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Evaluate Interaction of the Sunscreen cream Ingredients with the protein Interleukin 8 (IL8) to understand Skin irritant potency: An *In-Silico* study

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ABSTRACT

The increase in the case of sunburn, erythema and skin cancer has drawn the attention of the scientific world to the use and quality regulation of sunscreen. Sunscreen is an over-the-counter medication as regulated by FDA. Prior to the use of sunscreen, it is recommended to assess its safety and efficacy. To reduce time and cost scientific world is trying to use 'in-silico' testing methods for the safety assessment of the sunscreen ingredients. This article deals with the basis of sunscreen use, effects of UV exposure on the skin, sunscreen ingredients, classification of sunscreen, skin sensitisation methods for testing ingredients, why 'in-silico' method is needed. Our docking study found that compounds like Octinoxate and Avobenzone strongly bind to the protein 1IL8 with high docking sore and known to be strong skin irritant and skin sensitizers. Compounds like TiO_2 and ZnO_2 show low affinity for 1IL8 and are also not known to be potential skin irritant and non-skin sensitizers. Therefore, our in-silico study concludes that interaction between compounds and 1IL8 is particularly important for determining Skin irritation potency of the compound.

INTRODUCTION

The primary cause for the increase in skin cancer is the harmful effects of UV radiation. Solar UV radiation causes sunburn, aging, precancerous and cancerous lesions.[1] In sunburn the superficial blood vessels are dilated due to exposure to UV rays. Prolonged exposure causes skin to swell with or without blistering. Aging causes sagging and loss of skin elasticity. Squamous cell carcinoma, basal cell carcinoma and cutaneous malignant melanoma are the common forms of skin cancer. UV radiation are of 3 kinds: UVA, UVB and UVC. 100% of UVC rays and 90% of UVB rays are ingested by ozone layer. Whereas it can ingest only a negligible amount of UVA. UVA is associated with pigmentation as well as aging. It enters deep into the cell and damage DNA, producing free oxygen species.[2] UVB results in sunburn and breakage of DNA strands. Light skinned individuals are more prone to damage of skin by UV rays than dark skinned individuals. In lighter skin it is easier for UV rays to penetrate the epidermis to damage melanocytes and keratinocytes. Depletion of ozone layer expands transmission of UV radiation. Protection against such harmful radiations has brought forth the need for use of sunscreens. [3-8]

SUNSCREEN, AND ITS CLASSIFICATION

Sunscreens are lotion, gel, spray or foam that are applied topically to protect against harmful UV rays. They are actually UV rays filter having photo protector formula. Sunscreens are of two types chemical sunscreen and physical sunscreen.[1]

Chemical sunscreens absorb the UV rays and releases them from the body by converting them into heat. Whereas physical sunscreens scatter, reflect or absorb UV rays. Organic sunscreens mainly include aromatic compounds having carbonyl group. On the basis of the range of protection it offers organic sunscreens are further subdivided into three groups - UVB (290–320 nm) and UVA (320– 400 nm) and broad-spectrum sunscreens that cover the entire spectrum (290–400 nm). Ensulizole, octocrylene, padimate-O, octinoxate, octisalate are well known ingredients for UVB sunscreen. UVA filters cover oxybenzone, avobenzone, sulisobenzone, benzophenones, meradimate, ecamsule and methyl anthranilanate. Besoctrizole, silatriazole are broad spectrum organic filters. Physical barriers are inorganic sunscreens mainly comprising of zinc oxide and titanium dioxide. They almost cover the entire ultraviolet spectrum. FDA has approved 16 compounds as sunscreen ingredients. The approved compounds are Padimate O, Aminobenzoic acid, Cinoxate, Ensulizole, Avobenzone, Dioxybenzone, Sulisobenzone, Dioxybenzone, Homosalate, Meradimate, Trolamine salicylate, Octinoxate, Oxybenzone, Octisalate, Titanium dioxide and Zinc oxide. [1]

SUNSCREEN, AND ITS EFFICIENCY

Sunscreens affect the function and structure of the body by absorbing, scattering and reflecting the sunrays. The efficacy of a sunscreen is determined by sun protection factor (SPF), immune protection factor (IPF) and persistent pigment darkening (PPD). [3]

SPF is measured as the ratio of the minimal erythemal dose (MED) required to induce erythema on the protected skin and that dose required to induce the same on unprotected skin on the same individual.

SPF = MED of protected skin / MED of unprotected skin.

The SPF was introduced by Schulze in 1956. The SPF recommended to an individual is dependent on certain conditions like climatology, the extent of an individual's exposure to UV rays. Exposure to UV radiation also varies from place to place and is based on their latitudes. SPF only estimates the protection against UVB. However the SPF value claimed on the label of a sunscreen is not entirely spread on a consumer's skin, only 50% of it does. For a sunscreen with a label SPF 30 will provide protection of SPF 15.

The detrimental UV rays may also leads to immune suppression. The potential of a sunscreen to prevent immunosuppression produced by UV rays is referred to as immune protection factor (IPF). Prediction of IPF for a sunscreen is done by rather complex method. For a sunscreen IPF is measured on the basis of a sunscreen's ability to prevent sensitization to allergens like 2,4-dinitrochlorobenzene.

The capacity of a sunscreen to provide protection against UVA light is measured by persistent pigment darkening (PPD). It is the ratio between the minimal dose required to induce pigmentation (MPD) in the protected skin and the MPD observed on the unprotected skin.[9-13]

TOXICITY ASSESSMENT OF SUNSCREEN INGREDIENTS : ADVANCEMENT OF *in silico* TOOLS

The sunscreen ingredients provide protection against harmful UV radiations but may produce sensitization due to their application. Hence they should be properly assessed prior to their application. Various *in vivo* and *in vitro* testing methods are adopted for safety assessment of the ingredients.[14] HPIRT

(human repeat insult patch test) is one such *in vivo* testing method for the assessment of toxicity of the sunscreen ingredients. In this test a small amount of each sunscreen ingredients are applied on skin to check whether the ingredient induce any allergic response to the skin. The area is secured with a hypoallergenic tape for 24 hours. A part of the tape is lifted and sunlight is allowed to fall on that part to see any rash appears. Then the tape is put back for 72 hours to take the final reading.[15] However any test including human or any animals encounter various ethical issues. The *in vivo* and *in vitro* testing methods are also time consuming and expensive. The scientific world is looking forth to replace the *in vivo* and *in vitro* methods by *in silico* methods. These *in silico* methods are associated with 3R (refinement, reduction, and replacement of animal usage in laboratory procedures). The main advantage of the *in silico* method is prediction of results in short time and is also very cost effective. In recent times the QSAR models have successfully supersede the animal testing methods. Using descriptors,QSAR models can predict the physical and chemical properties of unknown compounds on the basis of known compounds.[16-18]

In this paper we have used *in silico* method to predict the toxicity of some sunscreen ingredients by using docking method. We have chosen protein IL8 for performing the docking studies with the sunscreen ingredients.

METHODOLOGY:

Protein structure:

The pdb structure of protein Interleukin 8 (1IL8) was downloaded from RCSB databank (www.rcsb.com). The protein has 72 number of amino acid residues. The whole structure of the protein was considered as docking target.

Ligand structure:

The SMILES strings of the 16 compounds were obtained by PUBCHEM (https://pubchem.ncbi.nlm.nih.gov/) and the SMILES were converted to pdb format uring the Corina demo server (https://www.mn-am.com/online_demos/corina_demo). The compounds are Aminobenzoic acid (Pubchem CID 978), Avobenzone (PubChem CID 51040), Cinoxate (Pubchem CID 5373773), Dioxybenzone (Pubchem CID 8569), Homosalate (Pubchem CID 8362), Meradimate (Pubchem CID 8633), Octocrylene (Pubchem CID 22571), Octinoxate (Pubchem CID 5355130), Octisalate (Pubchem CID 8364), Oxybenzone (Pubchem CID 4632), Padimate O (Pubchem CID 30541), Ensulizole (Pubchem CID 33919), Sulisobenzone (Pubchem CID 19988), Titanium dioxide (Pubchem CID 26042), Trolamine salicylate (Pubchem CID 25213), Zinc oxide (Pubchem CID 14806). These compounds were further subjected to docking simulation against the IL8 protein.

Protein-Ligand Interaction:

The docking study has been performed using patchdock server [19]. The protein and the compounds pdb were given in the required area. The complex type was chosen as **'protein-small ligand'** and clustering RMSD was kept as default (4.0). Later the top protein-ligand complex with best patchdock score was collected and submitted for docking analysis. The complex was analysed for binding of ligand on the IL8 proteins, binding affinities by calculating patchdock score and ranking of ligand based on their patchdock score. The best patchdock score obtained by the candidates is proportional to

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its affinity for 1IL8. The ligand with strong binding on the 1IL8 cavity considers to be toxic to the skin. Later, the Skin sensitization potency of the compounds were evaluated by ToxTree QSAR method.

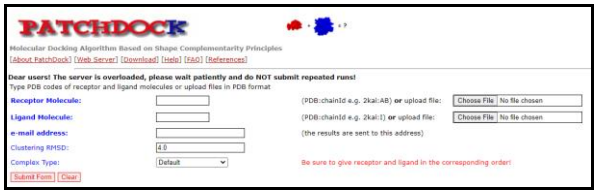

Fig 1: Patchdock server for submission of docking simulation.

RESULTS AND DISCUSSION:

Before performing docking of the compounds against protein Interleukin 8, we have obtained their biological efficacy from pubchem to compare our patchdock score with their toxicity. The patchdock score shows the binding affinity of different compounds with protein. Stronger the affinity of a compound for a particular protein, higher the patchdock score which in turn implies greater toxicity. The 'Safety and Hazard' part in pubchem gives the toxicity data for a compound.

Table 1: It shows the best patchdock score of 16 FDA approved sunscreen ingredients against protein 1IL8 and their biological efficacy.

Compounds	PubChem CID	Patchdock Score	Biological efficacy (Pubchem)	Skin Sensitization (By QSAR ToxTree)
Octocrylene	22571	FALSE POSITIVE 5508	Aquatic chronic	Yes
Octinoxate	5355130	4562	Skin irritaion,eye irritation, aquatic chronic	Yes
Avobenzone	51040	4510	Skin irritaion, aquatic chronic	Yes
PadimateO	30541	4380	Skin irritaion,eye irritation	No
Trolamine salicylate	25213	4020	Skin irritaion,eye irritation	No
Octisalate	8364	3972	Skin irritaion	No
Meradimate	8633	3874	Skin irritaion, eye irritation	No
Cinoxate	5373773	3804	Skin irritaion	Yes
Homosalate	8362	3784	Skin irritaion, eye irritation, aquatic chronic	No
Sulisobenzone	19988	3670	Skin irritaion,eye irritation, skin sensitization, eye damage	No
Ensulizole	33919	3488	Skin irritaion,eye irritation	Yes
Oxybenzone	4632	3452	Skin irritaion,eye irritation, aquatic chronic	No
Dioxybenzone	8569	3370	Skin irritaion, eye irritation	No
Aminobenzoic acid	978	2410	Skin irritation, skin sensitization, eye irritation	No
Titanium dioxide	26042	974	Aspiration hazard, reproductive toxicity	No
Zinc oxide	14806	672	Aquatic chronic	No

The table 1 shows the binding of the sunscreen ingredients against protein 1IL8. By comparing the patchdock results with the literature source like pubchem, it is seen that patchdock has almost correctly assessed the compounds. Compounds like Octinoxate (Fig 1a) and Avobenzone (Fig 1b) strongly binds to the protein 1IL8 and show high docking sore like 4562 and 4510 respectively (Table 1). They are also known to be strong skin irritant. These compounds are also predicted to be skin sensitizers by ToxTree QSAR tools. Aminobenzoic acid has a medium affinity for 1IL8 and shows docking score 2410 which is much lesser than that of Octinoxate and Avobenzone and predicted no skin sensitizer by QSAR method. Compounds like TiO_2 (Fig 1c) and ZnO_2 (Fig 1d) show patchdock score as low as 974 and 672 respectively with 1IL8. They have lowest affinity for protein 1IL8 and are also not known to be potential skin irritant and no skin sensitization potency has been detected by QSAR method. Therefore, our docking approach has been able to provide deep insight into understanding skin irritation and skin sensitisation mechanism where one of the factor is interaction of the compounds with the 1IL8 protein. However, one of the compound, Octocrylene (5508) which does not have any evidence for skin irritation and does not have strong affinity for Interleukin 8. It can be considered as a false positive result.

CONCLUSIONS:

Our docking study reveals that the compounds which show higher docking score have stronger affinity towards protein Interleukin 8 and hence are toxic to the skin. Also, we predict that interaction of the compound with the 1IL8 are one of the reasons for Skin irritant properties of the compounds on the skin. This will help the experimental biologist to design specific experiment considering 1IL8 as target protein during evaluation of Skin irritation potency of the Cosmetic compounds.

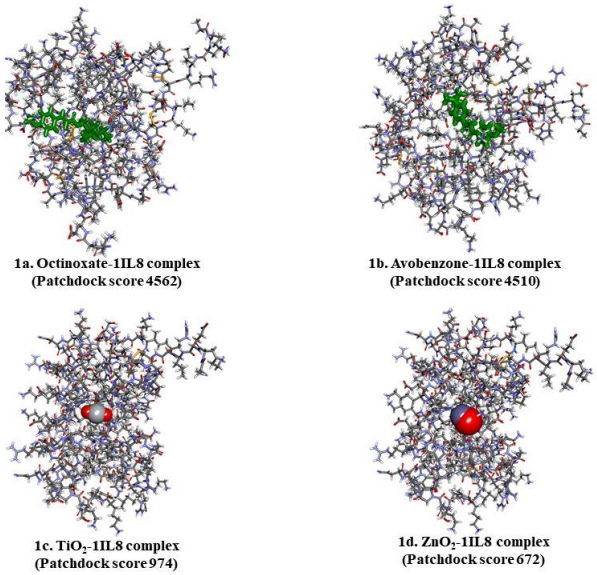

Fig 1. Sunscreen cream ingredients and 1IL8 complex after docking simulation.

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Conflict of Interest

Annotation Analytics pvt. ltd. confirmed that there is no conflict of interest in the paper.

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Drug Transporters: Past, Current, and Future

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ABSTRACT

This review emphasizes the importance of drug transporters in different parts of the body. Transporters are proteins which transports the drugs to target cells and also removes the unused or toxic particles of the drug outside the body. Transporters can be mainly divided into two superfamilies viz. ATP – binding cassette (ABC) transporter superfamily and Solute carrier (SLC) transporter superfamily. Drug – drug interactions are highly influenced by the presence of such transporters. Now – a – days, transporters are used in different technologies like in cosmetics and pharmaceutical products. Thus, transporters effect the nature, absorption, metabolism and elimination of the drug inside the body.

INTRODUCTION

Transporters are proteins that helps the body to digest the drug inside it, generate some special molecules which are useful to the body and excretes the remaining part of the drug.[1] Transporters are present in various parts of our body. They are as follows:

1. In blood: Blood transporters carry the drug from blood to liver.
2. In liver: Liver transporters carry the drug from liver to kidney.
3. In kidney: Kidney transporters excretes the drug outside of the body.

Therefore, the role of drug transporter is to distribute the drug inside the body, make them bio-available and remove the toxic substances of the drug from the body. Transporters which lubricates the entry of the drugs into the target cells are known as influx transporters, while the transporters which impedes the entry of drugs are known as efflux transporters.[2] The switching of these transporters helps the drugs to cross the membranes of different organs.[3]

Transporters mainly belong to two types of superfamilies (Fig. 1). They are as follows:

1. ATP – binding cassette (ABC) transporter superfamily: These transporters supply the energy required to translocate the drug across the membranes. These are primary active transporters.[4]
2. Solute carrier (SLC) transporter superfamily: These transporters enable the solutes of the drugs to flow upward or downward against or along their electrochemical gradient. These are secondary active transporters.[5]

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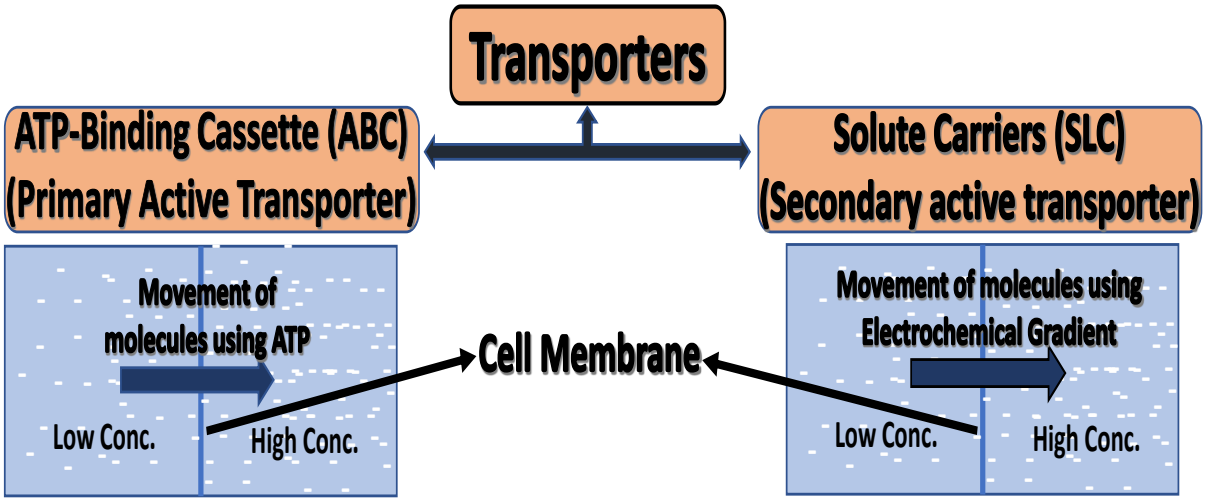

Fig. 1: Types of Transporters

According to the direction in which the transporters carries the substances, they are either termed as uptake transporters or export transporters (Fig. 2). Transporters which carries the drug substances inside the cells are known as uptake transporters and transporters which carries the substances outside the cells are known as export transporters.[6] Different types of transporters are found in these families (Table 1). Some of them are as follows:

Table 1: Drug Transporters [6]

Protein	**Direction**	**Family**
P-glycoprotein (P-gp)	Export	ABCB
Bile salt export pump (BSEP)	Export	ABCB
Multi–drug resistance protein 2 (MRP2)	Export	ABCC
Breast cancer resistance protein (BCRP)	Export	ABCG
Multidrug and toxin extrusion protein 1 (MATE1)	Export	SLC47
Organic anion-transporting polypeptide 1A2 (OATP1A2)	Export	SLC21/ SLCO
Organic anion-transporting polypeptide 1B1 (OATP1B1)	Uptake	SLC21/ SLCO
Organic anion-transporting polypeptide 1B3 (OATP1B3)	Uptake	SLC21/ SLCO
Organic anion-transporting polypeptide 2B1 (OATP2B1)	Uptake	SLC21/ SLCO
Organic cation transporters 1 (OCT1)	Uptake	SLC22
Organic cation transporters 2 (OCT2)	Uptake	SLC22
Organic cation transporters 3 (OCT3)	Uptake	SLC22
Organic anion transporters 1 (OAT1)	Uptake	SLC22
Organic anion transporters 2 (OAT2)	Uptake	SLC22
Organic anion transporters 3 (OAT3)	Uptake	SLC22

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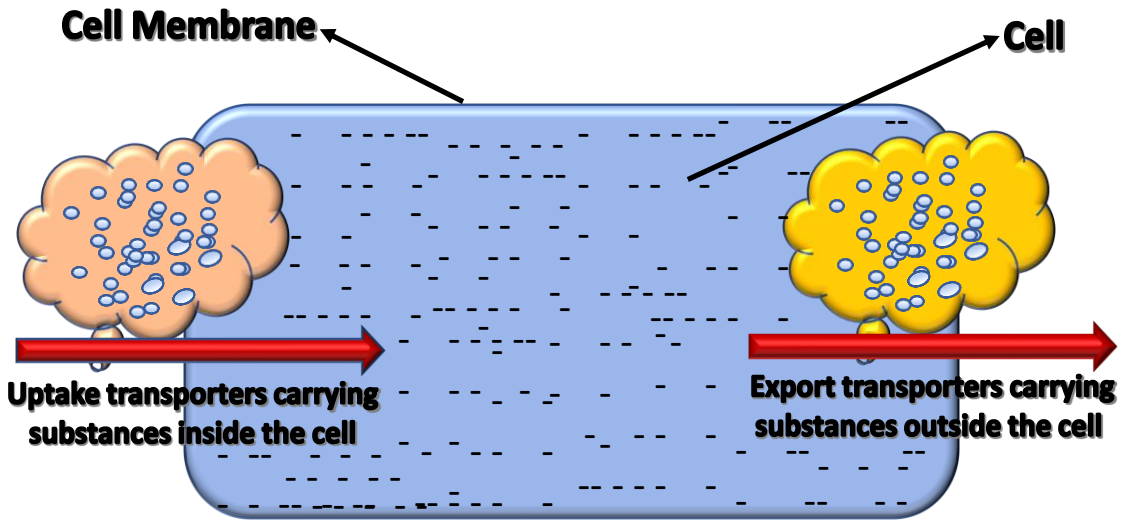

Fig. 2: Uptake and export transporters carrying substances inside and outside the cell respectively

SKIN

Skin, the largest organ of the body, plays a vital role in interrupting the invasion of external substances from the outside surroundings.[7] ABC transporters and SLC transporters are both found in the human skin. It was observed that drug transporters had significant effect in absorption of transdermal drug in the skin and carries drugs from the epidermis to the dermis. If the transporters are inhibited at the epidermis then drugs would remain in the epidermis part and this would be advantageous in treatment of dermatological diseases. Therefore, by targeting the transporters and holding the drugs at the epidermis, dermatological diseases can be treated.[8]

LIVER

Liver, an organ found in the vertebrates, plays a vital role in purifying metabolites, plasma protein synthesis and producing bile, that comprises cholesterol and bile acids, that helps in fat breakdown.[9-11] Hepatic transporters either lubricate the transport of nutrients and other internal substrate inside the cell using uptake transporters or removes toxic chemical substances from the cell using canalicular transporters.[12] It was observed that LST-1, a liver-specific organic anion transporter, primarily participates in clearing the internal and external toxic substances and transports bile acids in the human liver.[13]

KIDNEY

Kidneys, bean – shaped organs located in the vertebrates, are responsible for excreting the unabsorbed or unused drug outside the body. Renal drug transporters are mainly found in the renal proximal tubules and are involved in tubular secretion and tubular reabsorption of the drugs.[14] Drugs are deposited in the kidneys when they interact with the secretory and absorptive transporters present in the renal tubules.[15] The tubule lumen can properly secrete the drug molecules using the two different transporters, one which receives the drug molecules from the blood and another that transports the drug molecules to the tubule fluid.[16]

DRUG-DRUG INTERACTIONS

Drug – drug interactions occurs when the efficacy of a drug is increased or decreased by another drug that competes with the former one to interact with the same

transporter pathway.[17] Drug transporters can be used to study drug-drug interactions. In the past years, several equipment and methods had been developed which can be used to identify the substances that can inhibit or interact with the drug transporters and helps in examining the in vitro drug-drug interaction where the drug transporters act as the mediator.[18] Membrane transporters mediated drug – drug interactions are of two types which are as follows:

1. Interaction due to competition between transporters to reach the substrate binding site.
2. Interaction due to transporters' expression level alteration.

P-glycoprotein (P-gp) has greater substrate specificity, therefore its drug – drug interaction is highly appreciable.[19] It is often observed that type – 2 diabetic patients are medicated with more than one drug. So, it is very important to understand the drug – drug interactions that takes place inside the body. It has been observed that oral antidiabetic drugs significantly inhibit the hepatic uptake transporters which supports potential drug – drug interaction.[20]

DRUG UPTAKE AND DRUG METABOLISM

Drug metabolism refers to the disintegration of drugs carried out by different enzymatic systems. Drug molecules cannot diffuse through the cell membranes, therefore uptake transporters act as the mediator to take the drugs to the target sites.[21] Traditionally in pharmaceutical studies, drug metabolism mainly focuses on the characteristics like absorption, distribution, metabolism and excretion (ADME) of the drugs. It has major impact on the drug – drug interactions, exposure of drugs and on the clearance processes as well.[22]

Chronic kidney diseases have become an emerging threat to human life. These diseases mainly influence the uptake and efflux transporters thereby disturbing the excretion process of the drugs through non renal transporters since the dosage for reduce renal function is not adjusted. It is believed that drugs having narrow therapeutic window are important for patients suffering from kidney diseases. Moreover, adjustment of renal dosage can also lead to increased efficacy and reduced toxicity of the drugs in the body.[23]

APPLICATION OF TRANSPORTERS

Liposomes act as drug transporters and can be applied in drug delivery, topical applications and cosmeceutical applications as its formulation can be easily carried out in laboratory, that too, at a very large scale.[24-26] L'Oréal launched the first liposome containing cosmetic product named Action Liposome, a basic moisturiser, as a patented technology in 1980 and Dior launched another liposome containing cosmetic product named Capture, an antiaging cream, in 1986.[27] Hirsutism, an unusual man – like growth of hair on the face and body of females, can be treated using Tamoxifen – loaded liposomal gel.[28] Now – a – days, many liposome – based cosmetic products are available in the market as it can be actively absorbed by the epidermis and dermis of the skin.

Now – a – days, disorders in the central nervous system (CNS) have become very common and the most challenging part in the treatment of such diseases is the penetration of drugs in the CNS due to the presence of the blood – brain barrier. Nanoparticulate and immunoliposome systems were used as site-specific drug delivery systems which targets the ABC transporters that are responsible for the blood – brain barriers.[29]

People being diagnosed with cancer has also become very common now – a – days.

SLC transporters mainly delivers the anticancer drugs to the target tumor cells. It was also observed that by inhibiting the transporters that lubricates the survival of tumor cells, cancer can also be treated.[30]

CONCLUSION

Drug transporters play a very vital role in maintaining the systematic metabolism of the body when drugs are taken or cosmetics are applied on the body. Thus, transporters effect the nature, absorption, metabolism and elimination of the drug inside the body.

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