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RECENT DEVELOPMENTS ON NATURAL TRANSDERMAL PENETRATION ENHANCERS

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ABSTRACT: The drug delivery by oral route is so far most convenient and accepted route of drug delivery but now a days considerable interest has been increased in delivery of drugs through skin to the systemic circulation and for local effect. However, the outer most layer of the human skin, stratum corneum; possess the formidable barrier to drug penetration thereby reducing bio-availability. Most of the drugs do not have an ability to penetrate the stratum corneum. Owing to the side effects of chemical penetration enhancers interest has been aroused among researchers to find out natural sources as penetration enhancers to improve the bio-availability of drugs so that they can be delivered through skin. The current review aims to screen various natural sources of penetration enhancers for transdermal delivery of different drugs as they have minimum chances of side effects and have improved efficacy compared to chemical enhancers. Various natural derivatives have been proposed that could show potential penetration enhancing capacity with varied mechanism of penetration. Though a large number of natural sources of penetration enhancers have been discussed but still a lot of studies and research need to be done to explore the sources of natural penetration enhancers for effective delivery of drug *via* transdermal route.

INTRODUCTION: The transdermal route always provide innovative research area in drug delivery, and many drug delivery products are under clinical evaluation related to the transdermal or dermal system. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect [1]. Owing to some complexities skin have a barrier for penetration through it.

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To enhance the transport of drug through skin various techniques are applied called as permeation enhancement techniques and agents utilized in it are Penetration Enhancers [2] also called sorption promoters or accelerants) which penetrate into skin to reversibly decrease the barrier resistance [3].

Brief Anatomy of the Skin: Skin is a complex biological structure consisting of many layers of a thickness of 2.97 ± 0.28 mm. Its function is to safeguard the major internal parts of the body from the external effects, regulation of temperature, sensation and water balance. A normal adult human body skin cover around two square meters surface area and gets about one-third of the blood circulating in the body. **Fig. 1** shows the structure of skin.

The skin is considered to have four distinct layers of tissue [4].

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

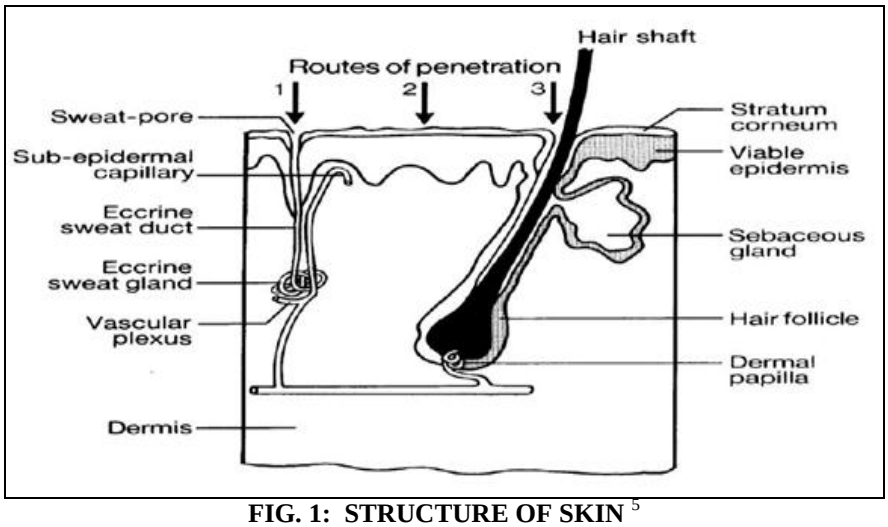

FIG. 1: STRUCTURE OF SKIN [5]

Advantages and Disadvantages of Penetration Enhancers: Various advantages of penetration enhancers include [6]

- They help to provide penetration rate of drug sufficiently high for therapeutic efficiency
- It facilitates the absorption of non-absorbable drugs through skin.
- It can improve the transdermal absorption of topical preparation completely.
- It determines the penetration rate of transdermal drug delivery system.
- The terpenes like limonene in propylene glycol solution are effective penetration enhancer for cytotoxic drugs.

Various disadvantages of penetration enhancers are [7]

- The effective concentration varies from drug to drug.
- The use of various penetration enhancers with various concentrations vary
- Physicochemical properties of enhancers are also affecting the side effects in the body.

Mechanism of Action of Penetration Enhancers: Skin Absorption Promoters may act by one or more of three potential mechanisms according to the lipid-protein-partitioning theory.

Firstly, penetration enhancers can alter the inter-cellular lipid structure between the corneocytes to increase diffusivity.

Secondly, they can modify intracellular protein domains within the horny layer.

Thirdly, they may increase the partitioning of the drug into the skin tissue [8]. **Fig. 2** demonstrates the possible mechanism of drug penetration.

The three main functions of penetration enhancers include: [9]

Lipid Disruption: They change the structure of stratum corneum lipid organization and make it permeable for the drug *e.g.* Azone, terpenes, fatty acids, Dimethyl sulfoxide (DMSO) and alcohol.

Protein Modification: They interact with keratin and corneocytes and open up the dense protein structure and make it more Permeable *e.g.* Ionic surfactants.

Partitioning Promotion: Many solvents change the solution properties of horny layer and increase the partition of a drug, co-enhancer and co-solvents.

Group of Substances That Could Show Potential Absorption Promoter Activity: Table 1 gives the example of various potential absorption promoters.

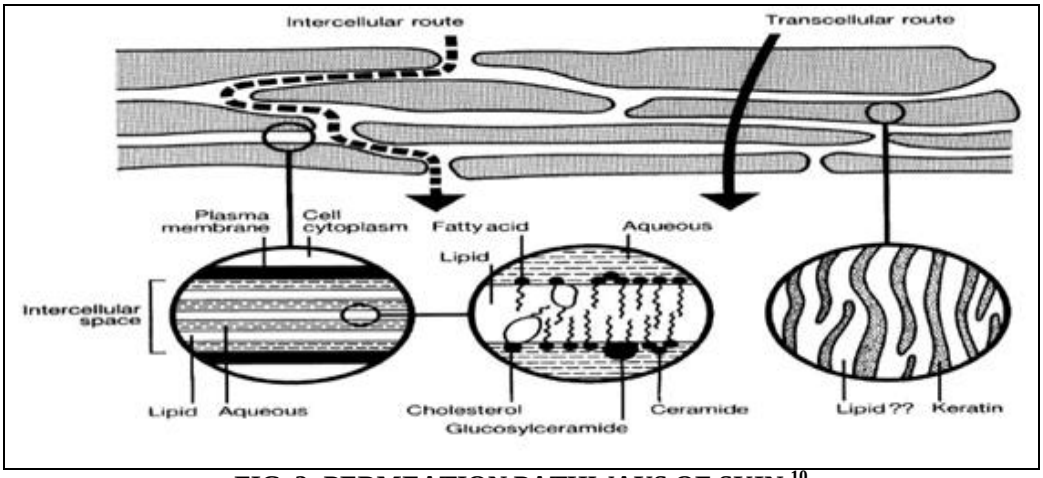

FIG. 2: PERMEATION PATHWAYS OF SKIN [10]

TABLE 1: GIVES THE EXAMPLE OF VARIOUS POTENTIAL ABSORPTION PROMOTERS

Type of Penetrate	Mode of Action	Example
Physical Penetration enhancers [11]	Rate control over the release and transdermal permeation of drugs	1. Iontophoresis 2. Sonophoresis 3. Phonophoresis 4. Magnetophoresis 5. Electroporation 6. Thermo-phoresis 7. Radiofrequency 8. Needleless injection
Chemical enhancers [12]	They act by three mechanisms 1. By disruption of highly ordered structure of stratum corneum lipid. 2. By interaction with intercellular protein. 3. By improved partition of the drug or solvent into stratum corneum.	Sulphoxides and similar chemicals-dimethyl sulphoxide(DMSO), Dimethyl formamide (DMF), dimethyl acetamide (DMAC) 2. Azones 3. Pyrrolidones 4. Fattyacids–Lauric acid, Myristic acid and capric acid 5. oxizolidinones (4 decycloxazolidine-2-one) 6. Amine and Amides – Urea
Essential oils and terpenes [13]	It may increase one or more of following effects 1. Partition coefficient 2. Diffusion coefficient 3. Lipid Extraction 4. Drug Solubility 5. Macroscopic Barrier Perturbation 6. Molecular Orientation of Terpenes Molecule with Lipid Bilayer	Essential oils: Niaouli Oil, Eucalyptus oil, Neem oil, Peppermint oil, *etc.* Terpenes: Geraniol, nerol, Menthol, Carveol, Camphor, *etc.*
Fixed Oils/ Fatty Acids [14]	Oleic acid might increase the permeability via a mechanism involving perturbation of stratum corneum lipid bilayer and lacunae formation as penetration enhancing effect. (1) lipids could alter the permeability of the stratum corneum by having a direct effect and/or (2) solubility of the drug could be increased	Fish oil, cod liver oil, Fatty Acids from Algae, Phospholipids, oleic acid
Polysaccharides [15]	Chitosan interact with negative charges in the skin to improve drug diffusion into the deeper layers of the skin *A. vera* gel had a higher permeation enhancement which was explained by the fact that a drug with a larger molecular weight effectively blocks the permeation routes allowing increased possibility for the drug to interact with the enhancing factor and complex with it prior to being transported across the skin.	Chitosan, Aloe vera Gel,
Miscellaneous [16]	Capsaicin reduces the diffusional resistance of the intercellular domains by inserting itself into the lipid bilayers within the intercellular channels thereby disrupting their stacking. moderate improvement in the permeability of the stratum corneum can be attributed to the restricted insertion of Vitamin E in the ceramide-rich bilayer structure.	Capsaicin, Vitamin E

Non-ionic Surfactant [17]	the surfactant interacted with skin to destructure lipids and thus increase permeability; however the ability of surfactant to influence skin permeation was dependent on the physicochemical properties of permeant.	Tweens and brij
Drug Vehicle based [18]	Based on drug section, vesicles and particles, prodrug, chemical potential of drug and eutectic system	Niosomes, liposome, aquasomes, Transfersomes, nanopartices

Natural Penetration Enhancers: Various natural sources have been investigated for potential skin penetration enhancement activity. Some of the natural sources have been discussed below:

Aloe vera: [19] *Aloe barbadensis* Miller (*Aloe vera* Linn.) is the most widely used both commercially and for its therapeutic properties. This plant is having various medicinal, cosmetic and nutra-ceutical purposes *Aloe vera* gel is the viscous, transparent and colourless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of *Aloe vera*.

Penetration enhancers work possibly by increasing the solubility of the drug within the SC by altering the partitioning of the drug into the SC and/or by influencing the diffusion of the drug across the SC by disrupting the ordered nature of the skin lipids. It can soak into all the layers of the skin and this may be helpful in increasing the penetration of certain drug molecules across the skin, as lignins can penetrate the toughened areas of the skin.

Histopathological examination of *Aloe vera* oil treated SC suggested additional mechanisms for permeation *i.e*. transient reduction in barrier resistance of SC and intracellular transport by dekeratinization of corneocytes which may be attributed to the presence of triglycerides as constituents of Aloe vera oil. It is feasible to deliver therapeutically effective dose of LP *via* transdermal route using *Aloe vera* oil as penetration enhancer [20].

Essential Oils: Essential oils are volatile, odoriferous substances found in the flowers, fruit, leaves and roots of certain plants. The skin penetration enhancing effect of several isolated essential oils has been thoroughly investigated [21]. Essential oils and their constituents have been widely investigated as safe and suitable skin penetration enhancers for both hydrophilic and hydrophobic drugs but the mechanism of their action is not fully understood. The predominant compounds within oils are terpenes, terpenoids, phenyl propanoids, as well as minor amounts of miscellaneous volatile organic compounds.

TABLE 2: NATURAL OILS AS PENETRATION ENHANCER

Ingredient	Chemical Composition	Drug Used	Ref
Clove oil	Eugenol, Caryophyllene, Eugenyl acetate, Caryophyllene oxide	Ibuprofen	22
Angelica oil	α-Pinene, trans-β-Ocimene, Ligustilide, Eugenol	Ibuprofen	23
chuanxiong oil	(+)-α-Pinene, γ-Terpinene, Terpinolene, Methyl 4-ethylbenzoate	Flurbiprofen	24
Eucalyptus Oil	1,8-cineole	ketoconazole	25
Peppermint Oil	L-Menthol	5-fluorouracil	26
Cyperus Oil	Cyperene, Dehydrofukinone, α-Cyperone	Ibuprofen	27
Cinnamon Oil	trans-cinnamaldehyde, (E)-Cinnamyl acetate, linalool	nifedipine	28
Turpentine Oil	a-pinene, β-pinene, camphene, longifolene, A3-carene, limonene and β-caryophyllene	Labetalol Hydrochloride	29
Cardamom Oil	b-pinene, a-phellandrene, limonene, p-cymene, terpinolene, 1,8-cineole, y-terpinene, linalool, linalyl acetate, a-terpineol acetate, citronellol, nerol, terpinen-4-oil, a-terpineol, geraniol, methyl eugenol and trans-nerolidol.	Piroxicam	30
Mint oil	Menthone, Menthol, α-terpineol, Eucarvone	Geniposide	31
rose oil	citronellol, geraniol, nerol, linalool, phenyl ethyl alcohol, farnesol	Losartan	32
tea tree oil	terpinen-4-ol, γ-terpinene, 1,8-cineole, α-terpinene, α-terpineol, p-cymene, and α-pinene	Losartan	33
Tulsi oil	Methyl eugenol, carvacrol, caryophyllene	celecoxib	34
Fennel oil	fenchone (ketone), trans-anethole (phenolic ester), α-pinene (monoterpene), linalol (alcohol), and methyl chavicol (phenol).	trazodone hydrochloride	35
Niaouli Oil	1,8-cineole (oxide) and limonene (monoterpene), a-pinene	estradiol	36

	(monoterpene), ß-pinene (monoterpene) and viridiflorol		
Black cumin oil	thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine and alpha-hederin.	carvedilol	37
Lemon grass oil	myrcene, citronellal, geranyl acetate, nerol, geraniol, neral and traces of limonene and citral.	hydrocortisone acetate	38
Rosemary oil	1,8-cineol, α-pinene, camphor, camphene, (E)-caryophyllene	diclofenac	39
Alpinia oxyphylla oil	1H-cycloprop[e]azulene, octahydro-1,8-dimethyl-7-(2-methylethenyl)-naphthalene, α-panasinsen, germacrene B, humulene 6,7-epoxide, cis-α-copaene-8-ol and nootkatone	indomethacin	40

Essential Fatty Acids: Fatty acids have been shown to accelerate skin permeation of drugs probably modifying intercellular lipid packing in the stratum corneum lipid domains and so reduce the barrier function. They can form lipophilic complexes with compounds. Although fatty acids can be used to enhance the permeation of both lipophilic and hydrophilic APIs, the flux of polar APIs is improved to a larger degree [41]. Unsaturated fatty acids (UFAs) with a C18 chain length (*e.g.* oleic and linoleic acids), increase penetration-enhancing effects with linolenic acid as the most potent, followed by oleic acid, palmitoleic acid, linoleic acid and arachidonic acid [42]. Some of the Fatty acids that has been studied as penetration enhancers are listed below in **Table 3**.

Vegetable oils: Various vegetable oils have been investigated for their penetration enhancement activity as shown in **Table 4**.

TABLE 3: FATTY ACIDS AS PENETRATION ENHANCERS

Ingredient	Chemical Composition	Drug used	Ref
Evening primrose oil (EPO),	linoleic acid (70%-80%), ϒ-linolenic acid (8%- 12%), and oleic acid (6%-11%)	Flurbiprofen	43
Vitamin F	linoleic (35.5%), linolenic (30.5%), and oleic acid (21.4%).	Flurbiprofen	44
fish oil	ω-3 fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)	atenolol	45
Botryococcus braunii (Algae)	unsaturated fatty acids	flurbiprofen	46
soya bean	phospholipids Phosphatidylcholine and 70% phosphatidylethanolamine	diclofenac	47
egg yolk	levo-α-phosphatidylcholine	naproxen	48

Table 4: VEGETABLE OIL AS PENETRATION ENHANCERS

Vegetable oil	Experiment	Ref
Sunflower oil, Sesame oil and jojoba oil	Studies revealed that this oil in concentration of 10 % w/w of polymer weight exhibited enhancing effects on losartan potassium release from transdermal patches, with the cumulative amount of drug release	49
Almond oil	It was used as penetration enhancer in various concentrations to significantly enhance the penetration of drug from transdermal gels and patch across synthetic membrane/rabbit skin but was most significant when used in 3% concentration.	50
Olive oil	In a study on preparation and evaluation of olanzepine transdermal patches, the formulation containing 10% olive oil has enhanced permeation through rat skin.	51
Corn oil	Corn oil containing unsaturated fatty acids was found to be promising natural permeation enhancer for transdermal delivery of olanzapine with no skin irritation. The therapeutic effectiveness of the optimized transdermal system was confirmed by tranquillizing activity in rotarod and grip mice model.	52
Coconut oil and pistachio oil	Permeation of clotrimazole gel was enhanced by various combinations of coconut oil, pistachio oil and sodium lauryl sulphate that exhibited a more pronounced and promising effect through rat skin.	53

Miscellaneous:

Capsaicin: Capsaicin (trans-8-methyl-N-vinillyl-6-nonenamide) is an alkaloid derived from hot chili peppers, belonging to the genus Capsicum of the Solanaceae family It contain a ring at one end of a long alkyl chain, with a log P value of 3.31. The penetration enhancing effects of capsaicin on naproxen was investigated with in vitro experiments employing full-thickness, female human skin and an *ex-vivo* perfused rabbit ear model. It was found that

capsaicin enhanced the permeation of naproxen through full-thickness skin approximately 2-fold [54].

Vitamin E: (α-tocopherol) enhanced the permeability coefficient of radio labeled hydrocortisone with an average enhancement factor of 1.81 through excised human cadaver skin. There was a reduction of lag time in skin samples treated with Vitamin E. This increase in the permeability of the stratum corneum can be due to the restricted insertion of Vitamin E in the ceramide-rich bilayer structure [55].

CONCLUSION: Transdermal drug delivery is effective over oral delivery of drugs and research is being carried out to overcome the skin barrier function. The penetration enhancer or sorption promoter functions by altering the barrier characteristics of skin membranes or by increasing the drug solubility inside the skin. Current review aims to summarize the natural sources that have been reported as promising transdermal penetration enhancers.

It can be concluded that research or exploration is beneficial for scaling up of the system of natural permeation enhancers and execute the manufacture of the dosage forms with natural permeation enhancers will play a prominent role in progress of useful and efficient transdermal products in future.

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