piperine materials improved the permeation. The FTIR study confirmed the involvement of partial biphasic SC lipids and interaction with keratin presence in the SC was the possible mechanism to enhance the transdermal permeation of aceclofenac by piperine molecules [59].

The enhanced permeation characteristics of capsaicin by azones as the permeation enhancer may benefit transdermal drug delivery systems. It was determined that increased penetration occurred when the animal skin was treated with azones as capsaicin, which can able to alter the SC layer in the skin [60]. Aloe vera gel was also found to increase the skin penetration depending upon the enhancement ratio and molecular weight of the compound and could be a possible alternative to use in the transdermal drug delivery system. The penetration effect of the aloe gel was demonstrated through the probable pull effect of complexes formed between the compound and thus enhance the permeation. Still, it was also asserted that the proposed mechanism of action has to be further investigated and authenticated. Some of the A. vera gel constituents can penetrate the skin, which was interestingly reliant on the molecular weight of the co-applied compounds. The higher the co-applied compound's molecular weight, the less the gel components were transported across the skin. This was demonstrated by the probable displacement of Aloe vera components from the penetration pathways, whereby restraining the permeation of the gel components more efficiently than the smaller compounds. Related to the analysis for intestinal drug absorption enhancement, Aloe vera gel could conceivably be utilized as a penetration enhancement agent for the transdermal delivery of drugs if established to be effective and safe [61].

Any herbal extract used as a penetration enhancer in the transdermal drug delivery system may work by two simple mechanisms: (a) herbal extracts improve the solubility of the drug within SC by altering the partition co-efficient and (b) increases the lipophilicity of the drug molecule in the SC layer, thus disrupting the lipid layer of the skin. Lignins are the cellulose content that can be used for penetration through the skin. Aloe Vera can absorb into all the skin layers, which may further increase the penetration of certain drug molecules across the skin, as lignins can penetrate the toughened areas of the skin [62].

2.1.5. Urea

Urea is a potent chemical substance that can also be adopted as a permeation enhancer in the transdermal drug delivery systems. Urea promotes the transdermal permeation by forming hydrophilic diffusion channels by facilitating hydration of the stratum corneum. Urea can increase the water content in the SC layer by acting as a humectant and retained the SC fluidity, which is a great disadvantage. Cyclical urea permeation enhancers are biodegradable and nontoxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, penetration enhancement may be a consequence of both hydrophilic activity and lipid disruption mechanisms [63].

Some investigators analyzed the permeation effect of urea by using corneometry even when applied in a formulation with reduced water activity. A subsequent study was also performed to investigate the molecular characteristics of the SC layer's keratin and macroscopic properties after adding the urea to dehydrated SC and corneocytes. This study results strengthened the hypothesis that urea functioned as a natural endogenous humectant by replacing water in low humidity conditions and maintained a fluidic SC. At more than 10% of concentration, urea acts as emollient or keratolytic action. At higher concentrations (>10%), urea exerts an emollient/keratolytic action. These studies showed that formulations with a high concentration of urea could treat ichthyosis and other hyperkeratotic conditions. Some studies suggested that urea could dissolve keratin at high concentrations by promoting the breakdown of hydrogen bonds. Further investigations have shown that urea can induce keratin conformational changes, causing the protein structure [63, 64].

2.1.6. Esters from natural sources

In chemistry, an ester is a chemical compound, generally derived from organic or inorganic acid, in which an alkoxy group replaces at least one hydroxyl group. Usually, esters are derived from carboxylic acid and alcohol. Many esters, such as a fatty acid ester of glycerol, are important esters in the biological division. Esters that are low molecular weight can be found in essential oils or vegetable oils. The most prevalent ester of ethanol and acetic acid is the ethyl acetate, which has been reviewed for transdermal penetration enhancers. Although the mechanism of action was not well understood, and the use of this molecule in transdermal preparation is not innoxious from the toxicity and sensitivity point of the landscape [65]. Sucrose ester is a very common surface-active agent which is generally practiced in several cosmeceutical products. Depending upon the composition, sucrose esters exist as solid, liquid, and waxy materials. Their properties are determined by the degree of fatty acid esterification and the nature of esterified fatty acid molecules in the sucrose. Furthermore, the shorter the fatty acid chain, the better the water solubility; thus, di and higher

esters are generally not water-soluble and can be adequately used in transdermal preparation [66]. Various studies revealed that the effectiveness of sucrose laurate as a penetration enhancer in transdermal patches incorporated poorly water-soluble drugs. Sucrose laurate hydrogel was formulated and investigated as a percutaneous delivery system of poorly water-soluble drugs and found an effective penetration enhancer when investigated in vivo [66].

The effects of sucrose esters on the permeability of the human stratum corneum and the percutaneous penetration of 4- hydroxybenzonitrile were investigated. Studies found that the hydrophilic sucrose oleate and sucrose laurate in water or Transcutol® found effective. Treatment of the skin with 2% SE in Transcutol® significantly increased the extent of 4-hydroxybenzonitrile penetration relative to the control. When skin treated with these formulations was examined spectroscopically, the C-H asymmetric and symmetric stretching bands of the lipid methylene groups were characterized by decreased absorbances and frequency shifts to higher wavenumbers. These effects on the stratum corneum lipids and 4-hydroxybenzonitrile penetration were more pronounced for sucrose laureate when combined with Transcutol®. These results showed that the combination of SEs and Transcutol® could temporarily alter the stratum corneum barrier properties, thereby promoting drug penetration if used in transdermal patches [67].

Several alkyl esters such as methyl acetate, ethyl acetate, butyl acetate, methyl propionate, ethyl propionate, methyl valerate, etc., were investigated as skin permeation enhancers for some drug molecules. The steady-state flux of the drug molecule as measured in vitro through excised rat skin was enhanced about more folds by ethyl acetate, methyl acetate, and methyl propionate relative to that from various solvents. Thus, using these esters as penetration enhancers in the transdermal drug delivery system is quite useful [68, 69]. Examples of these several chemical penetration enhancer findings are represented in Table 1 within vivo approach.

Table 1: List of naturally obtained chemical penetration enhancer used for topical drug delivery system.

Class	Permeation enhancer	Probable model drugs/permeant	Probable model type/skin type	Ref
Terpenes	Alpha-terpinol	Lidocaine	Porcine	[69]
	Carvone	Nicorandil, ondansetron hydrochloride, nimodipine, nicorandil	Neonatal rat epidermis, EVA 2825 membrane, epidermal membrane	[70-74]
	Menthol	ligustrazine, Osthole, paeonol, Risperidone, 5-fluorouracil	Modified Franz diffusion cell experiment, porcine skin, in vitro permeation studies and coarse-grained molecular dynamics.	[75-79]
	Anethole	Valsartan, selegiline hydrochloride, Etodolac	Rat skin, modified horizontal diffusion cells through cellulose membrane and rat skin.	[80-82]
	Menthone	Valsartan, ligustrazine hydrochloride, tamoxifen, Halobetasol propionate	Rat skin, porcine skin, human skin on Franz cells.	[80,83-85]
	Eugenol	Valsartan, glibenclamide and glipizide, tamoxifen	Rat skin, in vitro permeation study, porcine epidermis.	[80,86,87]
	α-Bisabolol	Propranolol hydrochloride, 5-fluorouracil	Rat skin, Human skin samples.	[88,89]
	Borneol	Propranolol hydrochloride, borneol, curcumine, ligustrazine	Modified Franz diffusion cells through piglet skin, epidermal keratinocyte HaCaT and dermal fibroblast CCC-HSF-1 cell cultures, rat skin *in vitro*, *in vitro* porcine dorsal skin.	[90-93]
	Verbenon-e	Genistein, valsartan, propranolol hydrochloride	*In vitro* human skin, rat skin and human cadaver skin, rat and human cadaver skin.	[94-96]
	Pulegone	Zidovudine, osthole, tetramethylpyrazine, ferulic acid, puerarin and geniposide, arginine vasopressin, insulin	Rat skin, rat skin, rat skin.	[97-100]
Saponins and Herbal extracts	Glycyrrhiza glabra (glycyrrhizin)	Diclofenac sodium	Abdominal rat skin.	[101]
	Glycyrrhizin	Carvedilol	Rat epidermis.	[102]
	Asparagus racemosus	Carvedilol	Rat epidermis.	[103]

	Aloe vera	Caffeine	Porcine ear skin.	[104]
	Aloe vera	Mefenamic acid	Porcine ear skin.	[104]
	Aloe vera	Colchicines	Porcine ear skin.	[104]
	Aloe vera	Oxybutynin	Porcine ear skin.	[104]
	Aloe vera	Quinine	Porcine ear skin.	[104]
	Quillaja saponaria and *Acanthophyllum squarrusom*	Gentamicin sulfate	Shed snake-skin and liposomal membranes.	[105]
	Coptis japonica and It's alkaloidal Isolates.	5-fluorouracil	Human skin.	[106]
	Senkyu (*Ligustici chuanxiong* Rhizome)	Herbal extracts	Hairless mouse skin.	[107]
	Asiaticoside (ASI)	-	*Ex vivo* skin permeation.	[108]
Fatty acids	Oleic Acid	Zinc phthalocyanine, Lamotrigine, Caffeine	Suine ear skin, Human skin.	[109-111]
	Linoleic acid	Bupivacaine, Insulin, Arginine Vasopressin, glimepiride	*In vitro* permeation, *ex vivo* study, rat skin, modified Franz diffusion cell.	[112-115]
	Lauric acid	Ondansetron, phenmetrazine, Alprazolam	Human cadaver skin.	[116-118]
	palmitic acid	5-fluorouracil, Diclofenac, Ketorolac tromethamine	Microwave-treated skins, *ex vivo* and *in vivo* drug permeation, rat skin	[119-121]
	Linoleic acid, oleic acid, margaric acid, cis-11,14-eicosadienoic acid, stearic acid	Carvedilol	Rat skin.	[122]
	Caprylic acid	Pranoprofen	Rat skin.	[123]
	Palmitic acid, oleic acid	Diclofenac	Rat skin.	[124]
	Eucalyptus, anise, chenopodium, ylang ylang oils	5-fluorouracil	Excised human skin	[125]
	Eucalyptus, peppermint, turpentine oils	5-fluorouracil	Excised human skin.	[126]
	Turpentine oil	Ibuprofen	Cellulose membrane, excised rabbit abdominal skin.	[127]
	Rosemary, ylang, lilacin, peppermint oils	Aminophylline	Human skin.	[128]
	Ylang, lavender, orange, nutmeg, chamomile, sage, eucalyptus, ginger, peppermint oils	p-aminobenzoic acid.	Human skin.	[129]

Essential oils	Basil oil	Labetolol hydrochloride	Rat abdominal skin.	[130]
	Tulsi, Turpentine oils	Flurbiprofen	Rat skin.	[131]
	Eryngium bungee essential oil	Piroxicam	Rat skin.	[132]
	Fennel, eucalyptus, citronella, mentha oils	Trazodone hydrochloride	Mouse epidermis.	[133]
	Ajuput, niaouli, cardamom, orange, melissa, myrtle oils	Estradiol	Hairless mouse skin.	[134]
	Niaouli oil	Estradiol	Hairless mouse skin.	[135]
	Turpentine, eucalyptus, peppermint oils	Ketoconazole	Pig skin.	[136]
	Eucalyptus oil	Chlorhexidine digluconate	Full-thickness human skin.	[137]
	Thyme, petit grain, basil oils	Nitrendipine	Rat abdominal skin and human cadaver skin.	[138]
	Alpinia oxyphylla oil	Indomethacin	Dorsal skin of rats.	[139]
	Basil oil	Indomethacin	Dorsal skin of rats.	[140]
	Cardamom oil	Indomethacin, diclofenac, piroxicam	Rabbit abdominal skin.	[141]
	Peppermint, tea tree, eucalyptus oils	Benzoic acid	Human breast or abdominal skin.	[142]
	Black cumin, tulsi, clove, eucalyptus oils.	Carvedilol	Excised rat abdominal skin.	[143]

3. FUTURE PROSPECTIVE

The supreme skin penetration enhancer should be stable, non-toxic, non-irritating, and, most importantly, should have the ability to permeate the stratum corneum. The permeation enhancer should be harmonious with the other excipients, especially the drugs present in the system. The release or diffusion mechanism of the drug candidate should not hinder by the incorporation of natural permeation enhancers in topical drug delivery systems. Despite decades of investigation on the natural chemical penetration enhancer, the researchers could not establish the effectiveness of natural penetration enhancers clinically. Several factors like solubility, solvent selection, experimental models, etc., restrict the application and development of natural penetration enhancers in topical drug delivery systems, especially in the patches. The effectiveness of human skin for characterization purposes is quite difficult due to regulatory ethics and constraints. Though, the porcine skin is also seemed to be effective and can be used as a surrogate for characterization purposes. The physicochemical nature of the natural penetration enhancers should be considered properly before selection for the formulation development. The dose of the penetration enhancer and the crystalline nature in the skin surface's temperature is a big concern, especially when used for transdermal drug delivery systems. There are some other scopes where natural penetration enhancers can be used along with other penetration enhancers; thus, the synergistic effect will systematically enhance the ultimate activity of the patches in biomedical applications. Some penetration enhancers generally utilized for any cosmetics preparation can also be studies for transdermal systems. The progressions in analytical techniques are also important to characterize the compatibility of the penetration enhancer with other excipients and the mechanical nature of the formulated patches. Thus, no penetration enhancer will not create any irritation on the skin surfaces. The scientist should concentrate on how the irritational effect can be reduced and should concern the cost of the product concurrently. Thus, more improved in vivo models are also required to justify the effectiveness and adverse effects of the transdermal systems as only in vitro studies cannot prognosticate the irritational impact on the skin.

4. CONCLUSION

The penetration of large molecules through the skin is a big concern for drug delivery society. Though the use of natural chemical penetration enhancers is quite effective from the

delivery point of view, but the irritational effect is again a big concern. The higher concentration of chemical enhancers in formulation increases drug transport across the skin but is proportionally related to their ability to cause skin irritation. Therefore, it is very complicated and challenging to maintain the concentration and adverse effect of penetration enhancers in topical drug delivery systems. Various essential oils, terpenes, fatty acids, and esters from natural sources have been used in cosmetics over time. The applications of these penetration enhancers in the drug delivery system can improve and resolve the drawbacks, especially in transdermal drug delivery systems. Various research has been performed by the top institutional societies throughout the world and has confirmed the potency or effectiveness of natural chemical penetration enhancers in the drug delivery systems except for mild irritational effects on the skin. Therefore, further investigation needs to do on skin irritation to decide natural penetration enhancers controlling optimum enhancement effects with minimal skin irritation.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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