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Nail Psoriasis: Notion, Treatment and Current stratagies- An Inclusive review

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Abstract : Psoriasis is a chronic epidermal disease to facilitate broadly affect people worldwide. Nails are epidermal appendages that are mostly prone to get affected in psoriasis patients with an estimate of about 80% likely to encounter psoriasis of nail. Crumbling, lanula red stops, leukonychia are such result in Nail matrix involvement. Sprinter hemorrhages, oil drop or salmon patches, subungual hyperkeratosis. Nail psoriasis leads to artistic as well as efficient impairment, and can also involve joints nearby infection site. The treatment for psoriasis of nail generally involves behavioral interferences, relevant medication and generalsystematic treatment is also available for more severe form of disease (with skin and joint involvement). Though since past few years many advances have been made in the treatment strategies and therapy for cutaneous form of the ailment, but still there is a space and need for new-fangled options in immunotherapy for nail psoriasis. Treatment selection for nail psoriasis is based on efficiency, safety, and optimal patient compliance. Though the literature suggest make use ofof radiation, intralesional, topical, combination, and systemic therapies for psoriasis of nail, but still selection of treatment mode is strenuous and systemic therapy associated side effects results in poor patient compliance. Hence, topical therapy is seems to be obliging amongst all with respect to toxicities and patient compliance. Topical formulations like gels, ointments, creams and nail lacquers are mostly used for psoriasis topical therapy; among which nail lacquers are most promising. The major hurdle in effective drug delivery via topical route is drug permeation via intense keratinized nail covering to attain up to nail bed and nail matrix. Physical as well as chemical permeation enhancing technique is frequently adopted intended for augmented delivery of drug and research in this field is progression. The present analysis covers anatomy and embryology of the nail, and diverse peripheral, systemic and topical treatments were clinical reported till date. Moreover, it chiefly focuses on relevant nail (polish) lacquer preparation and the factor the distressing penetration of drug transversely to the covering of nail (plate of nail). Lastly the medicated nail (polishes) lacquers are used as novel and efficient delivery system of for treating psoriasis of nail has been reviewed. It primarily focuses the lacquers nail as efficient topical formulation for nail psoriasis and also reviews in short factors affecting drug permeation in ungual drug delivery.
Keywords : Arthritis; Drug delivery; Nails; Topical delivery; Psoriasis.

1. Introduction

Psoriasis is a incurable, chronic skin diseases causes important morbidity and distress. It varies to the highest degree inranging, severity as of mild localdelivery to further severe erythrodermic forms. Subjective by both environmental and genetic factors, the pervasiveness of this multi-factorial disease is estimated to be between2.6 and 2.1%in the US.[1,2] It shows a inconsistency between different races and geographical regions, as it is most common in other country patients and in places of higher latitudes.[2]In the USA, the disease affect between 7 and 4.5 million people,[1,2] than in Canada, 1 million people comprise psoriasis.[3] While skin expression are characteristic psoriasis, clinical symptom of the disease. Though nail lesions as forclinical feature is rare in case of psoriasis but nail can be affected up to 15-50 %cases which was said based on older source,[4-8] these experiments are conducted based on the epidemiology study based on theprevalence and incidence of the nail psoriasis. Samman and Fenton,[9]has approximately involved 80 -90 % of psoriatic patients .As the people have clinically different in psoriasis and the patients have their specific nail structure which have extinctive range ofdystrophybasedon the range of pitting ,nail plate loosening, discoloration of the nail surface and even nailbed hemorrhage.

2. NAIL

There is a benign extensive source available to explanation about nail embryology, anatomy and clinical aspects of nail, nail diseases. Fenton[9],Dawber, [10] and Scher, Samman, Baran and Daniel, [11]have given information through the article; but the major information was collected fromZaias's publications.[12-15]

2.1. Function and purpose

The nail's main purpose is to offer protective shield covering, called as nailplate, which is present on the dorsal side of hands and feet. When finger tips get painful injury, then nail plate give some pressure to oppose that terminal phalanx from volar side by which it enhances sensory bigotedof the fingertips ability.[10]Accordingly, the finger nails are capable ofinfluence smaller substance with a furthersophisticated and exactagility.[11]Apart fromthe above function nail also have these palpable: like that of grooming (as a defense/ attack) ,scratching and are even decorated or modified as a cosmetic ornament which oftenly convey information of individual in the social position.[16]Structure of nail is composed of 4 epithelial structures and the nail plate**(Fig 1)**:the nail bed,the proximal nail fold (PNF),the hyponychium[15] and the matrix.

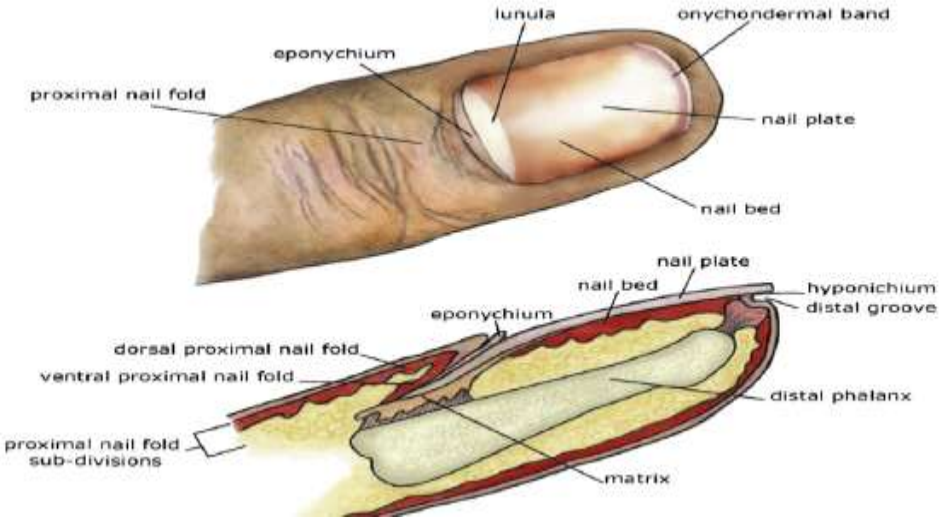

Fig. 1:Longitudinal cross-section displaying the dorsal and ventral proximal nail folds of the nail (reproduced from reference 17).

The nail plate is a flexible, translucent,rectangular structure that present on the surface of the feet and hand **(Fig. 1**). Beneath the PNF it a raisesand with the lateral folding of nail it is surrounded on either sides.The nail plate's proximaltypically most noticeablepart is thumb, which contain a semi circular white area called as lunulae which are visible on the distal template of nail matrix. As theyimproved from the vasculature of the

original nail bed, Becauseof the enhanced vasculature of the underlying nail bed, the abaxial surface visible as pink color on the nail unit.

2.2. Nail folds

The ventral and a dorsal epithelial are present in PNF surface. It is the extinction of the skin the dorsal surface (of each digit)that foldbelowitself, placedon top ofventralsurface (of thenail matrix)(**Fig. 1**).The link between the ventral and dorsal surfaces existon the or the cuticle,eponychium,[10],tht serves to protect the possible gaps between the nail plateand the PNF, which protect the matrix of the nail from harmful environment. Correspondingly, the folding on the lateralnail causes elongation of the surface of theskin sides present in the digits and linkthe nail bed on an average .

2.3.Nail matrix

The nail bed,[18]along with nail matrix is responsible for complete length of the nail**(Fig 2).**

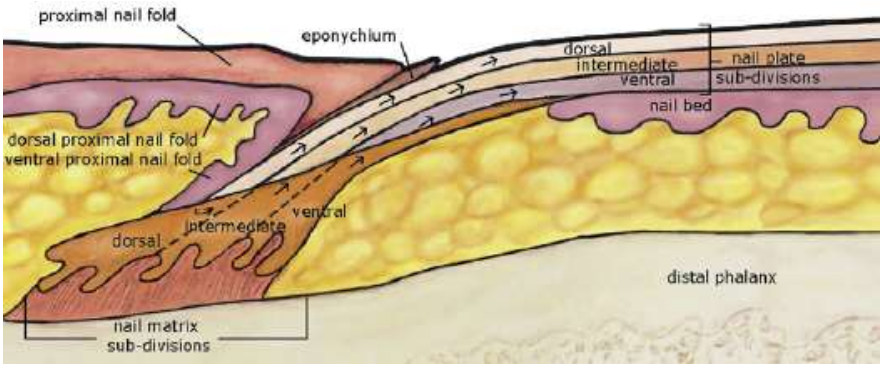

Fig.2: The subdivisions of the nail matrix and how they contribute to the different layers of nail plate (reproduced from reference 17).

The nail matrix is divided into 3 parts: the dorsal section(superficial layers of nail); intermediate region(the deeper layers from the matrix). And the ventralsubdivision (is the nail matrix's distal part)and it is lead by nail bed[18]which nail plate is between the hyponychium and the lunula**(Fig. 1**). Generally,nail bed role is less in formation of the deeper layer of the nail, 18Hyponychium in its matrix. The hyponychium is present below free ends of the nail plate (**Fig. 1**).However, it show the evolution of the nailbed to the epidermis of the toes and fingers. The portion of the hyponychium, also called as the onychodermal band, (reflects on the ventralsurface) of the nail.The nail parenchyma is protected by theband from the outer environment byacting as a barrier to infectiousorganisms andchemical agents.

2.4. Microanatomy

2.4.1. The Nail Plate

The nail plate is a raised from 3 layers which are as following, the intermediate layer is thickest of all three and the tiniest is ventral layer (**Fig 2**). The composition of nail plate is,flattened,granular squamouscells which are tightly packed lamellae sheets that are closely attached to each other.[10]The nail plate is composed of different minerals such as calcium(conc. at 0.1% to the weight), phosphate in the form of hydroxyapatite crystals.[10]Even though calcium does give potency to the nail plate, sulphur protein in the nailmatrix provides it primarily for the plate's density and inflexible relatively.[19]Other constituent like manganese, copper ,zinc andiron, but their significance is unknown.[18]

2.4.2. Nail Folds

The PNF is more likely seen on the skins epidermis, characteristically expecting that dorsal PNF devoid of dermatoglyphic markings of sebaceous glands, and hair follicles.[10, 12based] on the thickness of the dorsal surface, the PNF of ventral layer lacks epidermis distinctivly.[12]At thejunction of epidermal layer of PNF ventral, the eponychium show modified stratum corneum,[10] and consists of overlappingof sheets cells cornfield with no

nuclei.Nail matrixcontainingkeratinocytes, the matrix epithelium is composed of 2 to 3 actively separating basal cell layers. Thedirection at which the nail plate grows can beunderstood by the alignment of these proliferatingcells within the basal layers of the epithelium.[12]Thecuboidal cells distinguish, migrate to thesurface and become flatter by undergoing nuclearfragmentation and forming the keratogenouszone bylyses, [10, 12] during the development process, the cells become integrated by lose of significantportion of itsnuclear contextand develops as nail plate (**Fig 2)**. The nail matrix further subdivided into subsequent layers of the nail platei.e., Onychocytes[12]. As that of skin epidermis matrix of the nail is also keratinizing the cells event in the absence of granular layer, sokeratohyalin formation is not required.[12]The most importantdistinguishing features between, lateral nail folds of the PNF and the matrix, is both of themhold a granular layer. Eventually the matrix containssamelancetssurrounding keratinocyteswhich form pigment and evident as longer bands transversely on thenail plate[10]and easily detected easily in darker skinpeople.

2.4.3. Nail Bed

The nail bed is made-upof a epidermal thin layer, that is the ventral nail matrix anda dermal layer but lacks of subcutaneous fatin legitimate layer.[10]thekeratinocytes and Onychocytesis differed by the thickness of the layers by which nails are made of and it is a rapid process.10In general, the development within one cellular layer only. Finally, these cells are added to ventral portion of nail plate once they become keratinized.[12]Relativly to the healthy epidermis of nail bed significantly undergo keratinization without involvement of keratohyalin.[10,12]Andthe nail beds epidermis contains longitudinallyparallel ridges, that are stretching from lunula to hyponychium.[12]These ridgelock with equivalentdermal rete ridges at the junction of dermoepidermal, that binds strongly binding from nail plate to nail bed and the blood vessels runalong the ridges are conscientious for the splinterhemorrhages related with diseaseor trauma processes, called as endocarditic.[10, 12]The nail bed dermal layer of consists connective tissue present between the epidermisof the nail bed and terminal phalanx[10] and this significant for physiological structures, including blood vessels specifically which are supplying to the nail unit, in addition to it separations of the lymphatic system.

2.5. Embryology

The cellular growth signs in early stages and nail development are relatively seen in the 8 weeks of gestation only.[12]At early stage, an invagination of the primal epidermis forms acontinuousfurrow that delineate a firmedplane at the end of each finger or toe, called as the nail field (**Fig 3**).

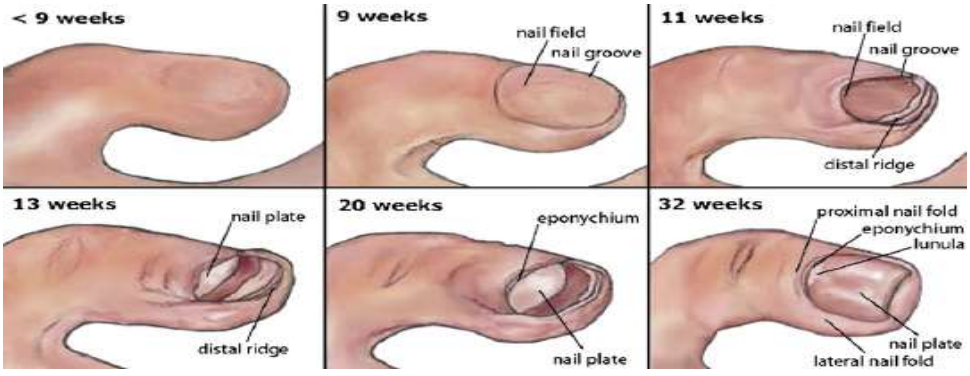

Fig 3: Development offetal structure of the nail apparatus (reproduced from reference 17).

At the 11 weeks, they show development of structure at proximal region of nail field called as the primordium matrix[12]which represents that cells arise from the proximal channel of the nail fieldand that buildsup in a proximal waykeen to the digit, which stop at a distance of approx'1mm commencing the phalanx. The matrix eventually develops into 2 structures: the PNFs epithelium dorsal cells are contributed and the ventral most region of the primordium will grown-up into the intermediate matrixand distal matrix epithelium. The distal nailundergoes changes at dorsum surface of the distal tip of cells, known as the distal ridg.[12]At the 13th week, PNF signs the nail plate growthat lunula, is seen.[12] and denotes the large extent of sulfydryl radicals which seen as staining. At 18 weeks stratum granulose start develop which seems like that of healthy adult.[12]However, at 20 weeks, the cellular maturation in matrix of nail is same as adults.[12A]pproximately 32

weeks gestation, near show all componsions of the nail can be seen (**Table 1**).[12]Finally, itis noted that the toesoccurrence the same stages of progress, approx 4 weeks of that of finger.[12]

Table 1.Summary of nail development[12](reproduced from reference 17)

	Development	No. of weeks gestation
1.	Nail field and grooves	9
2.	Matrix primordium and distal ridge	11
3.	Initiation of nail plate	13
4.	Normal adult keratinization in matrix	20
5.	Distinct nail unit structures	32

2.6. Pathogenesis

Historically Immunology of psoriasis considered discriminationof keratinocytes andproliferation. They identified that psoriatic patients who undergo transplantation of organ along with the cyclosporine[21] A showed change in the improved rejection for diseases and reduce disease state by opposition from keratinizationabnormal.[20]Denileukin difitox[22, 23] and cyclosporine[21]treats' psoriasis, with the help of T cells altering to both pathogenesis diseased cells. The T cells role in psoriasis is divided into 3 basic stages:

(1) Activation T cell;
(2) Migration of T-cell into the skin;
(3) The T-cell mediated cytokine buildingphysiological response of the skin and immunological extension**(Fig 4).**

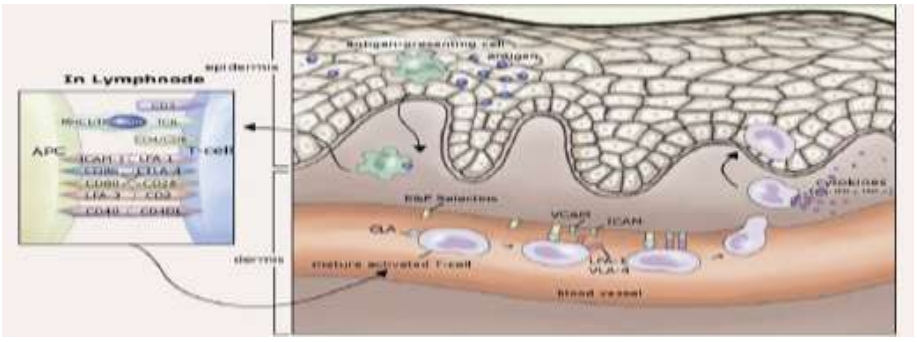

Fig 4: The psoriasis pathogenesis (reproduced from reference 17).

2.6.1. Activation of T cells

An antigen is necessary to activate adolescent T cell for suitable immune. Antigen presenting cells (APCs) present in epidermis should first confine these anonymous antigens, and this interfere stimulates to the APCs for mature and voyage to restricted lymph nodes **(Fig 4)**. Formerly the APCbearing antigen is present in lymph node, the T cell form complex with antigens of Apse and process of activation is continued thought the process is short period T cells require signals of co stimulation and primary specifications to activate them**(Table 2)**. In which the primary stimulus TCR (T cell receptors) identifies peptide antigens on both most important complex I and II called histocompatabiles(MHC) from the APC[24-27] set signals allude for co stimulation which are peptide antigenautarkic. There are many exchanges between APSes and t cells when connected to specific molecule surface of cell (**Table 2**).[24-28]If signals are failed to process the activation condition is stopped resulting in cell death or remain within the cells energy state.[29-31]

Table 2. Summary of corresponding molecules involved in antigen-specific activation processand co stimulation[24-28](reproduced from reference 17).

Antigen presenting cell	**T cell**	
MHC I/MHC II	**TCR (TCR/CD3 1 CD4/CD8)**	**Primary Stimulation**
CD40	CD40 L	Costimulation
CD80	CD28	
ICAM-1	LFA-1	
CD80	CD28	
LFA-3	CD2	
CD86	CTLA-4	
CD	CTLA-4	

On the other hand, if process is productive then T cells proliferation at this stage cells may be set apart to memory cell at which T cells tend to migrate to skin and are activated by moving to blood vessel by passing through inflammatory areas, so the process called as trafficking.This process result in slow movement of cells which helps them to interact with epithelium layer of blood vessel. This process is provided support with a mechanism known as rolling which is supported by factors like CLA antigens(i.e., lymphocyte associated cutaneous antigens),T cells with a glycoprotein and P,E sections molecules on the cells of endothelial surface**(Fig 4).**[32,33]Some other exchanges that facilitate rolling processis T cell addition to protein surface, like that of leukocyte related functions of antigen -1 and vascular cell attachment to the molecules which is followed by interaction of cells by which T cells completes trafficking process and move towards the skin dermis by crossing wall of blood vessel.T1 type of cells are cascades cytokine activation when T_cells reaches the surface of skin by charge inducing inside the keratinocytes.[24-28]The (IFN-g) interferongamma, interleukins -2 ,(TNF -a) are produced from T cells(CD81,CD41)**(Fig 4)**. Sequentially, by the addition of some proteins will result in increase inflammation and some characteristic changes resulting psoriatic lesions.[24-28]Generally, immune system of body will eliminate foreign antigens and show rapid response consequently come the end. But in case of psoriasis immune mechanism contently intensified, resulting inextension in this degenerative disease.[24]

2.7. The nail psoriasis epidemiology

The occurrence of nails association in patients psoriasis is appropriately50%.[45, 46]A study that is done in 2010 in German on 3531 patients suffering from psoriasis was found that involvement of nails in male mare common i.e., up to 11.2% and psoriatic arthritis patients involvestheir nails up to 80%.[46,47]nail psoriasis is even in the lack of involvement of cutaneous lesions (up to 1-5%).[49]

2.8. Nail psoriasis histopathology

The nail bed and nail matrix or either of them is affected during psoriasis, asa effect they are different treatments are involved based on clinical evidence. Based on the data it is expressed as lesions are commonly found on the nail bed in combination with nail matrix lesions (pitting) to some extent .Whereas lesions on nail matrix is less commonly occurred, but in case of hyperkeratosis or onycholysis pain is seen slightly.

2.8.1. Nail and its Related Psoriasis

2.8.1.1. Pathophysiology

Zaia discloses that pitting is mostly seen in cases of lesions on nails which is further leads to discoloration of nail, subungual hyperkeratosis , onycholysis, irregularity of nail plate formation and even may cause hemorrhage .Tham et al[34] identified that even a small change classify lesion occurrence. Hear the studies states that pitting is mostgeneralsymptom of psoriasis up to 68% in the patients suffering with psoriasis along

with 67% of abnormalities of nail like ungual discoloration. Whereas in internal nail hyperkeratosis up to 25% which is less seen in case of onycholysis discoloration of nail bed is not much extensive in abnormalities of nail(18% only).

2.8.1.2. Clinical Forms of Nail Psoriasis

Nail Pitting

Nail plate with depressions on superficial surface of nail may differ the distribution and morphology of nail.**(Fig. 5)**.

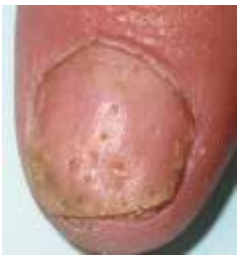

Fig.5: FingernailPitting (reproduced from reference 17).

In case of other diseases like alopecia aerates, lichenplanus and chronic eczema pitting is seen but, in case of individuals with the psoriasis pits are deeper typically. A pit is developed indicates from surface of proximal nail matrix which is shown as a blemish on the nail plates outermost layer. The normal process of keratinization in stratumcorneum was disrupted by primary parakeratotic clusters in the nail matrix in case of lesions of psoriatic nails[12].The exposer of parakeratotic foci to environment while outward development on nail there is a steady deplane of cells seen on the nail plate as a discrete depression**(Fig.6.1).**[12]

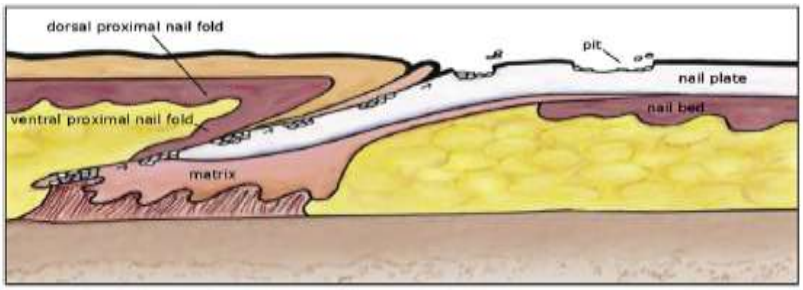

Fig.6.1:Arise of pit within the nailmatrix during the formation of nail plate (reproduced from reference 17).

The PNF promote the process of nail pitting which is already attached to the disease.[12]As PNF lies on the ventral side of the nail matrix surface and is said that the inflammatory cells and parakeratotic are generated from the structure it that entrant on the surface of nail plate in the parakeratotic focal region[12]**(Fig.6.2).**

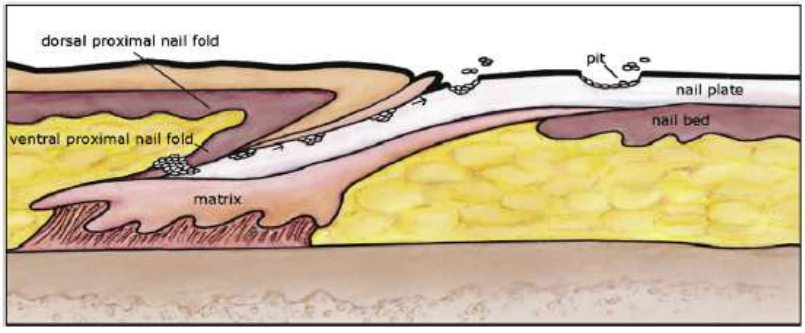

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Fig.6.2: Arise of pitwithin the nail fold of ventral proximal region during formation of nail plate (reproduced from reference 17).

The length of the pitting explain how much time is taken by the lesion to affect the nail matrix and the depth indicate ventral matrix or intermediate involvement in reference to the dorsal surface ,pitting pattern show psoriatic lesions in the nail matrix proximally. Finally, it is said that nail growth is directly proportional to the nail matrix free from lesions.[12]The situation can also be only intermediate and ventral area oaf matrix are effected instead of dorsal surface which appeared as whitishness on surface of nail, known as leukonychia due to internal peeling as a contrast to the external pitting of the nail from parakeratotica.[10] If the lesions are more it appears as transverse groove but in broader surface matrix of the nail.[12]

Trachyonychia

It is also known as sandpapered nails, as it indicates longitudinal ridges are seen as a characteristic feature on the toe and finger ,if the effects all the nails of toes and fingers (**Fig.7)**then it is said as dystrophy of twenty nails which is mostly seen in the male individuals in their childhood along with the Trachyonychia that out come on the proximal surface of nail as permanent modification as opalescent , slender ,tedious , brittle and delicate as a ridges longitudinally seen which result in dull and roughness of nail and distally unevenness is observed. This can be supported by other diseases such as atopic dermatitis, lichen planus , psoriasis and deficiency in the immunology , ichthyoids vulgarize ,atopic dermatitis ,can also result as a part of age also. ThisTrachyonychia condition is even found in the patients of vitiligo

Fig.7: Trachyonychia of nail

Onycholysisand discoloration

In this case we can observe salmon colored dots or oil drop like marks on entire nail plate duringlesions **(Figs: 8.a&8.b).**they is high chance of occurrence of onycholysis when there is involvement of hyponychium in case of parakeratosis**(Fig:8.c)**The air entrapped forms discoloration of nail(whitened) when it is allied along with onycholycis,which further leads to peeling off horny layer. This opening may lead to entrapment and buildup of environmental microorganisms, stated based on the etiology of nail. Prior to it psoriatic nail exhibit stratum corneum thickness along with increase in the number of parakeratolitic cells on the epidermis of nail.[12]**(Fig:8.d).**

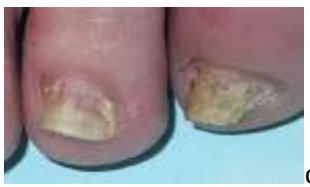
a  b  c  d 

Fig.8. Types of psoriasis: a. fingernailsshouted with salmon color;.Toe nails spotted with signs of Oil drop spots; c.subungual hyperkeratosis of the toenails; d. Onycholysis of the fingernails (reproduced from reference 17).

Based on the color and the specific clinical appearance the nail psoriases level is explained in some cases nail plate is removed off from the nail bed, such as hyponychium. In the case of internalhyperkeratinosis greasy yellow appearance is seen ofttenly. when this hyponychium when reacted with lymphatic cells a pathetic inflammation which further may lead as silver whitish counterpart with high level of inflammation due to deposition of serum of glycoprotine.[10,]further we can observe deposition of serum leads to disorders along with hyponychium on nail bed which is seen as lesion with greasy yellow color appearance.[12]these lesions can be for short durationon the matrix of nail due to involvement of PNF along with intermediate irritation that may cause damage to the nail plate ,as rigdigs and grooves which is generally called Beau's lines(**Fig:9.a**.).[11]

Onychorrhexis is occurred as alongterm therapy resulting in splitting and rigid nailsurface; with the involvement of ventral and intermediate matrix discoloration and spottes are appeared which can also be present in leukonychia of nails(**Fig9.b**.), by the involvement ofleukonychia of nails in combination with 3 parts of nail matrix, exhibit deeper pitting , roughing of nail plate and rigidity or either of them[10]. Eventually which help development of nail psoriasis on complete matrix of nail as a result seems as flaky appearance substantially poorly attached to nail surface (**Fig9.c**.).[10]These hemorrhages of Splinterthough less common than the earlierexplained hemorrhages andlesions realed with psoriatic of nails.

Fig 9. Types of psoriasis: a. Finger nails with onychorrhexis; b. Finger nails with leukonychia; c.Onychorrhexis and onychomadesis of the toenail (reproduced from reference 17).

Although a diminutive amount of hemorrhage may be occurred with respect to longitudinal and parallel ridges, if this hemorrhage is ruptured as delicate capillaries which assumes to be in the shape of splinteralong with epidermal ridges.[12]according to etiology, 20% of the linear structures results in tramma.[35]

Splinter Hemorrhages

In case of Hemorrhage or Splinter hemorrhages we can see distal and linear thready appearances are seen usually on the finger nails only. it is a small clot of blood which result in vertical movement below the nail, but they does not have any specific conditions to infect sub acutely ,endocarditic (SLE) systematic lump's erythematous,trichinosis,trama and hematological malignancy. Primarily they are in plum coloure; eventually they change from darkcolor to black or brown within few days. In case of endocarditic particularly migrate from valves of heart which are effected to other parts of body such as this if it tend to happen in nails or fingers result in damage of hemorrhage**(Fig.10.a.).**Which could be due to striking of nail called "trauma" and they may combine with cholesterol result in blockage of blood capillaters in the fingers. Thishemorrhage is occurred (upon 5 out of 6 persons) even though if an individual is not suffering from endocarditic.

Fig: 10-10.a Splinter hemorrhages; 10.b: Paronychia; 10. b.1: Types of Paronychia

The Paronychia

In psoriasis paronychia is commonly seen which is primarily seen along with scaly erythematous lesions of nails agile surface and longer lesions on the nail plate.**(Fig: 10.b).**

Types of paronychia

The swelling is seen on both right and left fingers in the same person as a result of paronychia (acute) and its division is as follows:

Acute paronychia:Seen for 6 weeks, generally starts as small infection on the lateral sides of nail. Additionally, shown as redness at the site of infection, pain and swelling is seen both in the fingers than in the toes **(Fig: 10.b.1)**. They are occurred due to small actions, such as washing dishes, bitingnails, pricks at hand nail, sucking of finger and inward growth of nail. Pusformation is seen along with regional warmth but these are not

completely evidentialproved. Cephalexin or clindamycin (antibiotics) are mostly used in the sight of effect and pus is removed if any is present.

Chronic paronychia: It is also last for more than 6 weeks, seen in tissues around the nail in finger region is infected most commonly than in the toe which are exposed to the moisture for longer period of time in surrounding environment. In this infection the cuticle is peeled off from nail plate by leaving the infection between nail folds at proximal region and nail plate **(Fig: 10.b.1).** Which is caused due to washing dishes ,sucking of fingers ,forceful trimmed of nails and even due to chemicals such as acids ,mild alkalis etc. It can be avoided by treating with steroids and antifungals, even by removing nail fold surgically. On the other hand paronychia is subdivided into pyogenic and candidial paronychia.

The Acropustulosis

It is seen along with subungual or periungual pustules acropustulosis presents with periungual or subungual pustules with perspective to Hallopeau as for acrodermatitis continua or, generalized or not much seen as psoriatic pustular cultures of fungus and even in observed in the cultures of bacteria also (green blemishes of nails are seen)**(Fig.11**).

Types include:

- Pustulosis Palmariset plantaris
- Infantile acropustulosis

Fig.11. Acropustulosis

Beau Lines

These Beau lines is emerged with intermediate or proximal matrix unnaturally all along the length of nail, though they are several reasons for beau's lines one of them was transitory termination of nail matrix cell division**(Fig.12.a)** and even by nail infections at nail folds (with the cause of injury at that area).It also includes some skin allergic diseases, trauma,hypocalcaemia, etc are involved. These can be considered as signs for some systematic diseases or somebodyillness, may also caused as side effects for malnutrition or chemotherapy .in case of Kawasaki disease in children beau line last atleast for 1-2 moths immediately after inception of fever.

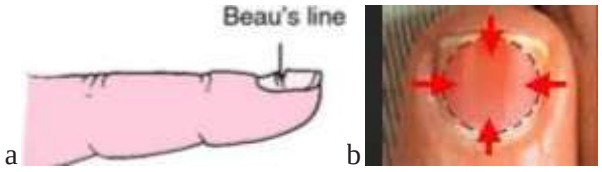


Fig.12.a. Beau Lines; b. Red lunula on the nail

Red Lunula

Lunula red is distinguished by grayish erythema restrainedas turnover of lunulae, alopecia aerate is reported along with it**(Fig.12.b).**It occurred as a consequence of proximal matrix.

2.9. Topical drug delivery, therapy based on formulation and clinical report

2.9.1. Treatment

Psoriasis is an autoimmune disease that has significant impaction the patient's social life that results in morbidity. The patient gradually progresses towards a state of depression and frustration that develop as a result of ineffectiveness of therapies in effective management of psoriasis. The pathogenesis of the psoriasis involves tumor necrosis factor-a (TNF- a), dendritic cells and T-cells [50]and is explained diagrammatically in [**Fig. 13]**.

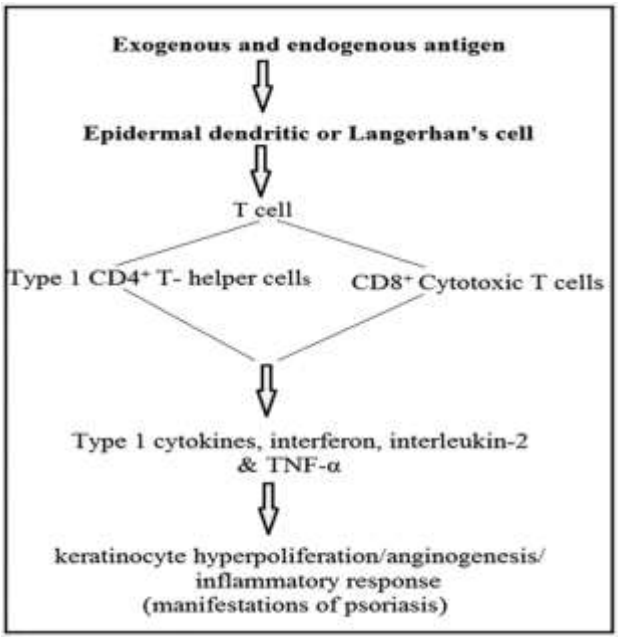


Fig. 13.Schematic representation of the mechanism of psoriasis(reproduced from reference 51).

Exogenous and endogenous antigens that provoke immune responses activate dendritic cells that are considered to be the key initiator of this disease. Their interaction with the T cells located in upper epidermis in perivascular location results in generation of inflammatory response. T cellsof cytotoxic(CD8þ)and T Helper cells (CD4þ Type 1)release large quantities of type 1 cytokines, interleukin-2, TNFathat results in keratinocyte hyper proliferation, angiogenesis and inflammatory responses observed in psoriasis in the form of scaly lesions.[52, 53]

Around 80e90% of the patients suffering from skin psoriasis develop nail psoriasis and that may lead to longer duration and greater extent of skin psoriasis.[54]Earlier research report has asserted that involvement of nails in psoriasis may lead to severe psoriasis.[55]A strong relation also exists in between nail psoriasis and psoriatic arthritis. Nail Involvement and long-term bed psoriasis beds of nail was higher in patient with psoriatic arthritis.[56]Moreover providence to get infected with dermatophytes increases in patients of nail psoriasis.[57]Nail psoriasis may result in high degree of pain and is associated with aesthetic concerns. Psoriasis involves two patterns of nail disorders. Manifestations that result from the involvement of matrix pitting ofnails, lanulaured spots, leuchonychia and nail coveringcollapse while when nail base is involved, and they are shown as discoloration of by oil drop like appearance subungual hyperkeratosis, hemorrhages andonycholysis[58]

NAPSI(Nail psoriasis severity index) is a recently developed scoreschemeuse to determine the sternness of psoriasis nail matrix and nail divan by the spotting that is involved in nail unit and it can be used for evaluating the reaction to management given in psoriasis of nail during experimental trials. As per NAPSI, a nail is separated into 4 quadrants. If any of theseepiphany as mentioned above for psoriasis nail matrix and nail bed psoriasis, are not present its score is 0, if present in 1 quadrant the score is 1, the score is 2 if two quadrants of the nail are affected, 3 if they exist in the nails 3rd quadrants, 4 on entire nail is involved. 0-4score is given or each nail matrix and nail bed. Total nail score is 0-8, which is the sum of two individual scores. The scale is from 0 to 32 for the nail.[59]

Systemic treatments are known to be effective against nail psoriasis but are associated with the various systemic side effects like hypertension and renal toxicity associated with cyclosporine, severe hypervitaminosis. A syndrome with retinoid, leucopenia and hepatotoxicity with methotrexate[60] to name a few, hence is not a proficient approach for the management of nail psoriasis. Topical therapy as a result of its localized effects, minimum systemic adverse effects and higher degree of patient compliance is recommended. However, poor permeability of drug through the nail plate makes topical therapy in effective.[61]Over the past few years various research reports on enhancing the drug delivery through the nail, based on chemical and physical methods of permeation enhancement have been published that seems to be essential to achieve successful treatment approach in nail psoriasis. In the present review various treatment approaches for nail psoriasis covering systemic, topical, intralesional, lesion and phototherapy are covered. Amongst these, topical therapy via nail lacquers, in particular, has been reviewed as the formulation offer commencing the drug to the nail matrix and nailbed, substantial adherence of the formulation at the site and patient compliance.

2.10. Treatment approaches for nail psoriasis management

For the dermatologist as well as for the patient the treatment of nail psoriasis is a challenging task. Due to the deliberateexpansion of the nail protection, reaction towards the treatment becomes protracted[62] and therefore patient looses faith towards the therapy. Various research reports can be found in literature but an effective treatment approach for nail psoriasis is still elusive. The following text describes the approaches for therapy of nail psoriasis.

2.10.1. Systemic Therapy

Methotrexate, cyclosporine and acitertin are used as a conventional treatment options for psoriasis as well as nail psoriasis treatment. Acitretin as a result of its gradual onset of effects is used in elongatedperiodcure of acanthosis as preservation therapy while methotrexate and cyclosporine provide hastyinception of execution. However, due to cumulative toxicities their long term use is not[66] M. Joshi et al. / J recommended.[63]These drugs when administered orally undergo hepatic first pass metabolism thereby reducing bioavailability. Furthermore, slow growth rate of nail and poor blood circulation to the affected nail bed necessitates the oral therapy to be taken for longer period of time with high doses. Even with this regimen, the therapeutic concentration at the target site is not achieved resulting in failure of the oral therapy.[61]New biological agents like adalimunab, entracept, infliximab and ustekinumab are also being used for nail psoriasis therapy and are administered parentally which is an invasive technique. An assemblage of research reports pertaining to systemic therapy (2005-2009) can be found in [**Table 3**] and relatively newer scientific reports are discussed in the preceding text.

Table 3: Systemic therapy for nail psoriasis based on Clinical report (2005-2009)(reproduced from reference 51).

Drug	Treatment description	Result	Reference
Methotrexat	11 year old girl suffering from painful deformity in all 20 nail treated with low dose methotrexate.(5 mg/week)	Severe nail dystrophy seems to be completely resolved after 9 and 13 months for fingernail and toes respectively	Lee et al., 2009[64]
Acitretin	35 patients with moderate to severe nail psoriasis treated with 0.3e3 mg/kg/d for 6 months	41% mean reduction of NAPSI score	Tosti et al., 2009[65]
Efalizumab	Administeredsubcutaneously1.0mg/kg weekly	After 12 weeks management treatment there was50% improvement from baseline in 21.4% of nail psoriasis patients	Katsambas., 2009[66]
Infliximab	5 mg/kg IV administration at weeks zero, two, six and every eight weeks through 46th period of weeks. Eighteen patients were 5mg/kg i.v	Mean improvement in nail bed and nail matrix feature52.9% and 69.2% respectively.	Rich et al., 2008[67] Rigopolus et al., 2008[68]

	administered and NAPSI score assesses at zero, fourteen, twentytwo, thirty and thirty 38 weeks.	At week 14, NAPSI reduced from 55.8 at baseline to29.8. Complete resolution was noted after 6 infusions after 38 weeks. 50% and 75% reduction in mean NAPSI at 14 and22 weeks were obtained respectively	Bianchi et al., 2005[69]
Etanercep	Twice weekly SC 25 mg throughout fifty-four week ortwice weekly SC 50 mg for twelve weeks followed 25 mg weekly twicefor the patientexperiencing decline.	NAPSI scores 8.9% reduction in 12week and 51% decrease at 54 week with absolute clearance in30% patients.	Luger at al., 2009[70]
Alfacept	Administered weekly 15 mg i.m for twelve weeks administered 15 mg i.m for weeks twelve followedby observation for additional 12 weeks	Improvement was observed in 3 patients while in3 patients no changes was observed and in 2 patients the symptoms was provoked. 30% improvement in NAPSI score was observed in 3 out of 6 patients	Korver et al., 2006[71] Cassetty et al., 2005[72]

2.10.2. Conventional Systemic Treatment

Systemic therapy with methotrexate, cyclosporine and acitretin serves as conventional systemic treatment for the nail psoriasis.[73]Methotrexate inhibits the T-cell proliferation and thus plays potential role in psoriasis treatment and its efficacy for nail psoriasis has also been demonstrated. Cyclosporine an immunosuppressant drug; acts by preventing dephosphorylation of nuclear factor of activated T cell by inhibiting calcineurin phosphates enzyme. It also exerts direct effect on keratinocyte proliferation through inhibition of calcineuricin thus serving as an effective therapy for psoriasis treatment.[60]Gumsum et al. (2011) evaluated the efficacy of methotrexate and cyclosporine clinically. 37 patients exaggeratedby means of nailacanthosis be treated through methotrexate with an initial dose of cyclosporineor mg/week 15 with an earlydosage of 5 mg*day/kg. followed by six months of managementof treatment denotes percentage decrease on NAPSI score was 43.3% for methotrexate with significant improvement in nail matrix score; and37.2% for cyclosporine with significant improvement in nail bed score.[74]Acitretin a pharmacologically active metabolite of exterminate has also proved its potential for psoriasis treatment. In are port by Ricceri et al. (2013) a 73 year old patient suffering from nail psoriasis, that involved all fingers and toe nails was treated with oral acitretin (a retinoid compound) in a 0.5 mg/kgof dose. After following six months majordevelopment was noticed further, authors suggested, employment of oral acitretin supportsby means of urea nail gloss / lacquer, might offer superior consequences in severe nail acanthosis.[75]

2.10.3. Biological Agents

The efficacy of the biological agents in support ofacanthosis arthritis and plaque acanthosis has been established. These are fusion of proteins and monoclonal antibodies that inhibit immune system and thus target specifically T cells or inflammatory cytokines.[76]Biological therapies have proved to be less toxic when compared to traditional systemic treatment.[77]Four biological agents namely adalimunab, entracept, infliximab and ustekinumab labeled officially for stable plaque psoriasis have also been identified for their therapeutic potential against nail psoriasis.[78] However very limited research reports are available that prove the efficacy of these agents for nail psoriasis. Adalimunab when given subcutaneously along with tumor necrosis factor(a) of monoclonal antibody of human Ig1 fully .[79]Twenty one patients suffering from plaque psoriasis, psoriatic

arthritis and cutaneous psoriasis with concomitant involvement of nails were administered 80 mg adalimunab subcutaneously at zero week and then fourty mg 6 months-weekly. Considerableenhancement in mean NAPSI for finger and toe nails was observed after 8th injection in all the patients.[80]In another study adalimunab efficacy was evaluated in 21 patients suffering from fair to rigorousconstant plaque acanthosisrelatingfeet or hands. The dose was in progressed at zeroweeksby means of 80 mg, and then fourty mg at eachfurther week initially at week 1. Significantly higher improvement in NAPSI was observed as compared to placebo after7 months of treatment.[81]

Another TNF blocker-etanercept that consists of two receptors ofTNF linked to Fc protein , be administered hypodermically in a dosage form of 50 mg twofold per week for 3 months curepath and maintained at 50 mg/week, if required.[82]Coelho et al., described two cases with the history of plaque psoriasis and observed as a result of severe nail psoriasis. In both the cases, improvement of nail alterations with etanercept after a treatment period of 1 year was reported.[34]The successful use of etanercept for nail psoriasis was supported by another clinical study that was conducted on 72 patients with average to severe psoriasisplaque. The patients were unsuccessful to response to no less than one figure of systematictreatment for nail psoriasis. One group of patient received etanercept twice weekly about 50 mg for twelve weeks follow by weekly once for twelve weeks and enabler50mg for twenty-four weeks to by another group of patients, significant improvement was observed with bothenabler regimen.[84]

Infliximab that also inhibits the action of TNF-a is a chimeric monoclonal antibody and is known to provide effective results in nail psoriasis treatment. A 34 old patient whose quality of life had been impaired as result of subungual hyperkeratosis, pitting and onycholysis appeared on fingernails; acitretin 25 mg daily was found to be ineffective after sixalots of the treatment and was changed coarse to infliximab that was injected in a 5 mg/kg dosage form for zero, two and six weeks. Drasticdevelopment was noticed and after third infusion, the psoriatic lesions got diminished.[85]Faroni et al., in2011 also reported successful long term efficacy of infliximab in a 5 mg/kg dosage form intravenously for nail psoriasis and after 14 weeks of treatment in about 85.4% of the patients in excess of 50% reduction in NAPSI score be seen.[86]

Ustekinumab, a human monoclonal antibody, inhibits interleukin12 and 23 and is known to have therapeutic potential against psoriasis. Its efficacy for nail psoriasis was also investigated[87]and concluded to be safe and effective for nail psoriasis.[88]Patsatsi et al. conducted a clinical trial on 27 patients suffering from plaque psoriasis with involvement of nail. Ustekinumab at a dose of 45 mg administered subcutaneously at stranded level and 4thweek and then at each weeks 12th. The median NAPSI significantly decreased from 73.0 at base line to 0 after 40 weeks and this data suggested effectiveness of ustekinumab in nail psoriasis.[89]A year later, Rich et al. reported the ability of ustekinumab within fingernail acanthosis in the Phoenix 1 trial. Patients were administered ustekinumab 90 mg or 45 mg in zero and four weeks maintained byfollowed dosing at every twelve weeks. Effective means improvement in NAPSI score from4.5 to 2.4 (45 mg) and from 4.4 to2.2 (90 mg) was demonstrated after a treatment period of 6 months.[90]These reports conclude the ability of biological (living) agents(promoter) in management of nail acanthosis psoriasis and have potential for clinical use.

2.10.4. Topical Therapy

Nephrotoxicity, renal dysfunction, high blood pressure, tubular dysfunction, and electrolyte disturbances are some of the side effects associated with the systemic use of cyclosporine[91]; Methotrexate use may develop hepatic, hematologic and pulmonary toxicity;[92]liver toxicity and increase in risk of coronary heart disease are the adverse effects with retinoids. In pregnant women, use of retinoids can be threatening due to its teratogenic effect.[93] Oral administration of these drugs may lead to wide range of systemic adverse effects. Further due to very less vascularity in affected nail bed, high dose of oral therapy are required to be taken for months which may result in increase in adverse effects another disadvantages like drug to drug interaction, long duration of treatment, high cost and high relapse rate, are also associated with the systemic administration of drugs.[94]The use of biological agents for psoriasis therapy is also associated with the adverse effects. Being immunosuppressive agents, these may give rise to various other infections and also the risk for variety of malignant conditions like lymphoma, leukemia and melanoma is increased. The use of TNF-∞ inhibitor may lead to active development of tuberculosis in some patients.[95]

A drug from topical formulation is delivered at the site of action and is the preferred formulation as it minimizes the systemic side effects, is usually preferred in elderly patients or patients receiving multiple

medications as it reduces drug to drug interactions, and in (sufferer)subject with soothing to modest state of disease.[94]Fluorouracil,anthralin,vtazarotene, cyclosporine, glucocorticoids and vitamin D3 analogue are the options available for topical(subjective) therapy in medication/remedy of nail acanthosis.[96]These are used topically as creams, ointments or gels. Various patented topical measures meant for the remedy of acanthosis of the nail are listed in [**Table 4]**.

Table 4: Patents for formulations intended for treatment of nail psoriasis (reproduced from reference 51).

Patent number, year	Title of the patent	Descriptive comment	References
US8784905B2, 2014	Oil-extracted product of indigo naturalisand, preparation process and uses thereof	relate to the oil extracted invention of Indigo naturalis, preparation method and the pharmaceutical composition of the same and the method of treating the patientsuffering from psoriasis or nail psoriasis	97
EP2345243A1, 2011	Urea based film forming solution fortreating nail psoriasis	Relates to the film forming solution comprising 10e20%of urea, 5e15% of film forming polymer, 40e65% of polarsolvent, 1e20% of co solvent and 0.01e5% plasticizer and water up to 100%.	98
US6352686, 2002	Antipsoriatic nail polish	Relates to nail lacquer comprising one or moreglucocorticoids, one or more physiologically tolerable solvent and film forming agents containing quaternaryammonium groups for stable nail enamel.	99
US6114314, 2002	Formulations containing hyaluronic acid	Relates to topically applied quick penetrating systemicsubstance for treatment of nail bed psoriasis and otherskin disease and formulation that includes therapeuticallyeffective non-toxic agent with hyaluronic acid or salt thereof.	100
US4250164, 1981	Method of treating psoriasis of the nailand composition	Relates to the nail lacquer for the effective management ofnail acanthosis/psoriasis prepared by mixing 0.1% valisone lotion inRevlon clear nail lacquer in 50:50 mixture	101

2.10.5. Cream/Ointment/Gel

Creams, ointments and gels are the traditional topical formulations that have been formulated for the effective administration of nail acanthosis / psoriasis's. Vitamin D analog like calcipotriol decreases the level of interleukin-1 (IL-1), IL-6 and reduces CD45RO and CD8þ T cells while it increases transforming growth factor-b1 and b2 that retards epidermal cell growth and thus normalizes inflammatory responses seen in psoriasis.[102]The preliminary studies result conducted on seven patients visceral by nail acanthosis / psoriasis and the calcipotriol cream was adopted for the handling the disease. Improvement in nail acanthosis / psoriasis has been observed within five patients after 3 months of treatment and complete clearing of lesion was observed in one patient after continuing the therapy for further 3 months.[103]Tosti et al., 1998 compared efficacy of 50 mg/g calcipotriol (emollient) ointment within a 64 mg/g betamethasone dipropionate steroid & salicylic acid (emollient) ointment 0.03 g/g. This double blind study was conducted on58 patients and the nail thickness was measured in millimeters at baseline. After 5 months of treatment 49.2% decreasewithin thehyperkeratosis was

seen in group of calcipotriol and group ofsalicylic acid and betamethasone dipropionate 51.7%. The result suggested calcipotriol to be as effectual as the amalgamation of salicylic acid and topical steroid.[104]Zakeri et al. conducted a case series study that further efficacy confirmed of calcipotriol for nail acanthosis and the authors reported 50 mcg/g calcipotriol ointment to be effective in interunguatic hyperkeratosis, discoloration and onycholysis observed within nails of psoriatic subjects(sufferers).[105] Traditionally, topical considered corticosteroids are to be the supported by treatment for nail psoriasis. 0.05% cream or gel of clobetasol propionate used to be the most recommended treatment for nail psoriasis.[106]Corticosteroids can also be used in combination of topical vitamin Danalog.[107]Rigopolus et al., 2002 evaluated the efficacy of calcipotriol cream with clobetasol propionate cream in forty eight patients suffering from psoriasis of the nail. The mean value of hyperkeratosis thickness was measured monthly to check the efficacy and after one year of treatment the mean thickness of hyperkeratosis is decreased by 81.19% for fingernails & 72.5 for toenails.[108]

Tazarotene, an acetylenic retinoid had been used effectively in skin psoriasis. In psoriatic patients, it normalizes epidermal differentiation and exhibits anti-proliferative effects. The potential of tazarotene was also evaluated for nail psoriasis in which 0.1%tazarotene efficacy was compared with 0.05% clobetasol propionate cream. In a double blind study on 46 patients the efficacy of improving pitting, onycholysis, discoloration and hyperkeratosis of tazarotene 0.1% cream was found to be same as that is 0.05% cream of clobetasol propionate after twelve weeks of treatment.[109]In another open observational study on 6 patients, 0.1% tazarotene hydrophilic ointment was applied to the patients. The mean NAPSI score was 14.3 at baseline that reduced to 2.3 after 6 months of treatment and about 87.9% improvement was observed at the end of treatment.[110]In yet another double blinded study, 31 subjects with fingernail acanthosis /psoriasis are medicated with 0.1% vehicle gel or gel of tazarotene and finger nails was targeted one under occlusion and one un-occluded. After twenty four weeks of medicationconsiderabledecrease in onycholysis was seen in non-occluded and occluded nails anddecrease in pitting was also was also examined. There was no significant difference between group in, nail plate crumbling,leukonychia,nail growth rate, pitting,subungual hyperkeratosis and splinter hemorrhages. Thus tazarotene 0.1% gel was found to be well tolerated in nail psoriasis with mild to moderate treatment related adverse effects seen in 16 out of 21 patients.[111]The efficacy of tacrolimus, an immunosuppressive drug, for psoriasis has also been proved.[112] Furthermore, a small open label study has proved its efficacy for nail psoriasis. In this study 21consecutive psoriatic patients were involved and the hands were randomly selected for the application of 0.1% tacrolimus ointment only to the affected nails and after 4 months of treatment period reduction in NAPSI score from 13 to 3.0 was observed.[113]The efficacy of tacrolimus for nail psoriasis needs to be confirmed by conducting experiments on large number of patients. Anthralin or dianthrol is known to have beneficial role in psoriasis treatment. Anthralin oxidizes in presence of light and thus generates free radicals and reactive oxygen species. Destruction of the DNA cells and inactivation of the enzymes associated with cell proliferation and inflammation occurs by the free radicals.[114]Yamamoto et al., in 1985 evaluated the efficacy of anthralin for nail psoriasis. In these study 20 patients of psoriasis vulgaris within nail participation was medicated within 0.4e2% emollient (ointment)in petrolatum of anthralin. The ointment was spread in affected nail bed once a day and was rinsed with the help of water 30 min later. In order to prevent underside pigmentation 10% triethanol amine cream was applied and after 5 months of therapy, improvement was observed in 60%of the patients.[115] 5-Fluorouracil is a cytostatic agent and has provided some beneficial effects in psoriasis treatment. For nail psoriasis in a study to 59 patient's 20%urea plus 1% 5-fluorouracilcream was applied twice daily and improvement in 50% of the psoriasis manifestations such as subungual hyperkeratosis, oil spots and combined sign of nail psoriasis was achieved.[116]

Cyclosporine an immunosuppressive agent primarily exerts its action by selectively inhibiting T-cell function mainly interleukin-2production[117] and thus cornification in the upper layer of epidermis is reduced that may help in preventing the alterations seen in nail psoriasis. Topical cyclosporine has shown improvement in sign of psoriasis of the nail. To eight patients, 70% w/v solution of cyclosporine dissolved in maize oil dissolved was applied for 12weeks. In 3 patients complete resolution of nail lesions and substantial improvement in 5 patients was observed.[118] A compilation of topical formulations available commercially are listed in [**Table 5].**

Table 5 Commercially available topical formulations for treatment of nail psoriasis.

Brand name	Active ingredient	Dosage form	Manufacturer
Temovate®	Clobetasol	Cream, ointment	Glaxo Smithkline,Philadelphia, USA
Curatoderm®	Tacalcitol	0.05% cream	Almirall, Germany
Tazorac®	Tazorotene	0.1% gel or cream	Allergen, Irvine, California
Umecta® nail film	Urea	40% Bioadhesive suspension	JSJ Pharmaceutical,Charleston, South Carolina
Dovonex®	Calcipotriene	Cream	Leo Phama. Inc, Dublin, Ireland

However these conventional topical formulations get promptly cleansed or wiped out and only a small fraction of active ingredient is able to diffuse through the nail. Non-permeation of the active at the application site is another constraint.[118]Therefore, there exists a need of formulation that can remain adhered in place and will continuously release the drug for prolonged period of time .Nail lacquer can be considered as viable option that can offer increased residence and continuous controlled/systemic release .The preceding text focuses on the pre-clinical and clinical details ascribing to nail psoriasis therapeutics.

2.10.6. Nail Lacquers

Medicated nail lacquers are relatively new dosage forms meant for transungual delivery of drug that when applied will form a film on nails after the solvent evaporation through which drug is released in sustained manner for longer period of time to arrive at the indentednail bed. and nail matrixsite. The medicated nail lacquer primarily contains active ingredient, film forming polymer, plasticizer and a volatile organic solvent.[120]Medicated nail lacquer provides the advantage of long duration of contact between the nail and drug and therefore the effective concentration can be reached at desired site. Drug dispersed in polymer acts as a matrix controlled release system. When nail lacquer is applied it will form a water insoluble film on nail plate after the evaporation of volatile organic solvent in few minutes. Film will contain the higher concentration of the drug when compared to original nail lacquer formulation.[121]This will provide a concentration gradient that will assist the diffusion of drug through nail [**Fig. 14**] represents the mechanism of drug release from nail lacquer. The drug release through planar surface of unit area is governed by the Fick's law of diffusion[122] and is defined by the following equation, J¼ -D dc=dx; (1)

Where, D is the drugs diffusion coefficient in film polymer and dc/dx ¼ differences in concentration across diffusion path length of dx.

The nail lacquer also provides an auxiliary advantage of reduction in the transonychial water loss. TOWL (Transonychial-water loss) is the loss of water through the body of the nail coat to the externalatmosphere. When the nail varnish is applied to the nail plate this TOWL is reduced[123]and thus water loss is prevented, resulting in hyper hydration of the nail plate. As a result of hydration and swelling, nail will form a network of aqueous pores which will further promote the diffusion of active ingredient.[124]

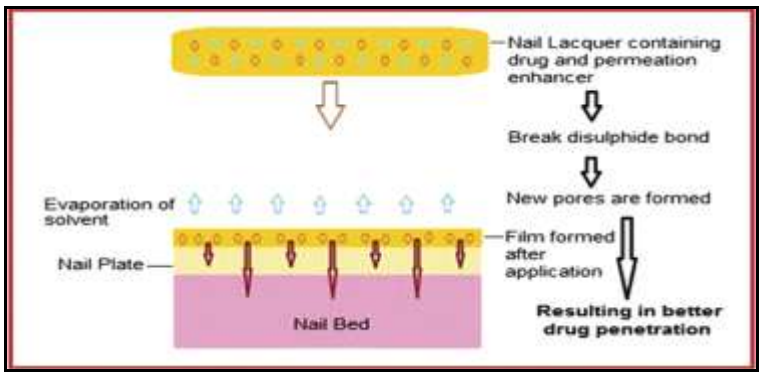


Fig. 14. Diagrammatic representation of release, penetration and permeation of drug From nail lacquer (reproduced from reference 51).

2.10.7. Clinical Reports

Nail lacquer formulations of a variety of anti-psoriatic drug shave been tested clinically for their efficacy. In a small clinical study the efficacy of nail lacquer (polish) formulapreparation contain clobetosol-17-propionate 8% beresolute. Usually formula preparation was applied to 10 patients with nail-bed and nail matrix psoriasis once daily for 21days followed by 9 months weekly twice. Decrease in all the nail alterationalong with pain in nail was seenin 1 month which is in turn dependent on the length of the therapy and no local side effects like atrophy and sober infection was seen. Thus nail lacquers can be regarded as a effective, safe & cosmetically tolerable for the subjectsof nail acanthosis / psoriasis.[127] Nakamura et al., 2012 conducted a study to establish the effectiveness and protection nail lacquer of clobetasol in fifteen subjects distress from nail matrix and nail bed psoriasis in 3 different concentrations (0.05%, 1% and 8%). After 16 weeks the patients were clinically evaluated by NAPSI score and pictorial reports. The authors concluded that in an8%, concentration of clobetasol nail polish(lacquer) was both effective and safe, cangive out as a high-qualitychoice for the topical therapy of nail acanthosis / psoriasis.[126]

3. Factors Influencing the Transport of Active Ingredient Through Nail Plate

3.1. Drugs molecular weight

The molecular weight of the drug has considerable influence on its permeability through the nail plate in comparison to its lipophilicity and dissociation.[128]The mathematical associationinvolvingpenetration of drug through the human ungula and its relative molecular mass has been established by Kobayashi et al. in accordance to the following quadratic equation:

Log P ¼ log D0=h _ β′MW (2)

Where, D0 is a hypothetical molecule that have diffusivity of 0 molecular weight, b0 is a constant, P is the coefficient of permeability,MW represents the molecular weight andh represent thicknessof the membrane.[129]In a study conducted by Miron et al. the effect of different permeation enhancers on geraniol penetration across membranes bovine hoof was evaluated. The diffusionimproving agents were able to boost the penetrationequal to twenty-five timesincomparison control. It has beenverified that acetyl cysteine along withinvolvement of ascorbic acid enlarged the penetration, acid in preparation. In count to, some antifungal drugs were incorporated into a gel formulation of hydroxypropyl methyl cellulose contain0.2% ascorbic acid and 5% acetyl cysteine, thepenetration coefficient throughout membranes ofbovine hoof was assesses. The association involving molecular weight and penetrability be recognized for nerol, geraniol, butenafine, terbinafine, miconazole andfluconazole. Nerol andGeraniol, with inminor molecular weight gives improved penetrability outcome. Demonstration of geraniol is similar otherwise still improved effectiveness catalog standards beside Trichophyton menthagrophytes,Microsporum canis and Trichophyton rubrumcompareamid miconazole and terbinafine.[130]

3.2. Hydrophobicity

The permeation of hydrophilic drug is favored through the nail plate as the nail plate behaves like a hydrophilic gel membrane and maximum flux through nail plate seems to be dependent on drug solubility in water or in swollen keratin matrix.[131]Initial studies have suggested that the lipophilic nature of drug plays a role in the permeation of drug but it was reported later that lipids are present in the dorsal and ventral plates, but only at very low levels in the intermediate plate which forms the main nail body.[132,133]

3.3. Dissociation constant

Dissociation of drug results in the decrease of permeability of drug throughout the nail cover. Mertin et al.1997 demonstrated that dissociation of pyridine and benzoic acid impeded its permeation during membrane bovine hoof (an suitablereplica for nail). This may be a result of Donnan effect which refers to the electrostatic repulsion between the diffused charged molecule and charged membranes. Keratin is having an isoelectric point 5 of a protein and keratin is known to have negative charge at pH 7.4 and is positively charged at pH 2.[131]Further studies were carried out to assess the relation between the amount of charge on the compound and its permeability throughout the nail cover. Southward et al.-1991 investigated the dispersal coefficient of for phosphate or citrate formsin the ionic forms. It seems which decrease in permeability due to dissociation could

not be establishedowed to the interface of a ions variety of in the solution of buffer.[134]The diffusion coefficients of the tri-ionic forms for citrate or phosphate were lower than that of the di-, mono-, and non-ionic forms. The diffusiveness of u-dicarboxylic acids decreaseregarding 5% subsequenttotal ionization.[135]In a comparison of compounds that have the similar molecular formula, the diffusiveness of the ionic complex is almost 10%a smaller amount than that of the unbiasedcomplex.[136]Kobayashi et al, also completedto facilitateimpair penetrability of dissociated compound independent of charge present in it and is as a result of hydration which ultimately leads to the increase in apparent molecular weight of drug.[129]Therefore it can be suggested which thenreduce penetrability is caused by a reduce in diffusivenessowing to ion hydration slightly than aelectrostatic repulsion or Donnan effect amidpenetrating drugand thenail keratin. It can be concluded than the weight of a molecular compound makes a betterdonation to the penetrability coefficient rather than that of water/octanol the dissociation constant or partition coefficient.

3.4. Nature of vehicle

As the nail coverbe have like a deliquescent membrane therefore application of an aqueous vehicle to nail plate may lead to nail swelling and expansion of the keratin network that will in turn facilitate drug transport.[94]However contradictory reports have been made by Mertin et al. (1997) who claimed that the lipophilic vehicles especially nail lacquers to be the most suitable topical preparation than aqueousdelivery system due to better adhesion. When the absorption of drug in nail polish (lacquer) is too elevated, as a result of formation of supersaturated system, greatest flux all the way throughbarrier equaling tostarting aqueous vehicle may be observed.[135]However, the penetration of drug to the dense keratinized nail plate is still a challenging task which can be accomplished by the use of suitable permeation enhancers or by use of suitable method of penetration enhancement.

4. Permeation Enhancement

Nail plate and skin both are derived from epidermis but the composition of nail differs from that of skin. The thickness of the nail plate is 500e1000 mm while stratum corneum is 10e40 mm thick although nail plate has ten folds higher water permeation rate than that of stratum corneum. The percentage of disulfide linkage in nail is 10.6 much higher as compared to 1.2% to that of stratum corneum and the concentration of lipid in nails is 0.1e1% is significantly lower than that of stratum corneum (10e20%).[138]Thus all permeation enhancers that are used for skin permeation enhancement cannot be used for ungual delivery because of the different route of deliverers areaccessible for drug penetration across nail and skin. For example absence of follicular route in nail which is presents in skin.[94]Only few permeation enhancers till date has been investigated for the delivery of active ingredient through nail and is detailed below.

4.1. Chemical enhancement

As huge digit bonds of disulphide is there inthiol compounds(thioglycolic acid ,2-mercaptoethanol ,N-acetyl-l-cystein), nail keratin can break the bonds effectively which leading to significant structural disturbance of nail cover and configuration of novelporeunified by transportationcarrier channels. Thus drug transport is facilitated as a result of increased network channels.[138][**Fig. 15]** represents the scanning electron microscopy image of clipping nail and dorsal surface of intact the nail open to the elements to solution of acid thioglycolic for a period of 48 h. The image clearly depicts the formation of pores and disturbances in dorsal surface of nail and it can be suggested that thioglycolic acid can serve as a potential permeation improver for enhancing the delivery of drug for treatment of nail matrix and nail bed psoriasis. The role permeation enhancer for therapeutic success of any formulation to treat nail psoriasis is highly critical. Murthy et al. (2009) have documented a Tran screen-N technique for the transmission of penetration enhancers. Briefly, two treatment procedures were followed (i) simultaneous exposure of drug and enhancer, and (ii) sequential exposure of enhancer followed by drug. A period of 24 h was selected for the incubation of nail segments with drug plus enhancer solution or enhancer solution. After the completion of incubation period the nail segments were dissolved and washed in sodium hydroxide solution and drug substance was determined.

[137]
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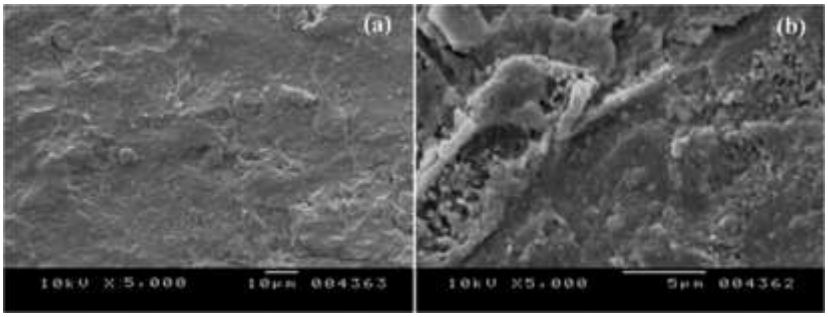

Fig.15:Micrograph byScanning electron to show dorsal surface of nail (a) crude, (b) After exposure to 72 h in 10 % w/v solution to thioglycolic acid (reproduced from reference ref.1).

In a research report from our laboratory intended at expansion of isotretinoin nail (polish)lacquer, acids of thioglycolic was chosen as penetrationimprovers and eugenol was included as anesthetic locally in the preparation. Adhesion inIn vitro and permeation through ex vivo transversely bovine hoof guide the collection of customizedpreparation that was spontaneous. Viscosity handling is to improve adjustment character which affected by additionof (6% by weight) ethyl cellulose that viscosity scales but does not affect the penetrationproperties significantly. LS microscopeConfocal,byfollowing 72 h of nail (polish)lacquer appliance, exposedwidespreadallocation of the fluorescent fragments across the nail cover of human in contrast to manage that was restricted to the outer most layer. The effectiveness of thioglycolic acid as permeation enhancer was retained despite formulation manipulation.[140]

Urea is another keratolytic agent that hydrates and softens the nail cover, and damages the nail surface. The swelling and hydration of the nail covering opens a network channels making structure of nail a less dense with hugepore openings that will promote the drug transport. Urea is known to act by unfolding and thus results in solubilizing and/or denaturing keratin.[122]

As nail plate is mainly composed of keratin keratolytic enzymes like keratinase and papain can be used as permeation enhancers .Mohorcic et al., effective study of keratinase on clipping of nail and the study signify that acts ofkeratinase on the matrix intercellular spaces that hold the cells of nail coverjointly as a result of which corneocytes get separated from each other &"lifted off" the nail covering. Moreover, the nail surface corneocytes corrodesalso. The inner layers are exaggerated to lower extent only and may be due to the high molecular weight of enzyme limiting its diffusion through the nail plate. However, disruption of dorsal nail surface by the enzyme is sufficient to enhance ungual drug delivery as the outer surface of the nail is the main barrier in case of drug permeation.[141]

Another class of compound: surfactants like sodium lauryl sulphate, tween 20, poloxamer168 have the capability of changing the overall permeability of nail plate by altering waterthe porosity packed pores of nail covering. Surface tension reduction and thus results in improving drug to diffusion through the nail covering.[142]In acomparative study, investigated in (2010) Voinovich et al. the effectiveness of dissimilarpreparations containing dissimilarpenetration enhancers: boric acid, dimethyl oxide, urea, fungal protein and docusate sodium salt , as such: cadaver nails byhydrophobins using customized Franz cells diffusion. Highest permeation was noticed for methanol and the order for penetrationimprovement was methanol> class II hydrophobins > DMSO > class I hydrophobins and urea.[143]As a well known fact, the outer most layer of nail covering is the main barricade for diffusion of drug transverselythrough the surface of nail. The permeation enhancers that act by disturbing lipidic bilayers seem to have minor role in enhancing permeation through the nail plate and therefore substances that act and cause disturbances on keratin structure are considered as the potential permeation enhancer for the permeability of drug through nail plate.[144]

4.2. Physical enhancement

In comparison to chemical means, the potential of physical permeation is known to be higher for hydrophilic drugs a macromolecular agents[145] and novel studies to demonstrate the effect of physical methods on enhancing the drug delivery through nail are still in progress. Of the variety of modes being researched, few prominent ones are discussed. Iontophoresis is an active delivery process in which electric field is utilized for transport of drug through the membrane. Electro repulsion, electro osmosis, electroporation, and interaction

between ionic permanent charge and electric field are some of mechanisms that take place during iontophoresis.[146]Dutet et al. measured the fluxes of chloride and sodium transport transversely the human nail (in-vivo) throughoutiontophoresis and passive transportion. When related to passive iontophoresis, diffusion enhancedchloride and sodium transport by 27 and 8fold respectively and the direct current iontophoresis was found to be well tolerated by volunteers.[146]In a report by Murthy et al., wherein the authors examined the griseofulvin and glucose transport of transversely the nail covering ofhuman (in vitro) and reported that nail plate showes permeation selectivity comparable to skin ofhumans. At pH larger than isoelectric point of nail, the nails carries net negative charge that will attract the cations and thus anodal iontophoresis will be high and the enhancement of the glucose transport is due to the cation transport associated with convective water flow in anode to cathode direction. In contrast, at pH less than 5, the convey of glucose to receiver from donor compartment is impeded due to reverse of the charge of humannail and the transport convectively will be in different direction: to anodefrom cathode. However the passive glucose flux was not artificial by changing the pH. Iontophoresis enhanced the transport of griseofulvin by ~8 fold.[147]this investigation provided affirmative result and advocates that iontophoresis can be used as an efficient means for enhancing transungual delivery. Nair et al. (2009) has experimentally proved the effectiveness of iontophoresis. The chemical and physical alteration of nail was carried below both iontophoretic and passive condition. Physical changes are involved scrape of ventral or dorsal layer while into-keratolytic or keratolytic was done in case of chemical alteration. In all the cases iontophoresis improves the permeation of terbinafine hydrochloride. The permeation of terbinafine was improved in case of abraded nail after appliance of iontophoresis as compared to abrades the nails without iontophoresis.

Ionto-keratolysis enhanced terbinafine permeation significantly when compared to untreated nails. Therefore the author shave suggested the use of into-keratolysis for the successful transungual delivery of drug.[146]In another study conducted by Kushwaha et al., iontophoresis be reported chosen more effective when related to passive drugdelivery of hydrochloride-intraconazole. Thus iontophoresis proved elect an efficient method for the delivery of drug addicted to and transversely the nail plate.[148]Further iontophoresis can be used to treat psoriasis associated with nail matrix. Manda et al., in 2012 revealed that application of iontophoresis transversely proximal nail collapse over can potentially intention nail matrix.[149] Use of ultrasound mediated delivery system is a new concept for enhancing the delivery through nail form topical formulations. Abadi and Zderic developed a new ultrasound mediated drug delivery system for enhancing the delivery so that it can reach to the target site nail bed or nail matrix for treatment of fungal disorder.[150] Ultrasound provides waves energy in the frequency greater than 20 kHz. The cavitations produced in ungual structure as result of ultrasound is the proposed mechanism to enhance ungual permeability.[151]For nail psoriasis also it may enhance the ungual delivery. However no research report is available for its use in nail psoriasis for enhancing the transungual delivery. Research is to be done inpresent area to estimate its effectiveness for nail psoriasis.

5. Other Treatment Modalities

5.1. Intralesional therapy

The long acting corticosteroids are given with the help of fine gauze needles directly into the nail folds with the added dose of local anesthetics to reduce the pain associated with the injection. Thetreatment has certain limitations like atrophy of the nail covering and the underlying nail bed and bone, and hematomas.[139]For the vigorous ingredient to reach in nail fold, proximal matrix nail is the site mainly used for injections as it lies directly over the proximal nail matrix and when target site is the nail bed lateral nail folds popularly serve as the site of injection. However local anesthetic is required as high pain occurs during the entry to the deep lateral nail fold[152] Intralesional corticosteroids injections are recommended for the management of nail alumbiasis..[153] Corticosteroid injections are associated with intense pain and the risk of atrophy is associated.[154] Hence the safety of intralesional corticosteroids is still in dilemma. Needle free injections can be visualized as a possible solution.[155] Methotrexate, a folic acid analogue that inhibits polyamine pathway is considered anti inflammatory. [156]

5.2. Phototherapy/laser therapy

Oral photo chemotherapy with high density ultraviolet radiation has been effectively used for nail psoriasis treatment. Marx et al.(1980) reported the use of arrangement of methoxalen and elevated density UV-A radiations and significant improvement in nail sign like onychorrhexis, onycholysis, proximal nail fold

psoriasis, nail plate crumbling, subungual hyperkeratosis , and oil drop change was observed.[157] Oral psoralen coupled with narrow band UVB phototherapy and photo chemotherapy with UVA have provided fruitful results in psoriasis treatment.[158] However no research report is available that proves its advantageous effect for psoriasis of nail. Study involves 25 patients the efficiency of narrow spectrum phototherapy (311nm) for psoriatic onychia was evaluated and 3-5times a week the patients underwent narrow spectrummono-phototherapy. In 21 patients the clinical recovery or the notable improvement was observed confirming the efficacy of narrow spectrum medium wave phototherapy for psoriatic onychia.[159]

Pulse dye laser at both short and long pulse duration can be used as an substitutecure for psoriatic nails. In study on 5 patients psoriatic nails were treated with PDL. Each patient received a pulse of 1.5 ms and the laser energy was 8e10 J/cm2 once monthly for 3 months. NAPSI score was decreased and nail bed lesions mainly onycholysis and subungual hyperkeratosis was improved markedly.[160] In a double blind randomized study 20 subjects with bilateral subungulua psoriasis was treated with pulse dye laser with 40 nails receiving 6-ms pulses and laser energy of 9 J/cm2 andwith 0.45 ms pulses 39 subjectsare treated and once a month with6 J/cm2 for 6 months in a row. A significant decrease in NAPSI score was noted in 3rd and 4th month of the treatment.[159]

6. Future Prospective

Psoriasis nail has a great bang on patient value of life as a result, high pain &aesthetic concerns. Topical formulations like cream, ointment, solutions, and gel itself associated with some limitations. More research in this area is needed to develop a suitable formulation that can effectively permeate and reached to nail matrix & bed for treating nail matrix and nail bedfor psoriasis. Medicated nail lacquer with suitable permeation enhancer can be an effective formulation. More evidences need to be gathered that prove its efficacy for nail psoriasis. For more severe nail disease its use in combination of systemic or biological agents may provide beneficial effects. Consequently much research into the formulation of pharmaceutical nail lacquer is ongoing. Newer permeation enhancement approaches are under review such as the use of thioglycolic acid, serratiopeptidases and other sulfydryl agents as reported by Joshi et al.[138] The research studies are being conducted to develop advanced in-vivo and in-vitro models so pharmacokinetics of dosage form absorption nail penetration and distribution can be measured more accurately and validated to evaluate the effect of hydration, nail pH and other related factors on the process of trans-ungual penetration.[139]An insight into the models for onycho pharmacokinetics is extensively deliberated in literature that may help the researchers in this area to find capablereleasetechnique that can pass through the barrier of nail.

7. Conclusions and Future Trends

In the field of dermatology there was a no clear evidence for treatment of psoriasis of nail.Even though it is unnoticed aspect yet it should be treated, it is being un treated based on incidence seen among i.e., upto90% which cannot be completelytreated. Though thetreatment therapeutic for psoriasis skin is significantly high than that of psoriasis for nails, but few treatments is available. However, there are no proper evidence available based on leaves choices and even clinical subject related data was unclear because of unconfirmed to most select management. Whilesuitable and topical therapies which are comparatively safe, show quite changeable in their efficiency compared to nail diseases. Vitamin-D derivatives and corticosteroids therapeutically are mostly popular, which are effectively demonstrated as efficient in decreasing hyponychium of psoriasis (subungual hyperkeratosis).but, we are not into the studies of other naildegenerative diseases

Although, we considered topical treatment is most effective for psoriasis of nail, with reference to the hyponychium but there is not proper proven documentation for other degenerative nail diseases.Infusion treatment seems to be much safer relatively and mostly use for treating psoriasis on the nail matrix as it is relatively effective. Treatment with injection of corticosteroid show relative improvement in the ridging and nail pitting, which was seen through major investigations. But, tediousness and pain masks its advantages.

PUVA, is more efficient in some forms and used for psoriasis treatment of nail which is shown as a effective during the radiation therapy but compared to it oral PUVA are more beneficial to the suffering subjects which has nail degeneration and PNF involvement. Whereas ,on onycholysis and pitting efficacy is demonstrated by topical PUVA.Though, topical treatment is more efficient and suitable for treatment of nail psoriasis for both nail bed and matrix. The systemic dosing of drug may show some side effects and intense

pain is seen during the treatment of intralesional. The effective treatmentis available with laser / phototherapy radiation quadrants was used but show some harmful side effects in future. Nail lacquares are used as as a localized drug delivering agents and as an pretty attractive option in the form of topical therapy.

Finally it is concluded as; the treatment management for skin psoriasis has wider range of studies compared to the treatment for nail psoriatic diseasesis insufficient and unpersuasive. Even though a few studies support the use ofradiation, systemic, intralesional, and topical treatments for therapy of nail psoriasis, on the other hand there is a necessitate for more research and investigations to accuratelycertify these therapeutic option. Amid thisdue lack of substantiation, it is regularly a difficult task for clinicians to give their subjects (patients) with the most optimal and proficient form of nail therapy. Apart from of the therapeutictreatment pattern, the future of psoriasis ofnail research must guide to additional information should be properly documented, that which will offer physicians amid a additionalproven and definitive approachevidences to treat nail psoriasis.

References

1. Kimball AB, Andrew PY, Signorovitch J, Xie J, Tsaneva M, Gupta SR, Bao Y, Mulani PM. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. J Am Acad Dermatol. 2012 ;66(2):67-76.
2. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin. 1996 ;14(3):485-96.
3. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, Stern RS, Feldman SR, Rolstad T. Epidemiology of psoriatic arthritis in the population of the United States. . J Am Acad Dermatol. 2005 ;53(4):573-1.
4. Gupta AK, Lynde CW, Jain HC, Sibbald RG, Elewski BE, Daniel CR, Watteel GN, Summerbell RC. A higher prevalence of onychomycosis in psoriatics compared with non- psoriatics: a multicentre study. Br J Dermatol. 1997 ;136(5):786-9.
5. Baker H, Golding DN, Thompson M. THE NAILS IN PSORIATIC ARTHRITIS. Br J Dermatol. 1964 ;76(12):549-54.
6. Calvert HT, Smith MA, Wells RS. PSOKIASIS AND THE NAILS. Br J Dermatol. 1963 ;75(11):415-8.
7. Pardo-castello V. Pardo OA-Diseases of the nails Springfield.
8. Strandberg J. Haut und innere Sekretion. InVererbung Innere Sekretion Stoffwechsel 1929 (pp. 166-251). Springer Berlin Heidelberg.
9. Crowley JJ, Weinberg JM, Wu JJ, Robertson AD, Van Voorhees AS. Treatment of nail psoriasis: best practice recommendations from the Medical Board of the National Psoriasis Foundation. JAMA dermatol. 2015 ;151(1):87-94.
10. Baran R. Diseases of the Nails and Their Management,(Baran R, Dawber RPR Eds).
11. Elewski BE. Diagnostic techniques for confirming onychomycosis. J Am Acad Dermatol. 1996 ;35(3):S6-9.
12. Piraccini BM, Tosti A. Drug-induced nail disorders. Drug Saf. 1999 ;21(3):187-201.
13. Zaias N. Psoriasis of the nail: a clinical-pathologic study. Arch Dermatol. 1969 ;99(5):567-79.
14. Zaias N, Alvarez J. The formation of the primate nail plate. An autoradiographic study in squirrel monkey. J Invest Dermatol. 1968 ;51(2):120129-7136.
15. Ditre CM, Howe NR. Surgical anatomy of the nail unit. J Dermatol Surg Oncol. 1992 ;18(8):665-71.
16. Murdan S. Drug delivery to the nail following topical application. *Int J Pharm*. 2002 ;236(1):1-26.
17. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J drug del sci tech. 2015 ;30:63-73.
18. Ditre CM, Howe NR. Surgical anatomy of the nail unit. J Dermatol Surg Oncol. 1992 ;18(8):665-71.
19. Baran R, Dawber RP, Haneke E, Tosti A, Bristow I, editors. A text atlas of nail disorders: techniques in investigation and diagnosis. CRC Press; 2003 .
20. Meinardi MM, Westerhof W, Bos JD. Generalized pustular psoriasis (von Zumbusch) responding to cyclosporin A. Br J Dermatol. 1987;116(2):269-70.
21. Ellis CN, Gorsulowsky DC, Hamilton TA, Billings JK, Brown MD, Headington JT, Cooper KD, Baadsgaard O, Duell EA, Annesley TM, Turcotte JG. Cyclosporine improves psoriasis in a double-blind study. JAMA. 1986;256(22):3110-6.

22. Gottlieb SL, Gilleaudeau P, Johnson R, Estes L, Woodworth TG, Gottlieb AB, Krueger JG. Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. Nature Med. 1995 ;1(5):442-7.
23. Bagel J, Garland WT, Breneman D, Holick M, Littlejohn TW, Crosby D, Faust H, Fivenson D, Nichols J. Administration of DAB 389 IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. J Am Acad Dermatol. 1998;38(6):938-44.
24. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. J Am Acad Dermatol. 2002;46(1):1-26.
25. Mehlis SL, Gordon KB. The immunology of psoriasis and biologic immunotherapy. J Am Acad Dermatol. 2003;49(2):44-50.
26. Benoit S, Toksoy A, Bröcker EB, Gillitzer R, Goebeler M. Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. Br J Dermatol. 2004;150(5):1009-12.
27. Walsh SR, Shear NH. Psoriasis and the new biologic agents: interrupting a T-AP dance. Can Med Assoc J. 2004;170(13):1933-41.
28. Guenther LC, Ortonne JP. Pathophysiology of psoriasis: science behind therapy. J cutan med sur. 2002;6(3_suppl):2-7.
29. Aringer M. T lymphocyte activation–an inside overview. Acta Medica Austriaca. 2002;29(1):7-13.
30. Hudrisier D, Bongrand P. Intercellular transfer of antigen-presenting cell determinants onto T cells: molecular mechanisms and biological significance. The Faseb J. 2002;16(6):477-86.
31. Friedl P, Gunzer M. Interaction of T cells with APCs: the serial encounter model. Trend Immunol. 2001 Apr 1;22(4):187-91.
32. Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS. Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. Nature. 1997;389(6654):978.
33. Picker LJ, Kishimoto TK. ELAM-1 is an adhesion molecule for skin-homing T cells. Nature. 1991;349(6312):796.
34. Tham SN, Lim JJ, Tay SH, Chiew YF, Chua TN, Tan E, Tan T. Clinical observations on nail changes in psoriasis. Ann Acad Med Singapore, Singapore. 1988 ;17(4):482-5.
35. Grando SA, Grando AA, Glukhenky BT, Doguzovc V, Nguyen VT, Holubar K. History and clinical significance of mechanical symptoms in blistering dermatoses: a reappraisal. J Am Acad Dermatol. 2003;48(1):86-92.
36. Miller A, Vaziri ND. Recurrent atraumatic subungual splinter hemorrhages in healthy individuals. South Med J. 1979;72(11):1418-20.
37. Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, Benelli C. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol. 1998;139:655-9.
38. Rigopoulos D, Ioannides D, Prastitis N, Katsambas A. Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream. Acta Derm Venereol (Oslo). 2002;82(2):140.
39. Abell E, Samman PD. Intradermal triamcinolone treatment of nail dystrophies. Br J Dermatol. 1973;89(2):191-7.
40. Bleeker JJ. Intralesional triamcinolone acetonide using the Port- O- Jet and needle injections in localized dermatoses. Br J Dermatol. 1974;91(1):97-101.
41. Peachey RD, Pye RJ, Harman RR. The treatment of psoriatic nail dystrophy with intradermal steroid injections. Br J Dermatol. 1976;95(1):75-8.
42. Berker DE. A simplified protocol of steroid injection for psoriatic nail dystrophy. Br J Dermatol. 1998;138(1):90-5.
43. Marx JL, Scher RK. Response of psoriatic nails to oral photochemotherapy. Arch dermatol. 1980;116(9):1023-4.
44. Handfield- Jones SE, Boyle J, Harman RM. Local PUVA treatment for nail psoriasis. Br J Dermatol. 1987;116(2):280-1.
45. Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martínez-Borra J, Santos-Juanesc J. Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients. Actas Dermo-Sifiliográficas (English Edition). 2011 J;102(5):365-72.
46. Augustin M, Reich K, Blome C, Schäfer I, Laass A, Radtke MA. Nail psoriasis in Germany: epidemiology and burden of disease. Br J Dermatol. 2010;163(3):580-5.

47. Brazzelli V, Carugno A, Alborghetti A, Grasso V, Cananzi R, Fornara L, De Silvestri A, Borroni G. Prevalence, severity and clinical features of psoriasis in fingernails and toenails in adult patients: It exper J Euro Acad Dermatol Venereol. 2012;26(11):1354-9.
48. Williamson L, Dalbeth N, Dockerty JL, Gee BC, Weatherall R, Wordsworth BP. Extended report: nail disease in psoriatic arthritis—clinically important, potentially treatable and often overlooked. Rheumatol Int. 2004;43(6):790-4.
49. Schons KR, Knob CF, Murussi N, Beber AA, Neumaier W, Monticielo OA. Nail psoriasis: a review of the literature. An Bras Dermatol. 2014 ;89(2):312-7.
50. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet Oncol**.** 2007;370(9583):263-71.
51. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J drug del sci tech. 2015 Dec 31;30:63-73.
52. Bayliffe AI, Brigandi RA, Wilkins HJ, Levick MP. Emerging therapeutic targets in psoriasis. Curr Opin Pharmacol**.** 2004;4(3):306-10.
53. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S. Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. N Engl J Med. 2012;366(13):1181-9.
54. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J drug del sci tech. 2015;30:63-73.
55. Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martínez-Borra J, Santos-Juanesc J. Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients. Actas Dermo-Sifiliográficas (English Edition). 2011;102(5):365-72.
56. Maejima H, Taniguchi T, Watarai A, Katsuoka K. Evaluation of nail disease in psoriatic arthritis by using a modified nail psoriasis severity score index. Int J Dermatol. 2010;49(8):901-6.
57. Larsen GK, Haedersdal M, Svejgaard EL. The prevalence of onychomycosis in patients with psoriasis and other skin diseases. Acta Derm Venereol. 2003;83(3):206-9.
58. Schons KR, Knob CF, Murussi N, Beber AA, Neumaier W, Monticielo OA. Nail psoriasis: a review of the literature. An Bras Dermatol. 2014 ;89(2):312-7.
59. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49(2):206-12.
60. Warren RB, Griffiths CE. Systemic therapies for psoriasis: methotrexate, retinoids, and cyclosporine. Clin Dermatol. 2008;26(5):438-47.
61. Shivakumar HN, Juluri A, Desai BG, Murthy SN. Ungual and transungual drug delivery. Drug Dev Ind Pharm. 2012;38(8):901-11.
62. Radtke MA, Langenbruch AK, Schafer I, Herberger K, Reich K, Augustin M. Nail psoriasis as a severity indicator: results from the PsoReal study. Patient Relat Outcome Meas. 2011;2(1):1-6.
63. Koo J. Systemic sequential therapy of psoriasis: a new paradigm for improved therapeutic results. J Amer Acad Dermatol. 1999 ;41(3):S25-8.
64. Lee JY. Severe 20-nail psoriasis successfully treated by low dose methotrexate. Dermatol Online J. 2009 ;15(11).
65. Tosti A, Ricotti C, Romanelli P, Cameli N, Piraccini BM. Evaluation of the efficacy of acitretin therapy for nail psoriasis.Arch Dermatol. 2009;145(3):269-71.
66. Katsambas A, Peris K, Vena G, Freidmann P, Wozel G, Daudén E, Licu D, Placchi M, De La Brassinne M. Assessing the Impact of Efalizumab on Nail, Scalp and Palmoplantar Psoriasis and on Quality of Life: Results from a Multicentre, Open- label, Phase IIIb/IV Trial. Arch Drug Inf. 2009;2(4):66-70.
67. Kyriakou A, Patsatsi A, Sotiriadis D. Detailed analysis of specific nail psoriasis features and their correlations with clinical parameters: a cross-sectional study. *Dermatology*. 2011;223(3):222-9.
68. Rigopoulos D, Gregoriou S, Stratigos A, Larios G, Korfitis C, Papaioannou D, Antoniou C, Ioannides D. Evaluation of the efficacy and safety of infliximab on psoriatic nails: an unblinded, nonrandomized, open- label study. Br J Dermatol. 2008 ;159(2):453-6.
69. Bianchi L, Bergamin A, de Felice C, Capriotti E, Chimenti S. Remission and time of resolution of nail psoriasis during infliximab therapy. J Amer Acad Dermatol. 2005;52(4):736-7.
70. Luger TA, Barker J, Lambert J, Yang S, Robertson D, Foehl J, Molta CT, Boggs R. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate- to- severe psoriasis. J Euro Acad Dermatol Venereol. 2009;23(8):896-904.

71. Körver JE, Langewouters AM, Van De Kerkhof PC, Pasch MC. Therapeutic effects of a 12- week course of alefacept on nail psoriasis. J Euro Acad Dermatol Venereol. 2006 ;20(10):1252-5.
72. Cassetty CT, Alexis AF, Shupack JL, Strober BE. Alefacept in the treatment of psoriatic nail disease: a small case series. J Amer Acad Dermatol. 2005;52(6):1101-2.
73. Sánchez- Regaña M, Sola- Ortigosa J, Alsina- Gibert M, Vidal- Fernández M, Umbert- Millet P. Nail psoriasis: a retrospective study on the effectiveness of systemic treatments (classical and biological therapy). J Euro Acad Dermatol Venereol. 2011;25(5):579-86.
74. Gümüşel M, Özdemir M, Mevlitoğlu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one- blind, randomized study. J Euro Acad Dermatol Venereol. 2011 ;25(9):1080-4.
75. Ricceri F, Pescitelli L, Tripo L, Bassi A, Prignano F. Treatment of severe nail psoriasis with acitretin: an impressive therapeutic result. Dermatol Ther. 2013 ;26(1):77-8.
76. Dubois Declercq S, Pouliot R. Promising new treatments for psoriasis Sci World J. 2013;2013.
77. Zaiac M. The role of biological agents in the treatment of nail psoriasis. Am J Clin Dermatol. 2010;11(1):27-9.
78. Kyriakou A, Patsatsi A, Sotiriadis D. Biologic agents in nail psoriasis: efficacy data and considerations. Exp op bio ther.13;13(12):1707-14.
79. Vena GA, Cassano N. Drug focus: adalimumab in the treatment of moderate to severe psoriasis. Biologics. 2007;1(2):93.
80. Rigopoulos D, Gregoriou S, Lazaridou E, Belyayeva E, Apalla Z, Makris M, Katsambas A, Ioannides D. Treatment of nail psoriasis with adalimumab: an open label unblinded study. J Euro Acad Dermatol Venereol. 2010;24(5):530-4.
81. Leonardi C, Langley RG, Papp K, Tyring SK, Wasel N, Vender R, Unnebrink K, Gupta SR, Valdecantos WC, Bagel J. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. AMA Arch Derm. 2011;147(4):429-36.
82. Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlén SE, Holgate ST, Meyers DA, Rabe KF, Antczak A, Baker J. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-α blockade in severe persistent asthma. Am J Respir Crit Care Med. 2009;179(7):549-58.
83. Coelho J, Diamantino F, Lestre S, Ferreira A. Treatment of severe nail psoriasis with etanercept. Indian J Dermatol Venereol Leprol. 2011 ;77(1):72
84. Ortonne JP, Paul C, Berardesca E, Marino V, Gallo G, Brault Y, Germain JM. A 24- week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. Br J Dermatol. 2013;168(5):1080-7.
85. Safa G, Darrieux L. Dramatic response of nail psoriasis to infliximab. Case Rep Med**.** 2011;2011.
86. Fabroni C, Gori A, Troiano M, Prignano F, Lotti T. Infliximab efficacy in nail psoriasis. A retrospective study in 48 patients. J Euro Acad Dermatol Venereol. 2011;25(5):549-53.
87. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB, PHOENIX 1 Study Investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.
88. Rigopoulos D, Gregoriou S, Makris M, Ioannides D. Efficacy of ustekinumab in nail psoriasis and improvement in nail-associated quality of life in a population treated with ustekinumab for cutaneous psoriasis: an open prospective unblinded study. Dermatology. 2011;223(4):325-9.
89. Patsatsi A, Kyriakou A, Sotiriadis D. Ustekinumab in nail psoriasis: an open-label, uncontrolled, nonrandomized study. J Dermatolog Treat. 2013 ;24(2):96-100.
90. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, Kerkmann U, Ghislain PD, Poulin Y. Ustekinumab improves nail disease in patients with moderate- to- severe psoriasis: results from PHOENIX 1. Br J Dermatol. 2014;170(2):398-407.
91. Prodanovic EM, Korman NJ. Traditional systemic therapy I: methotrexate and cyclosporine. In Treat Psor 2008 (pp. 103-120). Birkhäuser Basel.
92. Goodman TA, Polisson RP. Methotrexate: adverse reactions and major toxicities. Rheum Dis Clin North Am. 1994;20(2):513-28.
93. David M, Hodak E, Lowe NJ. Adverse effects of retinoidsMed Toxicol Adverse Drug Exp. 1988;3(4):273-88.

94. Hafeez F, Hui X, Chiang A, Hornby S, Maibach H. Transungual delivery of ketoconazole using novel lacquer formulation.Int J Pharm. 2013 ;456(2):357-61.
95. Sivamani RK, Correa G, Ono Y, Bowen MP, Raychaudhuri SP, Maverakis E. Biological therapy of psoriasis. Indian J Dermatol. 2010;55(2):161.
96. Gregoriou S, Kalogeromitros D, Kosionis N, Gkouvi A, Rigopoulos D. Treatment options for nail psoriasis. Exp Rev Dermatol. 2008;3(3):339-44.
97. Yin-Ku LI, inventor; Galderma Research & Development, SNC, assignee. Oil-extracted product of indigo naturalis, and preparation process and uses thereof. United States patent US 8,784,905. 2014.
98. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J Drug Delivery Sci Tech. 2015;30:63-73.
99. Bohn M, Kraemer KT, inventors; Aventis Pharma Deutschland Gmbh, assignee. Antipsoriatic nail polish. United States patent US 6,352,686. 2002 .
100. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J Drug Delivery Sci Tech. 2015;30:63-73.
101. Vakirlis E, Kastanis A, Ioannides D. Calcipotriol/betamethasone dipropionate in the treatment of psoriasis vulgaris. Therap clini risk manag. 2008 ;4(1):141.
102. Kokelj F, Lavaroni G, Piraccini BM, Tosti A. Nail psoriasis treated with calcipotriol (MC 903): an open study. J dermatol treat. 1994;5(3):149-50.
103. Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, Benelli C. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. Br J Dermatol. 1998;139:655-9.
104. Zakeri M, Valikhani M, Mortazavi H, Barzegari M. Topical calcipotriol therapy in nail psoriasis: a study of 24 cases. Dermatol online journal. 2005;11(3).
105. Baran R, Tosti A. Topical treatment of nail psoriasis with a new corticoid-containing nail lacquer formulation. J Dermatol treat. 1999;10(3):201-4.
106. Feldman SR, Yentzer BA. Topical Clobetasol Propionate in the Treatment of Psoriasis. Ameri j clinic dermatol. 2009 ;10(6):397-406.
107. Rigopoulos D, Ioannides D, Prastitis N, Katsambas A. Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream. Acta dermato venereol. 2002;82(2):140.
108. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. Acta dermatovenereol. 2007 ;87(2):167-8.
109. Fischer-Levancini C, Sánchez-Regaña M, Llambí F, Collgros H, Expósito-Serrano V, Umbert-Millet P. Nail psoriasis: treatment with tazarotene 0.1% hydrophilic ointment. Actas Dermo-Sifiliográficas (English Edition). 2012;103(8):725-8.
110. Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. Cutis. 2001 :68(5):355-8.
111. Jegasothy BV, Ackerman CD, Todo S, Fung JJ, Abu-Elmagd K, Starzl TE. Tacrolimus (FK 506)—a new therapeutic agent for severe recalcitrant psoriasis. Arch Dermatol. 1992 ;128(6):781-5.
112. De Simone CL, Maiorino A, Tassone F, D'Agostino MA, Caldarola G. Tacrolimus 0.1% ointment in nail psoriasis: a randomized controlled open- label study. Journal of the Europ Acad Dermatol Venereol. 2013 ;27(8):1003-6.
113. Pavithran K. Dithranol: Recent views on its mechanism of action. Indian Journal of Dermatology, Venereology, and Leprology. 2001 ;67(2):104.
114. Yamamoto T, Katayama I, Nishioka K. Topical anthralin therapy for refractory nail psoriasis. J dermatol. 1998 ;25(4):231-3.
115. Fritz K. Successful local treatment of nail psoriasis with 5-fluorouracil. Zeitschrift fur Hautkrankheiten. 1989;64(12):1083-8.
116. Rosmarin DM, Lebwohl M, Elewski BE, Gottlieb AB. Cyclosporine and psoriasis: 2008 National Psoriasis Foundation Consensus Conference. J Ameri Acad Dermatol. 2010;62(5):838-53.
117. Cannavo SP, Guarneri F, Vaccaro M, Borgia F, Guarneri B. Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study. Dermatology. 2003 ;206(2):153-6.
118. Jan S, Bora D, Bhise K. Preungual drug delivery systems of terbinafine hydrochloride nail lacquer. Asian J Pharm. 2008 ;2(1):53.
119. Elezovic A, Elezovic A, Hadzovic S. Simple, Inexpensive and Ecologically Friendly Derivative Spectrophotometric Fluconazole Assay from Nail Lacquer Formulations. American Journal of Analytical Chemistry. 2011 May 1;2(2):109.

120. Pittrof F, Gerhards J, Erni W, Klecak G. Loceryl® nail lacquer—realization of a new galenical approach to onychomycosis therapy. Clinic exper dermatol. 1992 ;17(s1):26-8.
121. Saner MV, Kulkarni AD, Pardeshi CV. Insights into drug delivery across the nail plate barrier. J drug target. 2014 ;22(9):769-89.
122. Murdan S, Hinsu D, Guimier M. A few aspects of transonychial water loss (TOWL): inter-individual, and intra-individual inter-finger, inter-hand and inter-day variabilities, and the influence of nail plate hydration, filing and varnish. Europ J Pharma Biopharma. 2008 ;70(2):684-9.
123. Hao J, Smith KA, Li SK. Chemical method to enhance transungual transport and iontophoresis efficiency. *Int J Pharm*. 2008;357(1):61-9.
124. Nakamura RC, Abreu LD, Duque-Estrada B, Tamler C, Leverone AP. Comparison of nail lacquer clobetasol efficacy at 0, 05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. Anais brasil dermatol. 2012 ;87(2):203-11.
125. Cantoresi F, Caserini M, Bidoli A, Maggio F, Marino R, Carnevale C, Sorgi P, Palmieri R. randomized controlled trial of a water-soluble nail lacquer based on hydroxypropyl-chitosan (hPCh), in the management of nail psoriasis. Clinic cosm invest dermatol. 2014;7:185.
126. Monti D, Saccomani L, Chetoni P, Burgalassi S, Saettone MF, Mailland F. In vitro transungual permeation of ciclopirox from a hydroxypropyl chitosan-based, water-soluble nail lacquer. D dev indus pharm. 2005 Jan 1;31(1):11-7.
127. Kobayashi Y, Komatsu T, Sumi M, Numajiri S, Miyamoto M, Kobayashi D, Sugibayashi K, Morimoto Y. In vitro permeation of several drugs through the human nail plate: relationship between physicochemical properties and nail permeability of drugs. Europ j pharm sci. 2004;21(4):471-7.
128. Miron D, Cornelio R, Troleis J, Mariath J, Zimmer AR, Mayorga P, Schapoval EE. Influence of penetration enhancers and 23molecular weight in antifungals permeation through bovine hoof membranes and prediction of efficacy in human nails. Europ J Pharm Sci. 2014 ;51:20-5.
129. Mertin D, Lippold BC. In- vitro permeability of the human nail and of a keratin membrane from bovine hooves: Influence of the partition coefficient octanol/water and the water solubility of drugs on their permeability and maximum flux. J pharm pharmacol. 1997 ;49(1):30-4.
130. Kobayashi Y, Miyamoto M, Sugibayashi K, MORIMOTO Y. Drug permeation through the three layers of the human nail plate. J pharm pharmacol. 1999 ;51(3):271-8.
131. Dawber RP. The ultrastructure and growth of human nails. Arch dermatol res. 1980 ;269(2):197-204.
132. Southard MZ, Dias LJ, Himmelstein KJ, Stella VJ. Experimental determinations of diffusion coefficients in dilute aqueous solution using the method of hydrodynamic stability. Pharm res. 1991;8(12):1489-94.
133. Spiro M, Price WE, Miller WM, Arami M. Kinetics and equilibria of tea infusion: Part 8—the effects of salts and of pH on the rate of extraction of theaflavins from black tea leaf. Food chemistry. 1987;25(2):117-26.
134. Flynn GL, Yalkowsky SH. Correlation and prediction of mass transport across membranes I: Influence of alkyl chain length on flux- determining properties of barrier and diffusant. J pharm sci. 1972 ;61(6):838-52.
135. Mertin D, Lippold BC. In- vitro permeability of the human nail and of a keratin membrane from bovine hooves: Penetration of chloramphenicol from lipophilic vehicles and a nail lacquer. J pharm pharmacol.;49(3):241-5.
136. Joshi M, Sharma V, Pathak K. Nail psoriasis: An updated review of clinical reports on therapy and formulation aspects for topical delivery. J D Del Sci Tech. 2015 ;30:63-73.
137. Murthy SN, Vaka SR, Sammeta SM, Nair AB. TranScreen- N™: Method for rapid screening of trans- ungual drug delivery enhancers. J pharm sci. 2009 Nov 1;98(11):4264-71.
138. Joshi M, Sharma V, Pathak K. Matrix based system of isotretinoin as nail lacquer to enhance transungal delivery across human nail plate. In j pharm. 2015;478(1):268-77.
139. Mohorčič M, Torkar A, Friedrich J, Kristl J, Murdan S. An investigation into keratinolytic enzymes to enhance ungual drug delivery. In j pharm. 2007;332(1):196-201.
140. Chouhan P, Saini TR. Hydration of nail plate: a novel screening model for transungual drug permeation enhancers. In j pharm. 2012 ;436(1):179-82.
141. Vejnovic I, Simmler L, Betz G. Investigation of different formulations for drug delivery through the nail plate. In j pharm. 2010 ;386(1):185-94.
142. Narasimha Murthy S, Wiskirchen DE, Paul Bowers C. Iontophoretic drug delivery across human nail. J pharm sci. 2007 ;96(2):305-11.

143. Elkeeb R, AliKhan A, Elkeeb L, Hui X, Maibach HI. Transungual drug delivery: current status. In j pharm. 2010 ;384(1):1-8.
144. Dutet J, Delgado-Charro MB. In vivo transungual iontophoresis: effect of DC current application on ionic transport and on transonychial water loss. J Con Rel. 2009 ;140(2):117-25.
145. Murthy SN, Waddell DC, Shivakumar HN, Balaji A, Bowers CP. Iontophoretic permselective property of human nail. J dermatol sci. 2007 ;46(2):150-2.
146. Nair AB, Sammeta SM, Kim HD, Chakraborty B, Friden PM, Murthy SN. Alteration of the diffusional barrier property of the nail leads to greater terbinafine drug loading and permeation. In j pharm. 2009 ;375(1):22-7.
147. Kushwaha A, Jacob M, Shiva Kumar HN, Hiremath S, Aradhya S, Repka MA, Murthy SN. Trans-ungual delivery of itraconazole hydrochloride by iontophoresis. D dev indu pharm. 2015 ;41(7):1089-94.
148. Manda P, Sammeta SM, Repka MA, Murthy SN. Iontophoresis across the proximal nail fold to target drugs to the nail matrix. J pharm sci. 2012 ;101(7):2392-7.
149. Abadi D, Zderic V. Ultrasound- Mediated Nail Drug Delivery System. J Ult Med. 2011 ;30(12):1723-30.
150. Walters KA, Abdalghafor HM, Lane ME. The human nail–barrier characterisation and permeation enhancement. In j pharm. 2012 ;435(1):10-21.
151. Saleem K, Azim W. Treatment of nail psoriasis with a modified regimen of steroid injections. J Coll Physicians Surg Pak. 2008 ;18(2):78-81.
152. Wozel G. Psoriasis treatment in difficult locations: scalp, nails, and intertriginous areas. Clinic dermatol. 2008 ;26(5):448-59.
153. Nantel-Battista M, Richer V, Marcil I, Benohanian A. Treatment of nail psoriasis with intralesional triamcinolone acetonide using a needle-free jet injector: a prospective trial. J cutan med sur. 2014 ;18(1):38-42.
154. Sarıcaoglu H, Oz A, Turan H. Nail psoriasis successfully treated with intralesional methotrexate: case report. Dermatology. 2011 ;222(1):5-7.
155. Marx JL, Scher RK. Response of psoriatic nails to oral photochemotherapy. Arch dermatol. 1980 ;116(9):1023-4.
156. Oram Y, Akkaya AD. Treatment of nail psoriasis: common concepts and new trends. Dermatol res pra . 2013 ;2013.
157. Green C, Ferguson J, Lakshmipathi T, Johnson BE. 311 nm UVB phototherapy—an effective treatment for psoriasis. Br J Dermatol. 1988 ;119(6):691-6.
158. Treewittayapoom C, Singvahanont P, Chanprapaph K, Haneke E. The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. J Amer Acad Dermatol. 2012 ;66(5):807-12.
159. Al Mutairi A, Elkashlan M. Nail psoriasis treated with pulse dye laser. Ind j dermatol. 2013 ;58(3):243.
160. Murthy SN, Maibach HI, editors. Topical nail products and ungual drug delivery. CRC press; 2012.

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